Clinical Practice Guideline for Diabetes Mellitus Type 1

NOTE:

More than 5 years have passed since the publication of this Clinical Practice Guideline, and **its validity has not been reviewed**.

Therefore, **it is unclear whether its recommendations remain valid**; they should therefore be treated with caution and applied in accordance with **clinical judgement and the individual circumstances of each patient**.

CLINICAL PRACTICE GUIDELINTES IN THE NHS
MINISTRY OF HEALTH, SOCIAL SERVICES AND EQUALITY

MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD
MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD
Plan de Calidad para el Sistema Nacional de Salud
EUSKO JAURLARITZA GOBIERNO VASCO
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DEPARTAMENTO DE SANIDAD Y CONSUMO

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This CPG is an aid to decision making in health care. The compliance of this guide is not mandatory, nor does it replace the clinical judgement of the health care personnel.

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Presentation

Documenting the variability of clinical practice, analyze its causes and adopt strategies to eliminate it have proven to be initiatives that promote effective and safe decision making by health professionals focusing on the patient. Among these strategies, the most significant is the preparation of clinical practice guidelines (CPG), a set of "*systematically developed recommendations to help professionals and patients to make decisions about the most appropriate health care, and to select the diagnostic or therapeutic options best suited to addressing a health problem or a specific clinical condition*".

The 2010 Quality Plan for the Spanish National Health System (NHS) aims to address the challenges that it has to face, increasing the cohesion of the system, guaranteeing equity in health care to its citizens, regardless of where they reside and ensuring that this care is of the highest quality. Its objectives include the promotion of the development and use of GPC strategies related to health, consolidation and extension of the Guía-Salud Project. In this context, the **CPG for Diabetes mellitus type 1** (DM1) can be framed.

Although DM1 usually represents only a minority of the total burden of diabetes on the population, it is the predominant disease in younger age groups in most developed countries and has a major impact on the patients' lifestyle as well as their self-esteem.

The purpose of this guide is to improve the quality, efficiency and equity of care for people with DM1 in the NHS. Thus, it addresses issues in the diagnosis of this disease and the detection of associated autoimmune diseases, diabetic education, glycaemic control, acute and chronic complications and organizational aspects of care, paying special attention to the approach to patient care in special situations and with special needs.

This guide is the result of hard work carried out by a very large group of professionals, doctors and nurses and a group of patients who gave their vision of the whole process and how it could be improved.

From the Quality Agency we thank them for all the work they have done and we congratulate them for the elaboration of this CPG which will certainly allow healthcare professionals optimize their clinical practice and provide patients with DM1, their families and caregivers, with information and education to meet the needs and problems that may arise during the course of the disease, thus improving self-care and their quality of life.

Carmen Moya García

Director General of the Quality Agency of NHS

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Diabetes Federation of the Basque Country belonging to the Spanish Diabetes Federation

Spanish Diabetes Society

Spanish Society for Paediatric Endocrinology

Spanish Society for Endocrinology and Nutrition

The members of these societies have participated in the creation, expert collaboration and external review of this CPG.

Declaration of interest: All members of the Working Group, as well as those who have participated in the expert collaboration and external review, have made the declaration of interest as appears in Appendix 14 of the full version.

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Questions to answer

Definition, diagnostic criteria for diabetes mellitus type 1

1. What is diabetes mellitus type 1?
2. What do the autoantibodies provide for the diagnosis of diabetes mellitus type 1?
3. What are the predictors of 'spontaneous remission'?
4. When is it convenient to carry out a genetic study to rule out MODY diabetes?
5. What other autoimmune diseases are associated with diabetes mellitus type 1?
6. Is it necessary to rule out autoimmune diseases that are associated with diabetes mellitus type 1?
7. How should autoimmune diseases that are associated with diabetes mellitus type 1 in the initial study be considered?
8. How often should autoimmune diseases associated with diabetes mellitus type 1 be taken into account in the monitoring stage?

Diabetes Education

9. Are structured educational programs aimed at people with diabetes mellitus type 1 and their families effective?
10. Structured education aimed at families and people with diabetes mellitus type 1: When, how, by whom and what content is to be included?
11. Are the arrangements for community or extra sanitary support (schools, diabetic associations, etc.) aimed at people with diabetes mellitus type 1 effective?
12. How to match the clinical management of diabetes mellitus type 1 in people with special needs?

Feeding

13. What is the most appropriate diet for people with diabetes mellitus type 1?
14. What meal plan is more advisable for people with diabetes mellitus type 1?

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Exercising

15. What are the benefits of exercise for people with diabetes mellitus type 1?
16. What kind of exercise is recommended for people with diabetes mellitus type 1?

Glycaemic Control

17. What are the target values of glycated haemoglobin?
18. What are the criteria for standardization and reporting of analytical results of glycated haemoglobin?
19. Do the continuous glucose monitoring systems provide better metabolic control?
20. What are the benefits and drawbacks of the management of patients with diabetes mellitus type 1 in the hospital at the time of diagnosis, compared with outpatient level management?
21. What is the effectiveness and safety of the different insulin preparations?
22. What are the indications for the continuous subcutaneous insulin infusion pump?
23. What are the safest and most effective methods of insulin administration?
24. What are the insulin administration techniques recommended for diabetes mellitus type 1?
25. Is it suitable to add metformin to insulin in adolescents?
26. What is the effectiveness of islet cells and pancreas transplantation?

Management of diabetes mellitus type 1 in special situations

27. What are the insulin therapy guidelines during hospitalization for patients whit diabetes mellitus type 1: surgical, critically ill and stable patients?
28. What are the preventive and treatment measures in case of ambulatory acute intercurrent diseases?
29. Are psychological disorders more common in people with diabetes mellitus type 1?
30. Does adolescence pose a risk for decompensation in diabetes mellitus type 1?
31. Is it important to plan pregnancy in women with diabetes mellitus type 1?
32. How does pregnancy affect the development of complications in diabetes mellitus type 1?
33. What should the before and during pregnancy metabolic control in women whit diabetes mellitus type 1 be?
34. What are the most recommended contraceptives in women with diabetes mellitus type 1?
35. How to adapt the clinical management of diabetes mellitus type 1 in patients whit special needs.

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Acute complications

36. When to suspect hypoglycaemia?
37. How to assess the severity of hypoglycaemia?
38. What should the performance measures against hypoglycaemic events be?

Chronic complications

39. How to evaluate the cardiovascular risk of patients with diabetes mellitus type 1?
40. Is there a medical (non-surgical, non-laser) treatment to prevent diabetic retinopathy?
41. What should the screening starting time for diabetic retinopathy be?
42. How often should screening for diabetic retinopathy be carried out?
43. What should the techniques for screening of diabetic retinopathy be?
44. What are the referral criteria to nephrology specialists for patients with diabetic nephropathy?
45. What is the pharmacological treatment for patients with diabetes mellitus type 1 and microalbuminuria?
46. What should the screening frequency for diabetic nephropathy be?
47. At what age or years of evolution should diabetic nephropathy screening be performed?
48. What methods should be used for diabetic nephropathy screening?
49. It is necessary to carry out a diabetic foot screening?
50. What should the screening frequency for diabetic foot be?
51. At what age or years of evolution is diabetic foot screening to be carried out?
52. What method should be used for the diabetic foot screening?
53. What is the best treatment for erectile dysfunction in patients with diabetes mellitus type 1?
54. What is the best treatment for painful diabetic neuropathy?

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Organising the medical consultation

55. How should the transition of patients with diabetes mellitus type 1 from paediatric services to adult services be?

56. What is the initial study to be done to newly diagnosed patients of diabetes mellitus type 1?

57. What tests should be performed for people with diabetes mellitus type 1 in the monitoring and control consultations, and how often?

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Levels of evidence and grades of recommendations

Levels of evidence and grades of recommendation SIGN [1:2]

Levels of evidence	
1++	High-quality meta-analyses, systematic reviews of clinical trials or high-quality clinical trials with very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews of clinical trials, or well-conducted clinical trials with little risk of bias.
1-	Meta-analyses, systematic reviews of clinical trials or clinical trials with high risk of bias.
2++	High quality systematic reviews of case-control or cohort studies. Cohort or case-control studies with very low risk of bias and with high probability to establish a causal relationship.
2+	Well-conducted case control or cohort studies with low risk of bias and a moderate probability of establishing a causal relationship.
2-	Case control or cohort studies with high risk of bias and a significant risk that the relationship is not causal.
3	Non-analytical studies such as case reports and case series.
4	Expert opinion.
Grades of recommendation	
A	At least one meta-analysis, a systematic review or a clinical trial rated as 1++ and directly applicable to the target population of the guide; or body of scientific evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
B	A body of scientific evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1 +.
C	A body of scientific evidence consisting of studies rated as 2 +, directly applicable to the target population of the guide and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2 ++.
D	Scientific evidence level 3 or 4, or extrapolated evidence from studies rated as 2 +

Studies classified as 1- and 2- should not be used in the process of developing recommendations due to their high potential for bias.

Good clinical practice

√ [1]	Recommended practice based on clinical experience and the consensus of the editorial team.

[1] *Sometimes the development group realises that there are some important practical aspects, which should be emphasised, and for which there is probably no scientific evidence that supports them. In general, these cases are related to some treatment aspect considered to be "good clinical practice" and usually no one would argue about them. These aspects are rated as points of good clinical practice.*

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Levels of evidence and grades of recommendation for diagnostic questions

NICE adaptation of levels of evidence of the Oxford Centre for Evidence-based Medicine and the Centre for Reviews and Dissemination [2; 3]

Levels of scientific evidence	Type of evidence
Ia	Systematic review with homogeneity of **level 1** studies.
Ib	**Level 1** studies.
II	**Level 2 studies.** Systematic review of level 2 studies.
III	**Level 3 studies.** Systematic review of Level 3 studies.
IV	Consensus, expert opinion without explicit critical appraisal.
Level 1 studies	Meet: • Masked comparison with a valid reference test (gold standard). • Adequate spectrum of patients.
Level 2 studies	• They have only one of these biases: • Non representative population (the sample does not reflect the population where the test will be applied). • Comparison with the inadequate reference standard (gold standard), (the test will be evaluated as part of the gold standard or the test result affects the implementation of the gold standard). • Comparison is not masked. • Case-control studies.
Level 3 studies	Include two or more of the criteria described in level 2 studies

Recommendation	Evidence
A	Ia or Ib
B	II
C	III
D	IV

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Recommendations of the CPG

Definition, diagnostic criteria for diabetes mellitus type 1

Autoantibodies in the diagnosis of diabetes mellitus type 1

B	The regular measurement of C-peptide nor specific autoantibodies is not advised to confirm the diagnosis of diabetes mellitus type 1, but its use should be considered to determine the autoimmune aetiology of diabetes in doubtful cases.

Predictors of 'spontaneous remission'

√	A discussion with the patient and their carers (in case they are children) should be held on the possibility of entering into a spontaneous remission or "honeymoon" within months of the diagnosis of diabetes mellitus type 1 involving a reduction of the dose of insulin. Likewise, it is necessary to indicate that it does not imply the curing the disease and that after this period, an increase in the doses of insulin will be necessary.

Genetic study to rule out MODY diabetes

D	In those cases in which prolonged mild hyperglycaemia in a young person, without obesity and/or with a history of mild diabetes in two generations, in the absence of anti-pancreatic autoimmunity and HLA incompatible for diabetes mellitus type 1 is identified, MODY 2 diabetes should be ruled out.
D	If hyperglycaemia is more severe and progressive, it is recommended to rule out MODY 3 diabetes.
D	If the genetic test is negative for MODY 2 and MODY 3, all the other varieties of MODY diabetes should be ruled out.

Study of antibodies to rule out other autoimmune multiglandular diseases

B	Autoimmune thyroiditis and celiac disease should be ruled out in the onset of diabetes mellitus type 1 in children and adolescents.
√	This study should be done every two years for the first 10 years of the disease progression and then every five years.

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Diabetological education

Structured education aimed at relatives and/or patients with diabetes mellitus

A	All patients with diabetes mellitus type 1 should have access to a structured diabetes education program delivered by a multidisciplinary team (physicians, nurse educators, psychologists, dieticians, etc.) with specific expertise in diabetes, both at the stage of diagnosis and subsequently, based on the patient's needs.
A	In cases of repeated hypoglycaemia, a specific educational program should be offered to the patient with diabetes and their families.

Education aimed at patients and family

D	**Structured diabetes education should be provided in the following circumstances:** • At the time of diagnosis (survival education). • In the period following diagnosis (deepening and reinforcement education). • In the long term: on periodic review on self-care and educational needs, depending on whether the objectives agreed between the patient and the practitioner have been achieved or not.
D	**Structured diabetes education should be provided to the following people:** • All patients diagnosed with diabetes mellitus type 1. • Parents and carers in cases where there is dependency due to age or disability reasons. • The people who make up the school environment of the children and young patients: teachers, caregivers, etc.
D	**Professionals who must provide structured diabetes education:** • Multidisciplinary teams: the members of these teams should have competencies and skills to convey information effectively. There must be enough professionals available to organize regulated educational programs for groups. The team should include, at least, specialists in endocrinology, paediatric endocrinology and diabetes nurse educators. It is also desirable that psychologists were included in these teams for people who many need them. • At extra sanitary level the associations of people with diabetes, who provide educational programs for specific groups, play a key role (camps for children, elderly patients, informative talks, gatherings, etc.) • The educational team should be characterized not only by their capacity for empathy, but also for their flexibility and ability to communicate.

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D	**Methods and materials used to provide structured education on diabetes:** • Attendance-based training sessions using audiovisual media, food, and objects related to learning about food: games, plastic food, and descriptive flashcards to facilitate understanding. • Complementary methods: o Books and leaflets: a great effort should be made for the guidelines contained in these materials to be useful in the daily management of the disease. o Internet: due to the lack of standardized certifications about the origin, source and credibility of the online content, it is important to facilitate reliable reference website addresses and that the learner has a basic knowledge of the disease and its clinical management for proper interpretation of the information available. o Media: Newspapers, magazines, television and radio. o Cards, identification bracelets or necklaces and transport equipment for carrying and storing of insulin devices. o Data on associations of people with diabetes and other support groups. o Psychological counselling at the time of diagnosis of diabetes mellitus type 1. o Provide contact phone numbers in case of emergency. o Other information and communication technologies (telemedicine, blogs, etc.)
D	**Aspects that structured diabetes education should include:** **Level 1: Survival education.** • What is diabetes mellitus. Types of diabetes. • Symptoms of diabetes mellitus type 1. • What is insulin. Treatment with insulin. • What are glucose and blood glucose goals. • Basic dietary advice. • Acute complications (hypoglycaemia, hyperglycaemia and ketosis). • Special situations (diabetes mellitus type 1 in school, intercurrent diseases, food celebrations, events, travels, etc). • Psychological impact of the disease, identification of prior beliefs, fears and expectations. • Insulin and glucagon injection techniques. • Self-analysis of capillary blood glucose meter techniques. • Urine self-analysis technique, measurement of ketonuria, ketonemia and interpretation of results.

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D	**Level 2: Advanced Education.** • Physiopathology, epidemiology and classification of diabetes. • Types of insulin: absorption, action profiles, variability and adjustments. • Food planning: qualitative and quantitative advice on immediate and fibre intakes, with special attention to carbohydrate intake. • Control objectives, including the concept of glycated haemoglobin. • Reinforcement of knowledge on acute complications. • Problem solving and adjustment of treatment. • Micro-and macrovascular complications: prevention and monitoring. • Adjustment of insulin and feeding patterns in special situations, such as exercising, holidays and travelling. • Tobacco, alcohol and other drugs. • Adjustment to work and driving. • Sexuality, contraception, teratogenic drugs, pregnancy and breast-feeding. • Updated research on diabetes mellitus type 1. • Continuous infusion pumps. • Foot care.
D	**Methods for teaching structured education about diabetes:** Several methods have been used successfully in diabetes education. The choice of one or another depends on the characteristics of the patient, the stage of the disease and the capacity of each team or health care centre. **Individualized education.** • An intensive individualized program should be provided to newly diagnosed diabetes mellitus type 1 patients and in the case of pregnancy. **Education in groups.** • The groups should be organized according to age, socio-cultural background, etc. It is desirable that family members and friends of patients also participate in the groups. Group education should include the following aspects: o Structured training by explicative lectures. o Discussion groups, with analysis of the perceptions and experiences of all the group members. o Identification of fears and anxieties. o Assessment of needs and expectations. o Manifestation of personal experiences regarding hypoglycaemia, physical activity, stress response, etc. o Audiovisual methods. o Support educational material, which the patient can read at home.

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D	**Characteristics which structured education programs on diabetes must contain:** • Actively involve patients in all the stages of the educational program (design, implementation, evaluation), providing them with the tools to make the best decisions about their own health. • Set the benefits of learning new skills, including the daily monitoring of the treatment. • Assess the educational needs of each patient. • Assess patients' personal perceptions. • Be flexible so that the programs are adapted to the specific educational, social and cultural needs. • Have educational goals agreed with patients. The expectations of professionals and patients may differ, so it is important to agree on common objectives, which may vary over time and require a continuous review. Any proposed therapeutic target should be achievable. • Have a syllabus and a fixed schedule. • Do not create a very concentrated program and schedule frequent breaks. • Schedule chats that do not exceed 25% of the total time, and include a time for asking and answering questions. • Pay attention to the choice of words and expressions, avoiding an overly technical language. • Provide standardized and consistent information between the different team members. • Plan meetings between the professionals involved, to exchange ideas, discuss cases and review the program and methods. • Facilitate that adults participate in their own health care by giving them the possibility to make judgments and choices about their own care. • It is advisable to establish a dynamic contact process with the patient, either through visits, group discussions between patients, telephone contact or computer systems.
D	**Other considerations:** • Discuss any changes that have taken place at biomedical level (new insulin requirements, glycaemia monitoring strategies, onset of ocular complications, etc). • Evaluation: the educational program and the goals should be assessed by process and results indicators. • Provision should be done of all the information needed to enable the development of the therapeutic education program: space required, enough qualified personnel, necessary educational materials and work agendas and schedules.

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Community Support arrangements

B (Adults)/ A (Children)	Updated information should be provided to adults, children and adolescents with diabetes mellitus type 1 and to their families at the time of diagnosis, and periodically thereafter, about the existence of support groups for diabetics, both locally and nationally and the way to contact them (Appendix 11.2.).
B	The diabetes care teams should be aware that a poor psychosocial support has a negative impact on various outcomes of diabetes mellitus type 1 in children and young people, including glycaemic control and self-esteem.
A	A young person with diabetes mellitus type 1 should be offered specific support strategies such as self-analysis tutorials based on problem solving, to improve their self-esteem and glycaemic control, as well as provide them with gatherings to exchange experience and to reduce conflicts related to diabetes among family members.
√	There is no formal relationship between the health care services and the associations of diabetics. This relationship can be beneficial if the actions are confluent. It would be advisable that a physician and/or a diabetes nurse educator would participate in diabetics associations, as technical support for the activities to be developed.

Feeding

General recommendations	
√	The nutrition recommendations for a healthy lifestyle which are valid among the general population, are also appropriate for people with diabetes mellitus type 1. Currently, several insulin options are available, allowing adapting the best-suited insulin regimen to the tastes and food choices of people with diabetes mellitus type 1 within the context of a healthy diet.
√	The improvement in glycaemic control with insulin therapy is often associated to weight gain. As the potential weight gain can affect negatively to glycaemia, lipids, blood pressure and general health, it should be prevented.
√	Although the carbohydrate content of the meal determines the pre-prandial insulin dose, the total intake of proteins and fats should also be taken into consideration.
Carbohydrates	
A	The dose of insulin should be adjusted to the carbohydrate intake in people with diabetes mellitus type 1. This recommendation must be accompanied by the support of health professionals through comprehensive nutrition education.

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A	In patients with diabetes mellitus type 1, foods with table sugar can be replaced by other food containing other carbohydrate sources.
√	If food with high sugar content is eaten, its absorption should be slowed by associating their food intake with fat or fibre.
Artificial Sweeteners	
B	In patients with diabetes mellitus type 1, it is preferable to use, artificial sweeteners, which do not interfere with glycaemic increase (see Appendix 2).
B	It is recommended to prevent the abuse of drinks and foods sweetened with fructose. This recommendation should not be extended to the fructose contained in fruits and vegetables, since these are healthy foods that provide small quantities of fructose in a normal diet.
Glycaemic Index	
√	For patients with diabetes mellitus type 1 who are evaluating the planning of their diet based exclusively on the glycaemic index of foods, health professionals should inform them about the lack of conclusive evidence regarding its benefits.
Fibre	
A	The recommendations for fibre intake in patients with diabetes mellitus type 1 are similar to those of the general population, that is, a diet containing 25 to 30 g fibre/day, with special emphasis on soluble fibre intake (7 to 13 g) is recommended.
Proteins in patients with nephropathy	
A	In patients with diabetic nephropathy, a protein intake of less than 0.8 g/kg/day is recommended.
A	In patients with advanced diabetic nephropathy (chronic renal failure in stages 3-5), a possible hypoalbuminemia should be monitored by modifying the protein and caloric intake to prevent malnutrition.
Diet for the prevention and treatment of cardiovascular disease	
B	Nutritional interventions should be implemented to improve metabolic control and the lipid profile in the prevention and treatment of cardiovascular disease in patients with diabetes mellitus type 1.

Advisable feeding plan for patients with diabetes mellitus type 1

√	The feeding plan ought to be adjusted depending on the age, insulin dosage, physical activity, weight and personal situation (pregnancy, hypercholesterolemia, etc.) of the patient and his/her ability to understand.

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Exercising

Benefits of exercise in people with diabetes mellitus type 1

A	In patients with diabetes mellitus type 1, it is recommended to practice physical exercise, especially for its positive effect on the lipid profile and blood pressure.
A	In children and adolescents with diabetes mellitus type 1, the recommendation of physical exercise should be more emphasized as there is some evidence about benefits on metabolic control.

Type, intensity and duration of physical exercise in people with diabetes mellitus type 1

A	People with type 1 diabetes should be encouraged to perform regular physical exercise.
A	People with diabetes mellitus type 1 should do moderate physical exercise at least for 135 minutes a week, without being more than two consecutive days without doing any physical exercise.
√	People with diabetes mellitus type 1 and their families should be informed that they could participate in all forms of exercise, provided they know how to make the appropriate adjustments to the food intake and the insulin.
√	People with diabetes mellitus type 1 who wish to participate in less common and/or specific extreme sports should be trained on this matter, and it is recommendable that they do not do it alone.
√	People with diabetes mellitus type 1 and their families should be encouraged to monitor blood glucose levels before and after exercise to learn about the glycaemic response to different exercise conditions, and make the necessary adjustments before, during or after exercising.
√	People with diabetes mellitus type 1 and their families should be informed of the risk of late hypoglycaemia in situations of intense and/or prolonged exercise, to take the necessary precautions.
√	People with diabetes mellitus type 1 and their families should be informed that no exercise is contraindicated if there are high levels of blood glucose and/or ketones in the blood or urine.
√	Young people and adults with diabetes mellitus type 1, who want to practice intense physical exercise, should ask their doctor in advance to rule out microvascular complications that may contraindicate it.

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Glycaemic Control

Glycosylated haemoglobin

Target figures of glycosylated haemoglobin

A	It is recommended to inform people with diabetes mellitus type 1 and their families of the benefits of a long-term metabolic control with HbA_{1c} levels lower than 7% (46 mmol/mol) without disabling hypoglycaemia, therefore, all care should be designed to achieve these objectives
√	The aims of the treatment should be individualized and agreed with the patient, taking into account the different risks and benefits.
√	The aims should be less demanding in people with a history of severe hypoglycaemia, non-recognition of hypoglycaemias, patients with limited life expectancy, young children and patients with concomitant diseases.

Criteria for the standardization and reporting of glycosylated haemoglobin analytical results

D	It is recommended to issue the HbA_{1c} results in two types of units simultaneously on all laboratory reports: NGSP/DCCT % Units (with a decimal) and IFCC (mmol/mol) (without decimals).

Continuous Glucose Monitoring Systems

A	Although continuous glucose monitoring can be a tool to improve or maintain metabolic control in patients motivated and trained in intensive care, if used continuously, it is not recommended for universal use in people with diabetes mellitus type 1.

Inpatient or outpatient clinical management of patients with diabetes mellitus type 1 at diagnosis

A	At the time of diagnosis of diabetes mellitus type 1, assistance and outpatient education can be provided, depending on the clinical needs, circumstances and wishes of the patient and the patient's home proximity to the health centre, provided there are no acute complications and that an adequate health infrastructure to ensure the quality of care can be made available.

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Preparations of insulin in the treatment of patients with diabetes mellitus type 1

Fast acting analogues vs. human insulin. Adults, children and adolescents.

A	In people with diabetes mellitus type 1, the widespread use of fast acting insulin analogues cannot be recommended, since they have effectiveness similar to human insulin and there is no evidence to ensure their safety in the long term. However, as they provide greater flexibility in their administration, they do increase patient satisfaction, which may improve treatment adherence. It is therefore advisable to make an individualized assessment of the treatment.

Fast acting analogues vs. human insulin. Pregnant women.

A	In pregnant women with diabetes mellitus type 1, it is recommended to use human insulin as it has been demonstrated to be more effective and safer in comparison with analogues.

Glargine vs. retarded human insulin (NPH). Adults

B	The use of glargine versus NPH in adults can be recommended, although the lack of data on long-term safety should be noted.
√	As for the safety of glargine at present, it is recommended not to entrust regulatory action or a change in the treatment of patients using insulin glargine until the results of the evaluation of the Committee for Medicinal Products for Human Use (CHMP) of the EMEA are published.

Glargine vs. retarded human insulin (NPH). Children

B	The widespread use of glargine in children over 6 years with diabetes mellitus type 1 is not recommended, since no benefit has been demonstrated with respect to the use of NPH. It is therefore recommended to individualize the treatment based on the preferences and circumstances of each patient.
√	The use of the treatment with glargine in children with diabetes mellitus type 1 aged 6 years or less is not recommended, since there is no evidence to compare glargine *vs*. NPH in this age group and there is already a safe and effective therapy.

Glargine vs. retarded human insulin (NPH). Pregnant women

B	For the time being and while waiting for new evidence on the safety of glargine, the use of NPH as basal insulin during pregnancy is recommended. Individually, its use could be considered in cases of significant worsening of metabolic control with NPH or if hypoglycaemias take place.

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Detemir vs. retarded human insulin (NPH). Adults

A	The use of detemir versus NPH can be recommended for adults with diabetes mellitus type 1, although the lack of data on long-term safety of this insulin should be noted.

Detemir vs. retarded human insulin (NPH). Children and adolescents

A	The widespread use of detemir in children with diabetes mellitus type 1 cannot be recommended, although this therapy should be considered for children with nocturnal hypoglycaemia or threat thereof.

Glargine vs. detemir. Adults

A	Both insulin detemir and glargine have similar effects on adults with diabetes mellitus type 1 regarding metabolic control and hypoglycaemia, being insulin glargine that which can provide a higher quality of life for patients than detemir insulin, as in some cases it has to be administered twice a day.

Indications on continuous subcutaneous insulin infusion pump (CSII or insulin pump)

√	The treatment with continuous subcutaneous insulin infusion pump is not a universal option for all patients with diabetes mellitus type 1, as candidates for this treatment must have a high level of diabetes education as well as have the support of an expert medical team in this type of therapy. Therefore, to achieve greater profitability of the treatment, a proper selection of suitable patients, should take place considering metabolic control, the risk of acute complications and a higher cost.
A	The use of insulin pumps in patients with poor glycaemic control or with disabling hypoglycaemias who have exhausted other conventional treatments (multiple doses of insulin therapy) and are able to achieve good adherence, is recommended.
√	The HbA_{1c} level is not the only criterion to consider when recommending the CSII therapy in pregnancy. This treatment option should be considered, when the HbA_{1c} target below 7% is not achieved, having previously optimized the other aspects, such as integrating data from metabolic control, presence of difficult to manage hypoglycaemia, the quality of life of patients and the availability of the resource in the workplace.

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Insulin administration methods in patients with diabetes mellitus type 1

A	The use of pre-filled pens is recommended because they can encourage adherence to the treatment, but the patient will be the one who ultimately decides on the way to administer insulin.

Insulin administration techniques

Administration site conditions: injection site

B	In patients with diabetes mellitus type 1, the fast insulin injection in the abdomen is recommended, to favour rapid absorption, especially in cases of hyperglycaemic decompensation.

Rotation of injection sites

A	Rotation of insulin injection sites is recommended to prevent lipodystrophy.
A	Changing the insulin injection site is recommended, if the current zone presents lipodystrophy symptoms, inflammation, oedema or infection.
√	A rotation scheme of injection sites should be taught to patients.
√	Dividing the injection area into quadrants and change the quadrant clockwise on a weekly basis is recommended.
√	The injections in each quadrant are to be spaced at least 1 cm in order to avoid repetition of tissue trauma.
√	The healthcare professional should check in every visit that the rotation scheme is being followed and offer advice when needed.

Injection techniques (injection angle and skin fold)

√	It is important to consider the preferences of patients with diabetes mellitus type 1 when assessing the most appropriate injection technique, as this aspect can improve the adherence to the treatment.
C	The skin fold must be made by grasping the thumb and forefinger in a clamp.
B	In thin people, when the injection is carried out on limbs or abdomen with 4 mm needles, it is advised not to use skin fold injecting perpendicularly in order to prevent potential intramuscular injections. If the needles are longer, it is advisable to inject with skin fold and at a 45° angle.
B	In thin people, the needle injections of 6 mm have to be carried out properly with skin fold and at an angle of 45°.
B	Adult patients with diabetes mellitus type 1 using 8 mm needles or larger, have to raise a skin fold or apply a 45º angle of inclination to avoid intramuscular injections.

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A	In children and adolescents who use 6 mm needles, the injection has to be applied at an angle of 45° and skin fold.
B	In children and adolescents who use 4 mm needles, the injection has to be applied at an angle of 90°, without skin fold. For some really thin people, they may require skin fold.
√	If children or adolescents only have 8 mm needles available (as in the case of those using syringes), the injection is to be applied with skin fold and with an inclination of 45º.

Reusing needles

√	It is recommended to change the needle at least every 3 or 4 uses, unless the user's skill allows using it on more occasions without any pain.

Injection through the clothes

A	Although not considered a best practice because it does not allow the correct elevation of the skin fold nor to visualize the injection site, the injection of insulin through a layer of fabric layer is not ruled out in specific situations.

Needle Size

A	In adults with diabetes mellitus type 1, 4, 5 and 6 mm needles can be used even by obese people and generally require no skin fold, in particular the 4mm needles.
B	There is no medical reason to recommend needles larger than 8 mm. The initial therapy must begin with needles that are as short as possible.
A	Children and adolescents with diabetes mellitus type 1 have to use 4, 5 or 6 mm needles. Thin people or who are injected in a limb, must increase the skin fold, especially when using needles larger than 4 mm.
B	There is no medical reason to recommend larger than 6 mm needles in children and adolescents with diabetes mellitus type 1.
A	Children with normal weight using 8 mm needles should inject in the skin fold and at a 45° angle.

Indications of the treatment with metformin added to insulin in adolescents with diabetes mellitus type 1

√	The widespread use of metformin associated with the insulin treatment in adolescent patients cannot be recommended, although its use may improve glycaemic control in some patients.

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Pancreas and islet cell transplants

B	Simultaneous pancreas and kidney transplantation should be offered to patients with diabetes mellitus type 1, who are young (under 45), well informed and motivated, with end-stage renal disease (ESRD) and without cardiovascular risk factors.
B	The only criteria for single pancreatic transplantation are: • Persistent failure in the insulin treatment on glycaemic control and to prevent further complications. • Emotional and clinical incapacitating problems and treatment with insulin.
C	At present, islet transplantation is only recommended in the context of controlled trials.

Management of diabetes mellitus type 1 in special situations

Insulin treatment guidelines during hospitalization of patients with diabetes mellitus type 1

Surgical Patient

A	The system of continuous intravenous insulin infusion is the ideal method to achieve a good metabolic control and avoid complications such as metabolic acidosis or hypoglycaemia in patients with diabetes mellitus type 1 who are to undergo major and minor surgery.
√	Hospitals should ensure the existence of a suitable protocol for surgery in patients with insulin-dependent diabetes. This protocol is to ensure the maintenance of normoglycaemia levels through frequent glucose measurements, which allow the adjustment of IV insulin, without risk of acute complications.

Critical Patient

A	In the case of critical patients with persistent hyperglycaemia, the treatment should start with a threshold which is not more than 180 mg/dl (10 mmol/l). Once the treatment has started, glycaemic goals must be set in a range between 140-180 mg/dl (7.8 to 10 mmol/l) for most of the critically ill patients.
√	It is necessary to establish a safe and effective protocol in order to achieve the adequate glycaemic range without an increase in severe hypoglycaemic episodes.

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Stable patient

√	All patients with diabetes admitted to a healthcare centre must have this diagnosis clearly identified in their medical history.
√	All patients with diabetes should have blood glucose monitoring and this information should be available to the healthcare team.
B	Monitoring of any non-diabetic patient who is administered a treatment with a high risk of hyperglycaemia, including high-doses of glucocorticoids, initiation of enteral or parenteral nutrition or other measures such as octreotide or immunosuppressive, must be initiated.
√	If hyperglycaemia is identified and persistent, treatment is needed. These patients should be treated with the same glycaemic targets for patients with known diabetes.
√	A hypoglycaemia treatment plan should be set out for each patient. Episodes of hypoglycaemia in the hospital must be registered.
√	All patients admitted to hospital should have a determination of HbA_{1C} if there is no data available of the 2-3 months prior to admission.
√	Patients with hyperglycaemia in the hospital without a previous diagnosis of diabetes should have a protocol for diagnosis and monitoring of care at discharge.

Preventive and treatment measures in the case of outpatient acute intercurrent diseases in patients with diabetes mellitus type 1

D	People with diabetes mellitus type 1 and/or their families or caregivers should be informed that intercurrent diseases could cause hyperglycaemia. In addition, these can lead to ketosis and hypoglycaemia, the latter being more frequent in children under 6 years.
D	All people with diabetes mellitus type 1 and/or their families or caregivers must be educated about the management in case of intercurrent disease and should have at hand fast acting insulin, glucose test strips, blood glucose meters, lancets, strips and meters for the measurement of ketones in the blood or urine, refreshments/fruit juice/lemonade or other drinks alike, know how to use glucagon, a thermometer, paracetamol or ibuprofen, emergency guides, diabetes manuals and a doctor's or hospital's contact telephone number.
D	The administration of insulin must never be omitted, even if the patient cannot eat.
D	Blood glucose and ketones in urine (ketonuria) or blood (ketonemia) must be monitored frequently.
D	Any illness must be treated immediately.
D	Additional oral fluid intake should be encouraged, especially if blood glucose is high or there are ketones.

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D	Additional boluses of fast acting insulin should be provided in an amount equal to 10-20% or more of the total daily dose, every 2-4 hours when the blood glucose is high or there are ketones.
D	Patients/caregivers must seek immediate medical help if, after extra insulin boluses, blood glucose stays high, ketones persist, the patient suffers from nausea or vomiting, or abdominal pain appears.
B	In young children, small doses of subcutaneous glucagon may be used to prevent or treat hypoglycaemia. For severe hypoglycaemia, intramuscular glucagon is recommended. Treatment with intravenous glucose should be performed within the hospital.

Psychological disorders in patients with diabetes mellitus type 1

Affective and anxiety disorders

B	Professionals involved in the care of patients with diabetes mellitus type 1 should be alert to the possible emergence of depressive and/or anxious symptoms, especially when the person states having problems with self-care.
√	Health professionals should have the necessary skills for the detection and management of non-severe forms of psychological disorders and be familiar with counselling techniques as well as the use of psychotropic drugs.
√	Moderate to severe cases should be referred to mental health specialists.

Prevalence of eating disorders

C	The professional team members involved in the care of patients with diabetes mellitus type 1 should be alert to the possible occurrence of cases of bulimia nervosa, anorexia nervosa and handling of insulin, especially in patients who express concern about their weight or body image, have a low body mass index or poor glycaemic control.
D	Given the risk of increased morbidity and mortality associated with poor metabolic control in people with eating disorders, in case of suspicion it is recommended to carry out the relevant diagnostic tasks and contact the department of psychiatry in order to carry out timely therapy.
B	Information on healthy lifestyles and particularly on diet for patients with diabetes mellitus type 1, especially during the teenage years, should be provided by qualified health professionals.

Decompensation risks of diabetes mellitus type 1 during adolescence

Adherence to treatment

C	Adherence to treatment is a key factor when managing diabetes, therefore, it is important to work on this issue with the adolescent patient together with his family, and analyse the barriers to an adequate adherence (anxiety, depression, eating disorders and behavioural problems).

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C	The professionals in charge of children and adolescents with diabetes mellitus type 1 should be aware that depressive and/or anxiety disorders might develop, particularly when there are difficulties in controlling the disease or if the disease is long lasting.
√	In children and adolescents with persistent poor glycaemic control, the level of anxiety and depression should be assessed.
√	Children and adolescents suspected to suffer from depressive or anxiety disorders should be referred to mental health professionals.
C	Given the high prevalence of eating disorders in adolescents with diabetes, especially among women, it is advised to be alert regarding the presence of symptoms that may indicate an eating disorder or handling insulin disorder. In case of suspicion, the department of psychiatry should be contacted and supported for diagnosis and setting of the appropriate therapy.
√	It is recommended to address the intake of alcohol, tobacco and other drugs with adolescents with diabetes mellitus type 1 to avoid its consumption and provide adequate strategies to prevent episodes of hypoglycaemia.

Pregnancy planning

B	As all patients diagnosed with diabetes mellitus type 1, adolescents and women of childbearing age should participate in diabetes education programs in order to facilitate the control of their disease and promote self-care. These programs should include specific notions on the importance of control before conception and general recommendations for pregnancy (vitamin supplements, suppression of teratogenic drugs, etc.). It is convenient to remind of these during consultation visits to ensure a pregnancy in optimal conditions.
B	In women planning to become pregnant, it is considered relevant to carry out a preconceptional consultation to establish control objectives, set out the appropriate treatment (folic acid, iodine, etc.), review the possible complications and give "green light" for pregnancy.

Complications of diabetes mellitus type 1 during pregnancy

B	It is advisable to plan the pregnancy in women with diabetes mellitus type 1 until an adequate glycaemic control is achieved and carry out the evaluation of possible retinopathy and nephropathy before and during pregnancy.
D	It is recommended to inform the couple's mutual impact between diabetes mellitus type 1 and pregnancy, making explicit reference to the possible complications that can arise and the methods to prevent them.

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Metabolic control during pregnancy

B	In pregnant women with diabetes mellitus type 1 individual targets have to be set out regarding self-monitoring of blood glucose, taking into account the risk of hypoglycaemia. They must try to maintain HbA_{1c} levels below 6.2% if these can be achieved safely.
B	These women should be informed that any decrease in the HbA_{1c} levels below 6.2% reduces the risk of congenital malformations and they should also be recommended not to exceed 6.9% levels.
B	Pregnancy should be discouraged for women with diabetes mellitus type 1 whose HbA_{1c} levels are above 8% temporarily until an optimal metabolic control is achieved.
D	When is pregnancy discouraged: • HbA_{1c} levels over 8%. • Severe nephropathy (plasma creatinine > 2 mg/dl or proteinuria > 3 g/24 hours and/or difficult to control hypertension). • Ischemic heart disease. • Severe proliferative retinopathy, with poor visual prognosis. • Severe autonomic neuropathy.
√	It is necessary to provide information to the future pregnant woman and her partner on the need, first, to assess the situation of maternal diabetes to detect possible contraindications of gestation and, secondly, to express the convenience of active participation of both in order to achieve the preconception objectives.
B	HbA_{1c} monthly or bi-monthly measures should be provided to women planning pregnancy.
B	Women who are planning to get pregnant and require intensification of insulin therapy should be informed of the need to increase the frequency to self-analyse blood glucose levels including controls in fasting both in pre- and post-prandrial situations. If necessary, treatment with a continuous insulin infusion pump will be offered.
√	Test strips for self-assessment of ketonuria or ketonemia if they are suffering hyperglycaemia or feeling bad, should be provided.
√	The care offered to the patient with diabetes mellitus type 1 before planning pregnancy, its monitoring and delivery should take place in a hospital provided with staff specialised in these issues (nurse educator, endocrinologist, obstetrician, and neonatologist).
√	During pregnancy, the frequency of visits, both to the endocrinologist and obstetrician, should be at least on a monthly basis.
√	As a monthly monitoring of HbA_{1c} levels is recommended, it would be advisable to perform it on a capillary sample and not a venous one.
√	An increase in the use of test strips for blood glucose, ketonuria and/or ketonemia should be considered.

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√	Glycaemic control optimization protocols should exist.
√	A treatment protocol in childbirth with general guidelines on the needs of carbohydrate and insulin intake, which must be known to the staff involved, as well as a protocol of newborn care is recommended.

Contraception and diabetes mellitus type 1

D	In women with diabetes mellitus type 1, it is recommended to use the copper IUD as the safest contraception method. The use of IUD that releases levonorgestrel should not be ruled out, since it has not been observed to affect the metabolism of glucose.

Clinical management of diabetes mellitus type 1 in patients with special needs

Immigrant population. General recommendations

√	If the patient with diabetes mellitus type 1 has difficulty understanding the language, the use of machine translation systems (telephone or audiovisual methods of open and closed questions) or direct translation during the consultation visit are recommended.
√	It is also advisable to use simple graphics to facilitate understanding of the disease and the guidelines to be followed.

Recommendations for Muslim patients during Ramadan

Before Ramadan

√	Inform the health care team about the concept of Ramadan and the risks posed by fasting.
√	Plan the process in time for the celebration of Ramadan.
√	Identify Muslim patients with diabetes mellitus type 1.
√	Carry out a clinical interview with these patients to know their desire to fulfil the precept of Ramadan.
√	Inform patients about the possibility of not celebrating Ramadan due to having a chronic disease and the risks involved.

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D	Evaluate the existence of major criteria to strongly discourage compliance of Ramadan: • Diabetes with poor metabolic control. • Chronic complications of advanced diabetes: renal failure, ischemic heart disease with unstable angor, advanced peripheral macroangiopathy. • Frequent hypoglycaemia, severe or without adrenergic clinic. • Diabetic ketoacidosis in the months prior to Ramadan. • Gestation. • Physical activity during the day. • Elderly with dependence on others.
D	In the event that these criteria are not met and the patient wishes to fulfil the precepts, making the corresponding therapeutic changes before and during Ramadan regarding diet and exercise is deemed appropriate: • Optimize glycaemic and metabolic control 1-2 months before. • Specific diabetes education (symptoms of hyper and hypoglycaemia, meal and physical activity planning, drug administration and attitude in case complications arise).

During Ramadan

√	Individualized care plan.
√	Frequent blood glucose determinations.
D	Avoid foods, which are rich in rapid absorption carbohydrates and fats.
D	Eat more food s composed of complex carbohydrates.
D	Fruits, vegetables and yogurt can be included in the diet.
D	Practicing suhoor immediately before sunrise and not in the early morning.
D	Drink unsweetened fluids to quench thirst.
D	Reduce fried foods.
D	Carry out regular physical activity, avoiding excessive exercise
D	Break fasting if blood glucose is less than 60 or higher than 300 mg/dl.
D	Ensure adequate fluid intake.
A	Adapt drug treatment with insulin: as a general rule, a basal bolus therapy which eliminates the bolus of meals not taken, is recommended.

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Patients with visual impairment

√	Provide educational materials in audio, Braille or large print edited format.
√	Facilitate attendance to educational sessions performing them in locations accessible by public transport.
√	Advertise informative talks with brief advertisements in audio format.
√	If slides are used to transmit key information at educational chats, these should also contain a simple verbal description of the contents of each slide.
√	Provide information on self-control tools and techniques for people with visual impairment, including: • "Talking blood glucose monitoring kits" that guide the patient through a voice message on the steps for testing and communicate the results orally. • Glucometers with a large screen and easily recognizable numbers. • Glucometers with backlit display. • Techniques for tactile inspection of the feet.
√	Insulin injectors: • Provide patients with injectors, which contain different touch buttons for fast or slow insulin. • Insulin injectors emit some sort of sound when going from dose to dose in order to facilitate the patient's autonomy, and thus the dose can be calculated without seeing the wheel.

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Acute complications

Hypoglycaemia

Symptoms of suspicion

<table>
<tr><td rowspan="3">D</td><td colspan="4">Hypoglycaemia will be suspected in the presence of one or more of the following symptoms:

Symptoms of hypoglycaemia</td></tr>
<tr><td colspan="2">Autonomic/adrenergic/neurogenic</td><td colspan="2">Neurological/neuroglycopenic</td></tr>
<tr><td>• Sweating
• Paleness
• Trembling
• Tachycardia</td><td>• Anxiety
• Hunger
• Nausea
• Weakness
• Tingle</td><td>Psychiatric symptoms:
• Confusion
• Altered behaviour
• Aggressiveness
• Slurred speech
• Lapses of consciousness</td><td>Neurological symptoms:
• Dizziness and weakness
• Headache
• Altered, double or blurred vision
• Aphasia
• Dysarthria
• Motor deficit, unsteady gait, lack of coordination
• Paresthesias
• Seizures</td></tr>
<tr><td colspan="4">* Adapted from hypoglycaemia for the Reversal Treatment of Mild, Moderate and Severe. Holders of Interdisciplinary Clinical Manual CC15-25.</td></tr>
<tr><td>√</td><td colspan="4">It is recommended that people with diabetes type 1, especially children and young people, carry identification (e.g. bracelet) to facilitate the identification of acute complications such as hypoglycaemia and acting at an early stage.</td></tr>
</table>

Criteria for evaluating the severity

√	Young children with diabetes mellitus type 1 always require adult assistance to solve hypoglycaemia. The severity of hypoglycaemia is only established depending on the symptoms.

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Performance measures in case of hypoglycaemia

Mild or moderate hypoglycaemia

A	• Mild or moderate hypoglycaemia needs to be treated by oral ingestion of 10-20 g of carbohydrates, preferably in the form of tablets or solutions of glucose, sugar or sucrose. These are preferred to fruit juices or glucose gels. Examples of options containing 15 g of carbohydrates: • 15 g glucose tablets. • 15 g of sugar dissolved in water (3 teaspoons of sugar or 3 sugar cubes). • 175 ml (3/4 cup) of juice or sugary drink. • 15 g (1 1/2 teaspoon) of honey.
√	Following the oral administration of carbohydrates, patients or family/carers must wait 10-20 minutes, measure blood glucose levels again and repeat the intake of carbohydrates if the blood sugar level is less than 72 mg/dl (4.0 mmol/l).

Severe Hypoglycaemia

√	Severe hypoglycaemia in a conscious person must be treated by oral ingestion of 10-20 g of carbohydrates, preferably in the form of glucose tablets or equivalent. One must wait 15 minutes, measure blood glucose levels again and repeat the intake of another 15 g of carbohydrates if the blood sugar level is below 72 mg/dl (4.0 mmol/l).
√	Severe hypoglycaemia in an unconscious person over 5 years old, if detected at home, should be treated with an injection of 1 mg of subcutaneous or intramuscular glucagon. If it is an under 5-year-old child, an injection of 1/2 mg of subcutaneous glucagon should be administered. When intravenous administration is possible, 10 g to 25 g of glucose (20 cc to 50 cc of dextrose at 50%) for 1 to 3 minutes should be given.
√	Caregivers or support people for patients at risk of severe hypoglycaemia should be trained in the administration of glucagon injections.
√	To prevent hypoglycaemia, once the episode has passed, the person must eat the normal food, which corresponds to that time of day. If the following meal is more than an hour later, a snack that contains 15 g of carbohydrate and a protein source is to be taken.

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Chronic complications

Cardiovascular risk in patients with diabetes mellitus type 1

√	Individual assessment of cardiovascular risk of patients with diabetes mellitus type 1 based on the presence or absence of risk factors such as age, sex, duration of disease, glycosylated haemoglobin levels, blood pressure, tobacco consumption or LDL cholesterol levels is recommended.
B	Clinical prediction rules for arterial risk are not recommended because they may underestimate cardiovascular risk in adults with type 1 diabetes.
√	The evaluation of arterial risk factors should be made at least annually and include: • Age • Time evolution of the disease • Family history of vascular disease • Smoking habits • Albumin excretion ratio • Blood glucose monitoring • Blood pressure • Complete lipid profile (including HDL-cholesterol, LDL-cholesterol and triglycerides) • Abdominal adiposity.
√	Adults with a rate of elevated albumin excretion (microalbuminuria) or two or more features of the metabolic syndrome should be managed as high-risk category.
√	Adults with diabetes mellitus type 1 who are not in the high-risk category but have some arterial risk factor (are over 35 years, a family history of premature coronary disease, high-risk ethnicity, or lipemia or blood pressure severe alterations) should be managed as a moderately high risk group.

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Diabetic retinopathy

Preventive medical treatment of diabetic retinopathy

A	It is important to inform people with diabetes mellitus type 1 and their families that the control of long-term blood glucose levels with HbA_{1c} equal or lower to 7% decreases the incidence and progression of diabetic retinopathy.

Screening techniques for diabetic retinopathy

B	Digital photography of the retina obtained by a non-mydriatic camera should be implemented in retinopathy screening programs for adults and children with diabetes mellitus type 1.
B	Should there not be a camera, screening will be carried out by ophthalmoscopy (with or without mydriasis), which will be evaluated by an ophthalmologist.
√	The use of digital photography of the retina obtained by a non-mydriatic camera electronically facilitates the performance of screening for both the patient and the health worker.
√	Although digital photographs of the retina can detect most clinically significant alterations, digital photographs of the retina should not replace the full initial examination of the retina with mydriasis.

Start time and frequency of screening for diabetic retinopathy

B	In people with diabetes mellitus type 1, it is recommended to start screening for retinopathy from puberty, or after they turn 5 from the diagnosis of diabetes.
B	If retinopathy is detected, it is considered advisable to carry out an assessment of the evolution of the retinopathy once a year.
B	In the case of not detecting the retinopathy during the basal examination of the retina, screening is recommended every two or three years.

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Diabetic nephropathy

Criteria for referral of patients with diabetic nephropathy to nephrology specialized care units

√	It is recommended to refer patients with diabetes mellitus type 1 with at least one of the following criteria to units specialized in nephrology: 1. With glomerular filtration rate (GFR)> 45 ml/min/1,73m^2 of body surface area: 1.1. Albuminuria increased or albuminuria/creatinine ratio > 300 mg/g. 1.2. Uncorrected anaemia (Hb <11g/dl) despite iron treatment. 1.3. HTA refractory to treatment (3 drugs). 2. With 30-45ml/min/ GFR, 1,73 m^2 body surface area: 2.1. Individual assessment, taking into account the age and rate of progression of renal failure, only if it meets the above criteria of proteinuria, anaemia and refractory hypertension. 3. With glomerular filtration rate <30 ml/min/1,73 m^2 of body surface area: 3.1. In all cases. **Preferred referral criteria** 4. Fast increase in serum creatinine: > 1 mg/dl in a month. 5. Hematuria associated to proteinuria once urologic diseases through renal ultrasound have been discarded. 6. Severe hyperkalaemia (> 7 mEq/l).

Treatment of patients with diabetes mellitus type 1 and microalbuminuria

A	The pharmacological treatment of choice in hypertensive and normotensive patients with microalbuminuria is an angiotensin converting enzyme (captopril, lisinopril, ramipril, enalapril and perindopril) inhibitor with a progressive increase in the therapeutic dose to achieve the desired response.
A	During pregnancy and in the case of having bilateral stenosis of the renal artery an angiotensin converting enzyme inhibitor drug treatment is contraindicated.
√	During the treatment with an angiotensin converting enzyme inhibitor, the levels of creatinine and potassium should be monitored.
√	In case of contraindications or intolerance to angiotensin converting enzyme inhibitors, an angiotensin II receptor antagonist treatment is recommended.
√	The aims of the treatment are to control blood pressure and reduce urinary albumin excretion. In normotensive patients, these will be given the maximum tolerated dose.

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Method and frequency of screening for diabetic nephropathy

B	Measuring the albumin/creatinine ratio in a sample of first morning urine is recommended as a method for the detection and monitoring of diabetic nephropathy.
D	5 years after diabetes mellitus type 1 has been diagnosed, an annual screening nephropathy is recommended.

Diabetic foot

Methods for screening

<table>
<tr><td>A</td><td colspan="3">It is recommended that patients with diabetes mellitus type 1 are included in structured programs of screening, risk stratification, and prevention and treatment of the foot at risk.</td></tr>
<tr><td>√</td><td colspan="3">The diabetic foot screening in people with diabetes mellitus type 1 should start after 5 years of disease progression from puberty.</td></tr>
<tr><td>D</td><td colspan="3">It should include a diabetes education module on foot care in line with the risk assessment.</td></tr>
<tr><td>B</td><td colspan="3">The diabetic foot screening should include a thorough annual examination of the feet to identify risk factors, predict ulcers and amputations, inspect the foot and soft tissues, assess footwear, carry out a musculoskeletal exploration, assess peripheral arterial disease symptoms by evaluation of foot pulses, supplemented by the determination of ankle-arm index, in some cases, and loss of sensitivity tests assessed using monofilament or alternatively tuning fork.</td></tr>
<tr><td rowspan="5">D</td><td colspan="3">Three monitoring levels are recommended depending on the patient’s risk factors:</td></tr>
<tr><td>Risk (Classification)</td><td>Features</td><td>Inspection Frequency</td></tr>
<tr><td>Low risk</td><td>Preserved sensitivity, palpable pulses</td><td>Annual</td></tr>
<tr><td>Increased risk</td><td>Neuropathy, absence of pulses and other risk factors</td><td>Every 3-6 months (monitoring visits)</td></tr>
<tr><td>High risk</td><td>Neuropathy or absent pulses together to deformity or skin changes or previous ulcer</td><td>Every 1-3 months</td></tr>
<tr><td></td><td>Ulcerated foot</td><td></td><td>Individualized treatment, possible referral</td></tr>
<tr><td>√</td><td colspan="3">Since diabetes is the most common cause of non-traumatic amputation of lower extremities, it is desirable to standardize the process of education and prevention, diagnosis and treatment of diabetic foot, in a multidisciplinary way with the aim of reducing the number of amputations and comorbidity involved.</td></tr>
</table>

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Erectile dysfunction in people with diabetes mellitus type 1

Treatment of erectile dysfunction

A	The treatment with phosphodiesterase inhibitors is recommended as first option for erectile dysfunction in people with type 1 diabetes.
A	In case of contraindications or poor tolerance, intracavernosal alprostadil is proposed as a second option.
B	As a third option of treatment, mechanical methods such as vacuum devices and inflatable prosthesis (in this order) may be considered.
A	In case of failure of the above methods, the treatment with sublingual apomorphine can be considered.
A	It is advisable to associate psychotherapy, in all cases enabling the improvement of results.

Painful Diabetic Neuropathy

Treatment of painful diabetic neuropathy

√	As a first line, the treatment with analgesics such as acetaminophen or ibuprofen or paracetamol or aspirin is recommended for mild cases, as well as local treatments, like the arch to isolate the foot.
A	When these measures fail, the use of tricyclic drugs (low to medium dose) is recommended, taken just before the time of day when the symptoms are more annoying. The patient with diabetes is to be informed about the type of therapy trial, as it is not always successful.
A	When the response to treatment is insufficient, drugs may be associated with different action mechanisms, such as antiepileptics (gabapentin or pregabalin), opioids (such as morphine, oxycodone, or tramadol) or duloxetine, monitoring the response and the adverse effects.

Organizing the medical consultation

Transition of patients with diabetes mellitus type 1 from paediatric services to adult services

C	It is recommended to carry out at least one transition consultation involving the paediatrician monitoring the treatment during childhood and the endocrinologist who will assist the patient with diabetes mellitus type 1 in the future, so that the treatment is agreed and set together with the adolescent.

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Initial study of people newly diagnosed with diabetes mellitus type 1

√	**Medical History**	• Domestic, social, educational, cultural, recreational and lifestyle aspects. • Emotional state. • Rating of family, social support.
√		• Prior diabetic history.
√		• Vascular risk factors. • Smoking.
√		• Family history of diabetes and arterial or autoimmune disease.
√	**General exploration**	Height, weight, BMI, TA.
A	**Further tests**	$HbA_{1c.}$
B		Full examination of the retina with mydriasis.
B		Albumin excretion (timed microalbuminuria or albumin/creatinine ratio).
√		Lipid profile once the glycaemic profile is stabilized.
B		Anti TPO, FT4 and TSH antibodies.
B		Transglutaminase and IgA antibodies to assess celiac disease.
D		Regular measuring of C peptide or specific autoantibodies or to confirm the diagnosis of DM1 is not advised, but its use should be considered to determine the aetiology of DM in doubtful cases.
B		Discarding autoimmune thyroid disease and celiac disease in the early onset of diabetes mellitus type 1 in children and adolescents is discarded.
D	**Genetic Study**	In cases in which mild sustained hyperglycaemia is identified in a young person, without obesity and/or mild diabetes history in two generations, in the absence of anti-pancreatic autoimmunity and HLA not compatible with DM1, MODY 2 diabetes must be ruled out.
D		If hyperglycaemia is more severe and progressive, it is recommended to rule out MODY 3 diabetes.

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D		If genetic test is negative for MODY 2 and MODY 3 diabetes, then the rest of MODY varieties should be ruled out too.
B (Adults)/ A (Children	**Educational and support material**	Updated information should be provided to the adults, children and adolescents with diabetes mellitus type 1 together with their families at the time of diagnosis, and periodically thereafter, on the existence of diabetic support groups, both locally and nationally and how to contact them. (Appendix 11.2)

√	It is recommended to design an individualized care plan, which should be reviewed annually to adjust it to the desires, personal circumstances and medical findings of each patient. The specific details of this individual plan must be registered in writing and include aspects related to: • Diabetes education, including dietary advice. • Insulin therapy. • Self-assessment and management of blood glucose (insulin dose modification, mild and severe hypoglycaemia and awareness of it and hyperglycaemia ketosis). • Assessment and management of late complications, including foot exam. • Assessment and management of arterial risk factors. • Psychosocial problems and dental disease. • Communication frequency with the professional team. • Next consultations scheduled, including the next annual review.

Strength of recommendation	**Periodic reviews**	**Children and young people**	**Adults**
D	**HbA_{1c}**	From 3 to 4 times a year or more regularly if there is a concern about poor glycaemic control.	
C	**Inspection of injection sites**	In each visit.	
√	**Measurement of height, weight and calculation of BMI**	In each visit in a private room.	The same with the exception of size in the case of adults.

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Monitoring and control consultations: tests and periodicity

Assessment of arterial risk factors

Strength of recommendation		Children, adolescents and young people	Adults
√	**Blood pressure**	Annually.	In each visit.
√	**Complete lipid profile**	Annually after the age of 12.	Annually
√	**Abdominal circumference**	-	Annually
√	**Smoking**	Annually from adolescence.	Annually
√	**Family history of arterial disease**	-	Annually
D	**Eye exam**	As the general population.	Visual acuity every 2-3 years.
D	**Dental exam**	As the general population.	
√	**Nephropathy**	An annual measuring of the albumin/creatinine ratio in a sample first thing in the morning 5 years after the evolution of the disease is recommended.	
B	**Arterial risk**	The use of arterial risk tables, equations or calculation programs is not recommended because arterial risk calculation programs may underestimate the risk in adults with diabetes mellitus type 1. Individual assessment is recommended depending on the presence or absence of risk factors.	
B	**Retinopathy**	If there is no retinopathy or it is mild, it is recommended to carry out screening every 2-3 years after puberty or after 5 years of evolution. If there is retinopathy, assessing the evolution once a year is recommended.	
√	**Rating autoimmune thyroid disease and celiac disease**	Every two years for the first 10 years of the disease progression and then every five years.	

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1. Introduction

Diabetes mellitus (DM) comprises a group of metabolic diseases characterized by secondary hyperglycaemia to an absolute or relative defect in insulin secretion, which is accompanied, to a greater or lesser extent, by alterations in the metabolism of lipids and proteins. The chronic hyperglycaemia is associated with long-term alterations in various organs like eyes, kidneys, the nervous system and the circulatory system.

Diabetes mellitus type 1 (DM1) corresponds to the entity formerly termed insulin dependent or juvenile diabetes mellitus, in which the destruction of the pancreatic β cells leads to an absolute insulin deficiency.

The prevalence of DM in Spain is around 13.8% in people over 18 years. (95% CI 12.8, 14.7%). For DM1 the prevalence is between 0.2 and 0.3%, representing between 10 to 15% of all people with diabetes. The annual incidence per 100,000 inhabitants ranges from 9.5 to 16 in people under 14 years, and 9.9 for those between 15 and 29 years. The incidence is low between 0 and 5 years, and the highest is in people aged 13-14 years. In the age group ranging from 0 to 14 years there is no difference in incidence regarding genre, while between 15 and 30 years there is a clear predominance of males[4]. Although DM1 normally represents only a minority of the total number of diabetes in the population, it is the predominant form of the disease in younger age groups in most developed countries[5].

The Spanish Interregional Council of the National Health Service (NHS) decided on June 16, 2004 to address a joint strategy on Diabetes for the entire NHS, and thus created "Estrategia en Diabetes del Sistema Nacional de Salud" (Diabetes Strategy of the National Health System), submitted and approved by the Interregional Council of the NHS on 11 October 2006[5].

In addition, the Quality Plan 2010 for the Spanish National Health System (NHS) aims to address the challenges facing the NHS, increasing the coherence of the system, ensuring equity in health care to all citizens, regardless of where they live and ensuring that this care is of the highest quality. Its aims include the promotion of the development and use of CPGs related to Health strategies, reinforcing and extending the "Guía-Salud" Project[2].

The Department of Health of the Basque Government, an entity which belongs to the Agency for Health Technology Assessment of the Basque Country-Osteba, was commissioned to develop a CPG that would address the clinical management of diabetes mellitus type 1 in adults and children based on the latest evidence from scientific research. This document has been produced within a collaboration framework provided in the Quality Plan for the National Health System, under the collaboration agreement signed by the Instituto de Salud Carlos III, an autonomous body of the Ministry of Health and Social Policy and the Agency for Health Technology Assessment of the Basque Government-OSTEBA.

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2. Scope and Aims

The CPGs are a set of instructions, guidelines, statements or recommendations systematically developed which aims to help health professionals and patients make decisions about appropriate health care modality for specific clinical circumstances.

Although this term has spread to different products, good quality CPGs are documents that pose specific questions and organize the best available scientific evidence so as to be used in clinical decision making, in the form of flexible recommendations.

This guide has been developed according to the following principles:

- Be useful and usable for all professionals.
- Take into account the perspectives of individuals with DM1 and their caregivers.
- Indicate areas of uncertainty or controversy needing further investigation.

2.1. Scope

This guide focuses on key issues affecting the care of people (adults, children and pregnant women) with DM1 and addresses issues related to diagnosis, prognosis, screening, treatment, acute and chronic complications and the clinical monitoring of the disease.

2.2. Aims of the CPG

Main aim: to provide guidance on the various alternatives for the care provided to people with DM1, establishing the most relevant and up-to-date evidence-based recommendations. Under no circumstances does it replace the clinical judgment of professionals.

Specific aims:

- Develop standards that can maximize the quality, efficiency and equity of care for people with DM1.
- Help patients make informed decisions to facilitate self-care.

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2.3. Approach

This CPG is focused on supporting health care in children, adolescents and adults with DM1, assisted in primary and specialty care, both in the intra-and outpatient means within the Spanish National Health System.

2.4. People who should read this CPG

This CPG is aimed at specialist care professionals within the Spanish National Health System involved in the treatment and care of patients with DM1, such as specialists in endocrinology, paediatric endocrinologists, specialized care staff and specialists treating the complications of DM1.

In addition, this guide is also aimed at patients, families and educational groups or scientific societies, as well as healthcare managers.

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3. Methodology of the guide

This CPG has been created following the Methodological Manual "Elaboración de Guías de Práctica Clínica en el Sistema Nacional de Salud" (Development of Clinical Practice Guidelines in the NHS)[2] and the document "Descripción de la metodología de elaboración-adaptación-actualización empleada en la Práctica Clínica sobre Asma en la CAPV" (Description of the development – adaptation – update methodology used in the Clinical Practice on Asthma within the Basque Autonomous Community)[6] which can be consulted on the website of the Library of CPG of the NHS, GuíaSalud.

During the development process of this CPG, a mixed methodology has been applied, using a strategy of renovation and adaptation to the questions that are answered in the CPG "Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults 2004 " from the *National Institute for Health and Clinical Excellence* (NICE) published in 2004 (CPG NICE 2004)[7] previously selected by the AGREE instrument for its highest quality. To address those questions that are not answered in the aforementioned guide the "de novo"[6;8] development process has been followed.

For questions, regarding pregnant women with DM1, the upgrading and adaptation process has been made from the CPG 'Diabetes in pregnancy management of diabetes and its complications from preconception to the postnatal period. National Collaborating Centre for Women's and Children's Health Commissioned by the National Institute for Health and Clinical Excellence 2008" by NICE (NICE CPG 2008)[9].

For questions 11.1 and 11.4, the upgrading process has been carried out from the diabetes CPG on diabetes type 2[509] of the Spanish NHS.

The steps that taken during the preparation of the CPG were as follows:

3.1. Constitution of the guide development team

DM1 specialty care professionals (endocrinologists, paediatric endocrinologists and diabetes nurse educators) with proven expertise, experienced professionals in the development of CPG and evidence-based medicine, as well as experts on scientific literature and systematic revisions have collaborated in the development of this CPG. Likewise, people with DM1 and carers have participated and contributed in various stages of the development process (defining the scope and focus of the CPG, formulating research questions, developing and reviewing the recommendations).

All the team members groups have provided a "declaration of interests" which is included in Appendix 14 of this guide.

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3.2. Systematic review

Systematic reviews (SR) have been made for the development of this CPG in the following phases:

3.2.1. Formulation of clinical questions

It has been carried out using the PICO format: P (patients), I (interventions), C (comparisons) and O (outcomes or results). For proper formulation, a training workshop was provided previously for people involved in this process (doctors and nurses in DM1, experts in systematic reviews, people with DM1 and caregivers).

3.2.2. Bibliographic Search

There has been a search for CPG to identify the latest and of highest quality and clinical studies to identify the highest quality evidence available.

CPG Search:

Search period from 1998 to March 2011. Languages: Spanish, English, French and German. The following were consulted:

Agencies databases from collector bodies:

- Tripdatabase (European, American and English guides).
- NeLH *(National Electronic Library of Health, United Kingdom)*.
- Canadian Medical Association.
- Guía Salud (Clinical Practice Guidelines in the NHS).

Databases from developing bodies:

- NICE *(National Institute for Health and Clinical Excellence in the UK)*.
- SIGN *(Scottish Intercollegiate Guidelines Network)*.
- FISTERRA Atención Primaria en la Red
- NGC *(National Guideline Clearinghouse, U.S.)*.

A search of medicine databases based on evidence and general databases was also performed: MEDLINE (PubMed) and EMBASE (Elsevier).

Search for research studies. Search period: from 2003 to March 2011 (including warnings) for updated questions from the NICE CPG 2004. For the questions about pregnancy, which were based on the NICE CPG 2008, the search term was from 2007 to 2011 (including warnings).

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After the identification and selection of a CPG, a specific research was carried out on studies for each clinical question in *Cochrane Library Plus* and the database of the *National Health Service (NHS) Centre for Reviews and Dissemination,* which in turn includes the HTA database *(Health Technology Assessment)* on assessment reports and the DARE base of reviews of effectiveness. General databases such as MEDLINE (PubMed) and EMBASE (Elsevier) were also used.

The whole process was completed using a general Internet search (scientific organizations and societies) and reverse lookup in articles from the most relevant studies to locate other relevant information.

The bibliographic search strategies are included in the document "Methodological material" available on the GuíaSalud website: http://www.guiasalud.es/ecpg/index.html.

3.2.3. Assessment of the methodological quality

The methodological quality of the CPGs found by the AGREE instrument[10] was assessed, and the NICE CPG 2004[7] was selected for having the highest score. It was considered a reference CPG for its update/adaptation according to the methods proposed by the document "Descripción de la metodología de elaboración-adaptación-actualización empleada en la Práctica Clínica sobre Asma en la CAPV" (Description of the development – adaptation – update methodology used in the Clinical Practice on Asthma within the Basque Autonomous Community)[6].

For those questions that were not addressed by this guide, a new search on research studies was carried out and the system proposed by SIGN[11] for assessing the methodological quality of the studies was used.

3.2.4. Data Extraction

Performed by two independent reviewers.

3.2.5. Development of evidence tables

The evidence tables are included in the document «Methodological material» available in the website of GuíaSalud: http://www.guiasalud.es/ecpg/index.html.

3.2.6. Classification of studies and grades of recommendations

For the classification of levels of evidence and grades of recommendations, the SIGN[11] scale was used for questions about effectiveness and safety of interventions or treatments and the Oxford[12] classification for the diagnostic questions.

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3.3. Edition of the Guide

Throughout this CPG there are recommendations based on publications of «consensus or expert opinion» qualified with the letter «D».

The symbol «√» is used to define «consensus of the development team». This last grade of recommendation is used in cases where there are no publications or when despite having studies, evidence must be adapted due to the context of application.

Along the document, the information provided by studies about the type and level of evidence reflecting the possibility of bias in the literature reviewed is presented.

The text has undergone an external review by a multidisciplinary group of professionals. The final version of the guide has been reviewed and approved by the development team.

The different scientific societies involved have been contacted:

- Federación de Asociaciones de Diabéticos de Euskadi (Federation of Diabetes Associations of the Basque Country) belonging to the Federación de Diabéticos Españoles (Spanish Diabetes Federation),
- Sociedad Española de Diabetes (Spanish Diabetes Society),
- Sociedad Española de Endocrinología y Nutrición (Spanish Society of Endocrinology and Nutrition), who participated through the development team and the external review.

This document is the «full» version of the Clinical Practice Guideline on Diabetes Mellitus type 1. The CPG is organized by chapters that provide answers to the questions at the beginning of it. A summary of the evidence and recommendations is presented at the end of each chapter. A "summarised" version of the CPG with the appendixes from the «complete» version and an educational guide aimed at young people and adults with DM1 is also available.

The link http://www.guiasalud.es/ecpg/index.html contains different versions of the CPG and the methodological material, which presents the information in detail with the preparation of the CPG, the search strategy for each clinical question and the evidence tables.

The update of this guide is scheduled every five years without ruling out, if required, more frequent updating of the electronic version.

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4. Definition and diagnostic criteria of diabetes mellitus type 1

4.1. Definition of diabetes mellitus type1

Key question:

- What is diabetes mellitus type 1?

Diabetes mellitus (DM) comprises a group of metabolic diseases characterized by secondary hyperglycaemia to an absolute or relative defect in insulin secretion, which is accompanied, to a greater or lesser extent, by alterations in the metabolism of lipids and proteins, which leads to micro- and macro-vascular impairment affecting different organs such as eyes, kidneys, nerves, heart and vessels.

Diabetes mellitus type 1 (DM1) corresponds to the entity formerly termed insulin dependent or juvenile diabetes mellitus, in which the destruction of the pancreatic β cells leads to an absolute insulin deficiency. In the current classification, the DM1 is divided into two subtypes: DM1 A or autoimmune and DM1 B or idiopathic.

DM1 A or autoimmune: autoimmune disease in which there is a selective destruction of pancreatic β cells mediated by T lymphocytes activated in people with predisposing HLA haplotypes. After a preclinical period of variable duration, during which the patient is asymptomatic, when the mass of insulin-producing cells reaches a critical value the patient has classic symptoms: polyuria, polydipsia, polyphagia, weight less and a progressive ketosis that can lead to ketoacidosis, if not treated with exogenous insulin.

DM1 B or idiopathic: as opposed to DM1 A, DM1 B includes patients with the same or similar characteristics, without auto-immunity or predisposing HLA haplotypes data. As it has only been described recently as entity, little is known of its aetiology, development and prognosis.

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4.2. Autoantibodies in the diagnosis of diabetes mellitus type 1

Key question:

- What do the autoantibodies provide in the diagnosis of diabetes mellitus type 1?

DM type A or autoimmune is related to the destruction of β cells of the pancreatic Langerhans islet, usually because of an autoimmune response against specific molecules of the islet: insulin, glutamate decarboxylase, tyrosine phosphatase (IA-2), carboxypeptidase H, ICA69, etc.

The autoantibodies against these antigens can be detected in the serum of patients with DM1, and this has been used as an aid in the diagnosis, classification, and prediction of the disease[13]. The autoantibodies can be detected even during the prodromal stage, as in the case of DM1 type A, during which although there are no clinical symptoms, there is a destruction of the β cells[14]. It is also possible to use these antibodies as markers of disease activity, and its measurement can help to define the nature of the diabetes, providing autoimmune markers to classify as autoimmune or not, depending on the presence or absence of antibodies associated with the disease.

The NICE CPG 2004[7], based on a report carried out by consensus by the WHO[15], does not recomm end regular measuring of the C-peptide nor specific autoantibodies to confirm the diagnosis of DM1, but it does recommend its use if this will help to differentiate DM1 from DM2.

Expert consensus 4

This same CPG[7], based on a consensus guide prepared by ISPAD[16], recommends measuring specific immunological markers against β cells (abnormal levels of anti-islet cell antibodies, anti-insulin and anti-glutamate decarboxylase antibodies) when there are doubts about the diagnosis of the type of DM.

Expert consensus 4

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An SR of observational studies[17] analyzed the clinical usefulness of the determination of some immunological markers, such as the antiglutamate decarboxylase 65 (GADA) antibodies, the islet cell antibodies (ICA), the insulin antibodies (IAA), the anti-tyrosine phosphatase antibodies (anti-IA2) and zinc antiporter (anti-ZnT8) in clinical practice, and described the utility of autoantibodies in the classification of diabetes. The anti-islet antibodies (ICA) are associated with a different clinical course to that of patients who do not experience them: they are leaner, progress faster towards the need for insulin and have a lower secretion of the C-peptide. Moreover, the presence of GADA determines a slowly progressive autoimmune diabetes in adults. In the UKPDS study[18] 12% of patients with DM2 had ICA or GADA at the time of diagnosis, and 4% had both. The phenotype of patients with both antibodies was similar to that classically described for DM1 and at different ages, 59-94% required insulin within 6 years compared to 5-14% for those without either ICA or GADA. Both autoantibodies (isolated or combined) are associated with an intermediate phenotype (lower body mass, greater HbA_{1c} and lower β-cell function, compared with patients without antibodies). The positive predictive value for insulin requirement was also intermediate.

SR of observtional studies 2++

In ketosis-prone diabetes: the isolated determination of autoantibodies has low sensitivity, but shows good results when combined with the functional determination of β cells. In people with maintained β function two weeks after an episode of ketoacidosis, the absence of autoantibodies was associated with greater functional preservation of β cells in the long term.

Summary of evidence

SR of observational studies 2 + +	The determination of autoantibodies is valid for the differential diagnosis of DM1 with other types of diabetes [17.]

Recommendations

B	Regular measurement of the C-peptide or specific antibodies to confirm the diagnosis of diabetes mellitus type 1 is not advisable, but its use should be covnsidered to determine the aetiology of autoimmune diabetes in doubtful cases.

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4.3. Predictors of 'spontaneous remission'

Key question:

- What are the predictors of 'spontaneous remission'?

In newly diagnosed DM1 patients, a partial reset of the β function, shortly after diagnosis, is frequent leading to a reduction in the need for exogenous insulin and improved metabolic control. This phenomenon is known as "spontaneous remission" (SR) or 'honeymoon'. The majority of patients still need a certain amount of insulin (even low doses) and very few can do completely without it.

The clinical definition of SR varies among the authors depending on the dose of insulin considered necessary for the correct metabolic control (ranging between 0.3 and 0.5 IU/kg/day) and according to HbA_{1c} levels from which a metabolic control is considered adequate [19,20,21].

The Guide Development Group (GDG) has agreed that the definition of period of "spontaneous remission" applicable in this CPG is that proposed by Bonfati[22], according to which an SR period is considered that in which the need for exogenous insulin falls to doses lower than 0.3 IU/kg/day for a metabolic control in HbA_{1c} levels lower than 6% (36 mmol/mol) is reduced.

Different factors of individual, clinical, metabolic and immune character have been identified as potential inducers of SR and determinants of its duration.

The NICE Guide 2004[7] evaluated the SR for diabetes in the section *'Natural History of Diabetes "*. In this text SR is defined as the period in which with insulin doses lower than 0.5 IU/kg/day, a patient has HbA_{1c} levels below 7% (46 mmol/mol) [23], or when with insulin doses lower than 0.3 IU/kg/weight/day the patient has HbA_{1c} levels below 6% (36 mmol/mol)[22]. The prevalence detected in different studies presents a very wide range (30-80%).

Factors that determine the occurrence of spontaneous remission

The NICE Guide 2004 includes in its review two observational studies[23;24] that found no association between genre and the emergence of SR or its duration, while a third observational study[25] found that men with DM1 are more likely to experience partial remission than women (73% vs. 53%) and during a longer period of time [mean (SD) 279 days[22] *vs*. 210 days [25]]

Observational studies
2 +

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With respect to the influence of the age in the onset of SR, these same studies found that children with younger age at diagnosis were less likely to experience a phase of SR, which in turn showed that remissions were shorter.

A total of eight articles published after the NICE CPG 2004 have been found. Most are very heterogeneous observational studies regarding the definitions of SR and none of them matches the definition adopted by the development group of this CPG. Therefore, the results of two of these studies were not considered adequate to answer the question posed, according to the established criteria.

Summary of evidence

Observational studies 2 +	Currently there is not enough evidence on the predicting factors of spontaneous remission according to the criteria proposed by Bonfati *et al*.[23, 24, 25,] therefore the recommendations presented are based on the consensus of the Guide Development Group.

Recommendations

√	The patient and their caregivers (in case they are children) should be informed about the possibility of entering into a spontaneous remission or "honeymoon" stage within months of the diagnosis of diabetes mellitus type 1 that would imply a reduction of insulin doses. Likewise, it is necessary to point out that this entails no cure for the disease and that after this period insulin doses will have to be increased again.

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4.4. Genetic study to rule out MODY diabetes

Key question:

- When should a genetic study be carried out to rule out MODY diabetes?

In the final classification of diabetes from the American Diabetes Association diabetes MODY *(Maturity Onset Diabetes of the Young)* is included in the group «other specific types of diabetes», and specifically in the «genetic defects of β cell»[26]. MODY diabetes is considered a monogenic disease, of autosomal dominant inheritance (presence of the mutation in heterozygosity), and currently at least seven different genes responsible for it have been identified (Table 1).

Table 1. Classification of subtypes of MODY diabetes

MODY subtype	GEN	Monogenic phenotype
MODY 1	HNF4A	Progressive and severe ß-cell dysfunction.
MODY 2	Glucokinase (GCK)	Mild to moderate and stable hyperglycaemia; glucose regulation exists, but at a higher level.
MODY 3	HNF1A (TCF1)	Progressive and severe ß-cell dysfunction.
MODY 4	IPF-1 (PDX1)	Progressive and severe ß-cell dysfunction. Pancreatic agenesis if the mutation is homozygous.
MODY 5	HNF1 B (TCF2)	Progressive and severe ß-cell dysfunction; renal and genital abnormalities.
MODY 6	Neuro D1	Progressive and moderately severe ß-cell dysfunction.
MODY 7	CEL (Carboxyl ester lipase)	Variable diabetes. Exocrine pancreatic insufficiency.

Adapted from Weedon, Frayling and Raeder[27 28]

Mutations in the glucokinase gene (MODY2) are diagnosed in the paediatric population and the mutations in the *HFN1A* gene (MODY3) in the adult population. The people with MODY2 are diagnosed at younger ages than those with other types and, in general, are well controlled by diet and exercise. Those people without MODY2 have higher levels of fasting glucose and sensitivity to reduced insulin [29; 30; 31].

The involvement of different genes leads to the different subtypes of MODY diabetes, having variable characteristics in relation to the age of appearance as with the severity of hyperglycaemia or associated clinical characteristics. The phenotype presented by the different subtypes of MODY diabetes can guide the molecular genetic diagnosis and, depending on the affected gene, can predict the evolution and adaptation of the treatments. The cases of diabetes with MODY criteria, but without alteration in any of the known genes, are called MODY X.

Sometimes a diagnosis of diabetes in a child or adolescent with few or inexistent symptoms leads to an erroneous diagnosis of DM1. It is therefore important, in the absence of specific positive autoantibodies and an incompatible HLA, to assess the possibility of a study of monogenic DM.

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The personal and family history, the severity and frequency can orientate towards the specific type of study which to begin from. Performing a diagnosis of monogenic subtype DM can predict the most likely course of the disease and modify the treatment. Furthermore, the detection of gene alteration will allow early identification of family and an earlier treatment.

The latest information regarding the indication of the genetic study to discard MODY diabetes comes from good practice guidelines for molecular genetic diagnosis of MODY diabetes developed by consensus by a group of European clinicians and scientists[32]. Consensual clinical criteria are as follows:

Expert consensus 4

Mild fasting hyperglycaemia: evidence for mutations of the GCK gen

In a significant proportion of young non-obese patients who presented mild and persistent fasting hyperglycaemia, a heterozygous mutation in the glucokinase gene will be found. The features that suggest a mutation of this gene are the following:

- Fasting hyperglycaemia > 99 mg/dl (5.5 mmol/l) (in 98% of patients), persistent (at least on three separate occasions) and stable over a period of months or years.
- HbA_{1C} just above the upper limit of the normal range and rarely exceeds 7.5%.
- In the oral glucose tolerance test, the glucose increase is small (glucose after two hours - fasting glucose). In a major study conducted in Europe, 71% of patients had an increase <54 mg/dl (3 mmol/l). An increase of 83 mg/dl (4.6 mmol /) is used as a priority for testing and corresponds to the 90 percentile.
- Parents can be diagnosed with DM2 without complications or diabetes. In testing, one parent will usually undergo a slight increase in fasting glucose (99-144 mg/dl (5.5 to 8 mmol/l), unless the mutation has occurred *de novo*.

Gestational diabetes: evidence for mutations of the GCK gene

Patients with this disorder have slow and continuous fasting hyperglycaemia, and babies who do not inherit the mutation can be macrosomic. Its diagnosis is important, since the management is different in the case of this mutation to that of prediabetes type 2. The characteristics that suggest a mutation of this gene are the following:

- Persistent increase in fasting blood glucose in the range 99-144 mg/dl (5.5 to 8 mmol/l) before, during and after pregnancy.
- Increase of <83 mg/dl (4.6 mmol /) at least in an oral glucose tolerance test during or after pregnancy.
- A parent may have been diagnosed with mild DM2 but it often happens that it has not been detected; therefore, the absence of family history does not exclude the diagnosis.

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Children and young adults with diabetes and family history of diabetes: evidence for HFN1A mutations

HFN1A mutation, along with that of *GCK*, is the most common cause of MODY diabetes. The characteristics that suggest a mutation of this gene are the following:

- Young-onset diabetes (often before the age of 25 in at least one family member).
- Appearance of "non-insulin dependent" (does not develop ketoacidosis in the absence of insulin, good glycaemic control with doses of insulin lower than usual, or measuring of detectable C-peptide when with insulin with glucose > 144 mg/dl (8 mmol/l) during the normal "honeymoon" period.
- Family history of diabetes (at least two generations). These can be treated with insulin and considered DM1 or DM2. At least two of the members have been diagnosed at the age of 20 or 30. There may be an affected grandparent, often diagnosed after the age of 45. The oral glucose tolerance test, in early stages, usually shows increases of > 90 mg/dl (5 mmol/l). Some people may have normal levels while fasting, but diabetes range levels after two hours.
- Absence of autoantibodies against pancreatic islets.
- Glycosuria with blood glucose levels at <180 mg/dl, because of the low renal threshold.
- Marked sensitivity to sulfonylureas, with hypoglycaemias despite a poor glycaemic control prior to treatment.
- Characteristics suggesting monogenic diabetes compared to young-onset DM2: marked obesity is not seen nor evidence of insulin resistance in family members with diabetes, absence of *acanthosis nigricans* and ethnic background family with low prevalence of DM2.

Children and young adults with diabetes and family history of diabetes: evidence for HFN4A mutations

It is less frequent than the *HFN1A* mutation. It is associated with macrosomia (approximately 56% of mutation carriers) and transient neonatal hypoglycaemia (approximately 15% of the mutation carriers).

- It is similar to diabetes by *HFN1A* gene mutation, but there is no low renal threshold and the age of diagnosis may be later.
- This mutation should be considered when although molecular studies of the *HNF1A* gene are negative do not detect it, and the clinical characteristics are very suggestive.

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- Sensitivity to sulphonylureas.
- Family members with diabetes and marked macrosomia at birth (> 4.4 kg to conclusion).
- Diagnosis of neonatal hyperinsulinism sensitive to diazoxide in the context of family diabetes.

Babies with neonatal hyperinsulinemic hypoglycaemia sensitive to diazoxide and family history of diabetes: evidence for HFN4A mutations

- Macrosomic babies with hyperinsulinism sensitive to diazoxide and a family history of diabetes.

Summary of evidence

Expert consensus 4	In cases in which sustained hyperglycaemia is identified in a young person without obesity and/or a history of diabetes in two generations, in the absence of antipancreatic autoimmunity and with HLA incompatible with diabetes mellitus type 1, MODY diabetes should be ruled out. The most common types are MODY 2 and 3 diabetes. In children, macrosomia and hyperinsulinism are signs of suspicion. Diagnostic confirmation must be made by genetic study [32].

Recommendations

D	In cases in which mild continuous hyperglycaemia is identified in a young person, without obesity and/or diabetes history of mild to two generations, in the absence of antipancreatic autoimmunity and with HLA not compatible to diabetes mellitus type 1, MODY 2 diabetes should be ruled out.
D	If hyperglycaemia is more severe and progressive rule, it is recommended to rule out MODY 3 diabetes.
D	If genetic testing were negative for MODY 2 and MODY 3, the rest of MODY varieties would have to be ruled out.

Reference centres where these determinations can be made are detailed in Appendix 1

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4.5. Study of antibodies to rule out other autoimmune multiglandular diseases

Key question:

- What other autoimmune diseases are associated with diabetes mellitus type 1?
- Is it necessary to rule out autoimmune diseases that are associated with diabetes mellitus type 1?
- How should autoimmune diseases associated with diabetes mellitus type 1 in the initial study be considered?
- How often should autoimmune diseases that are associated with diabetes mellitus type 1 be assessed in monitoring?

DM1 is associated with other autoimmune diseases with organ-specific autoantibody production, such as celiac disease, autoimmune thyroid disease and Addison's disease. An estimate of the prevalence of these autoimmune diseases associated with DM1 is shown in Table 2.

Table 2. Autoimmune diseases associated with DM1

Disease	Autoantigens	Antibodies in patients with DM1 (%)	Disease patients with DM1 (%)	Antibodies in general population (%)	Disease in general population (%)
Hypothyroidism	TPO	17-27%	28%	13%	<1% obvious
	TG	8-16%		11%	5% subclinical
Celiac Disease	EM	10%	4-9%	<1%	0.9 to 1%
	TTG	12%	<0.5%	1.5%	
Addison's disease	21-OH	1.5%		Rare	0.005%

TPO: Thyroid peroxidase. TG: Thyroglobulin. EM: Endomysium. TTG: Transglutaminase. 21-OH: 21 Hydroxylase. Adapted from Barker JM et al. [33].

These diseases can arise associated, conveying syndromes with different physiopathology and characteristics:

- Type 1 autoimmune polyglandular syndrome *(Autoimmune Polyendocrinopathy Candidiasis ectodermal dystrophy: APECED)* caused by mutations in the Autoimmune Regulator Gene *(AIRE, Autoimmune Regulator Gene)*, is inherited in an autosomal recessive manner and occurs with a low frequency. It is defined by the existence of two or three of the following conditions: mucocutaneous candidiasis, adrenal failure and/or hypoparathyroidism. About 20% of the patients have DM1 too.

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- Type 2 polyglandular autoimmune syndrome: it is the combination of two major autoimmune endocrine disruptions (DM1, autoimmune thyroid disease and Addison's disease). It is the most common and includes patients with DM1 and associated autoimmune diseases such as autoimmune thyroid disease, Addison's disease, primary hypogonadism, myasthenia gravis, celiac disease, arthropathy and vitiligo. It has a genetic basis based on HLA just as DM1.

The screening of these autoantibodies in DM1 patients can detect organ-specific autoimmunity prior to the development of the disease and an early detection can prevent significant morbidities and long-term complications of these diseases.

4.5.1. Thyroid disease

In connection with thyroid disease associated with DM1, the CPG by the *International Society for Paediatric and Adolescent Diabetes* (ISPAD) 2006-2007[34] indicates that 3-8% of children and adolescents with diabetes suffer primary hypothyroidism due to autoimmune thyroiditis. Antithyroid antibodies appear in the first years in 25% of patients and are prone to develop both clinical and subclinical, hypothyroidism. Hyperthyroidism, either by Graves disease or by the hyperthyroid phase of Hashimoto's thyroiditis, is less common than hypothyroidism in patients with diabetes. However, hyperthyroidism is more common in patients with diabetes than in the general population.

Consensus document 4

Based on these data, the ISPAD group recommends by consensus to carry out screening of the thyroid function based on the analysis of TSH and circulating antibodies at the time of diagnosis of diabetes and, thereafter, every two years in asymptomatic patients without goiter or absence of thyroid autoantibodies. These recommendations are consistent with those issued recently, also by consensus, by the *American Diabetes Association* [26].

In an SR[35], the results show that antithyroid peroxinase antibodies (Ac. Anti-TPO) and thyroglobulin antibodies (Ac. Anti-Tg) are more frequent in patients with DM1 than among the control population (Ac. Anti-TPO *vs*. 5.5 to 46.2%. 0 -27.0%, Ac. 2.1 to 40% Anti-Tg *vs*. 0-20%). Prevalence rates appear to be higher in women and increase with age and duration of DM1. The prevalence of clinical and subclinical hypothyroidism, depending on whether they have Ac. Anti-TPO, Ac. Anti-Tg or both, is between 6 and 72% in patients with DM1 compared with a prevalence reaching up to 25% in the control population.

RS of observational studies 2++

In other standardized, prospective and multicenter observational study36 conducted in Germany and Austria from a database on children and adolescents with diabetes *(Diabetes patienten Verlaufsdokumentationsistem)*, the frequency of screening for celiac disease and Hashimoto's thyroiditis was assessed in 31104 under 18 year-old patients with DM1 in 177 paediatric centres in Germany and Austria.

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15% of patients had thyroid antibodies and they were more frequent in women. The antibody-positive patients were older at the time of diagnosis of diabetes (8.4 *vs*. 8.1 years, P <0.001) and had a longer duration of diabetes (6.4 *vs*. 5.1 years, P <0.001). In the long term, there was a decrease in patients with positive antithyroid antibodies (1995: 21% *vs*. 2006: 12.4%, p <0.001), unlike in the case of celiac disease specific antibodies.

Observational study 2+

4.5.2. Celiac disease (CD)

According to data provided by the CPG ISPAD, the prevalence of CD is associated with DM1 from 1 to 10% in children and adolescents with diabetes[34]. Often, the disease is asymptomatic and not necessarily associated with lower growth or poor glycaemic control.

Expert consensus 4

The screening was based on the detection of anti-endomysial antibodies (EMA) and anti-transglutaminase antibodies (TG2), the first more specific (100% *vs*. 96%) and the second more sensitive (91% *vs*. 86%). The authors of this CPG recommend carrying out an intestinal biopsy to confirm the diagnosis when there is a rise in antibodies. The long-term benefit of a gluten-free diet in asymptomatic children diagnosed with EC by routine screening has not been documented. The recommendations stated in this guide in relation to screening are:

- CD screening is recommended at the time of diagnosis of diabetes and, thereafter, every two years. Should the clinical condition suggest the existence of CD or in case the child has a first degree relative with CD, assessment should be done more frequently.
- Children with DM1 to which CD has been detected in the screening should be referred to a paediatric gastroenterologist and, after confirmation of the diagnosis, support from a paediatric dietician with expertise in gluten-free diets should be provided.

The American *Diabetes Association*[26] has issued the following recommendations:

Expert consensus 4

- After the diagnosis of diabetes, children with DM1 should be assessed promptly by measuring antiendomysial antibodies or anti-tissue transglutaminase with data on normal IgA levels for the detection of CD.
- These determinations should be repeated if there were increasing deficits in growth, weight gain, weight loss or gastrointestinal symptoms.
- Regular assessment of asymptomatic individuals should be considered.
- Children with positive antibodies should be referred to a paediatric gastroenterologist for evaluation.
- Children where the diagnosis of celiac disease is confirmed should consult a dietician and follow a gluten-free diet.

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In an SR[35], the prevalence of EMA was higher in patients with DM1 (1.5 to 10%, IQR 5.1 to 8.7, P5-P953.4 to 9.8) than in the control population (0-2%, IQR 0 to 0.3, P5-P95 0 to 1.5) and showed no consensus regarding the age, sex and duration of diabetes. The biopsy confirmed the diagnosis of CD between 44 and 100% of patients with DM1 and positive EMA.

SR of observational studies 2++

A retrospective observational study[37], conducted in Spain in 261 children and adolescents under 18 years with DM1, found an 8% prevalence of CD (21 of 261 patients studied). In 51% of cases, the diagnosis of CD took place after the diagnosis of DM1. Of these, 67% of cases were diagnosed after diagnosis of DM1in the first 5 years; 2 cases after 8 years; 1 case after 10 years and 1 case after 13 years.

Observational study 2+

In a multicenter observational study[36], the presence of CD if TG2 antibodies were greater than 10 U was assessed. Antigliadin antibodies were also analysed and those values higher than 25 U/L were considered positive.

Observational study 2+

11% of patients with DM1 had EMA antibodies and/or positive TG2, and if antigliadin antibodies are also taken into account, the figure raises to 21%. The antibody-positive patients were younger at the time of diagnosis of diabetes (7.5 *vs*. 8.1 years, p <0.001) and had a longer duration of diabetes (5.5 *vs*. 4.9 years, p <0.001). In the long run, there was a slight increase in antibody-positive patients (1995: 11% *vs*. 2006: 12.4%, p <0.001).

A retrospective observational study[38] conducted in a cohort of 950 children with DM1 in monitoring in the department of paediatric endocrinology of the University Hospital *Robert Debré* in Paris, assessed the prevalence of histologically documented CD. The analysis of antigliadin, antireticulin, EMA and TG2 antibodies was carried out between one and seven times in each patient and all patients with positive antibodies underwent an intestinal biopsy.

Observational study 2+

1.6% of patients (15/950) confirmed the diagnosis of CD by biopsy. The suspected diagnosis was made based on the symptoms in 40% of patients [mean (SD): 7 years (4.6)] and by screening in 60% of patients [mean (SD): 6.1 years (3.6) in the time of diagnosis of diabetes]. CD was diagnosed after diagnosis of DM1 in 73% of cases, and the mean duration of DM1 at the time of diagnosis of CD was 4 years (0-13 years). The EMA antibodies were positive in 15 patients and antinuclear antibodies were positive in three patients. EMA seroconversion was observed in two patients after 2 and 6 years of diagnosis of diabetes, respectively.

The authors concluded that the prevalence of CD is higher in children with DM1 (16 ‰) than in the general paediatric population (0.41 ‰), while in the general population prevalence studies usually include only symptomatic forms of CD.

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A prospective cohort study[39] investigated the prevalence of CD in a cohort of 300 children and adolescents with newly diagnosed DM1 and evaluated the screening procedure and the possible role of human leukocyte antigen (HLA-DQ) for a five-year follow up. This analysis was performed at the time of diagnosis and then a screening was carried out on an annual basis for EMA. In patients with positive EMA an intestinal biopsy was performed.

Observational study 2+

0.7% of children (2/300) had evident CD in the moment of diagnosis. 3.3% (10/300) had positive EMA and the intestinal biopsy confirmed a silent CD at the time of diagnosis of DM1. During follow-up 6% (17/300) developed positive EMA and confirmed CD: 10 cases the first year, 5 after 2 years; 1 after 3 years, and 1 case after 5 years. The cumulative frequency of confirmed CD by intestinal biopsy was 10% (29/300).

The genotypes among patients with DM1 who developed CD were not different from those with only DM1.

The results of this study confirm the low prevalence of CD at the time of diagnosis of DM1. By screening, an increase in the prevalence of silent CD over five years of follow up, with increased risk of development during the first two years of diagnosis is observed.

4.5.3. Addison's disease

In connection with Addison's disease associated with DM1, ISPAD, as published in its CPG in 2007[34] indicates that up to 2% of patients with DM1 have detectable adrenal antibodies and that Addison's disease is associated with DM1 in autoimmune syndromes. ISPAD does not establish specific recommendations for screening.

GPC Descriptive studies 3

In the SR by Graaf *et al*.[35], the results of the various studies show that adrenocortical antibodies (ACA) are more prevalent in patients with DM1 (0-4%) than in the control population (0-0.7%). There is no clear association of the presence of ACA with the age, sex and duration of diabetes. The data in this review suggest that between 3 and 40% of patients with positive ACA develop DM1 and Addison's disease.

SR of observational studies 2++

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Summary of evidence

SR of observational Studies 2++	Autoimmune thyroid diseases, celiac disease and Addison's disease occur more frequently in people with diabetes mellitus type 1 than among the general population [34; 35; 36; 37].
SR of observational Studies 2++	The presence of antithyroid autoantibodies is more common in women and more frequent at an older age at the time of diagnosis of diabetes and when the duration of diabetes is longer [36].
Descriptive studies 3	The presence of specific antibodies for celiac disease is more common at a younger age at the time of diagnosis of diabetes and when the duration of diabetes is longer [39].
	Regarding Addison's disease, there is currently not enough evidence available to make a recommendation on the systematic screening of autoimmune suprarenal disease.

Recommendations

B	Autoimmune thyroid disease and celiac disease at the onset of diabetes mellitus type 1 in children and adolescents should be ruled out.
√	This study should be done every two years for the first 10 years of disease progression and then every five years.

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5. Diabetes Education

5.1. Structured education aimed at families and/or patients with diabetes mellitus

Key question:

- Are structured educational programs aimed at people with diabetes mellitus type 1 and their families effective?

The education of a patient with DM1 is critical to have a proper control of the disease. The aim is to enable patients to take control of their disease in order to be autonomous, integrating the treatment in their daily lives.

According to ISPAD[34, 40], the aspects that characterize a structured educational program are the following:

- It comprises a structured plan, which has been agreed and written.
- It is taught by trained educators.
- It is quality assured.
- There is a proper evaluation of the program.

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The CPG NICE 2004[7] partially addresses the issue of effectiveness of the structured educational programs in DM1: it assesses the effectiveness of educational interventions in general, but not specifically that of the structured educational programs. However, this CPG includes some studies that provide evidence of interest regarding this question. — GPC

Regarding the effectiveness of these interventions in children and adolescents, a report on health technology assessment[41] that analyzed a large number of educational programs for children and adolescents with DM1 aged 9 to 21 years should be considered. The studies included in this review have a medium to high quality and most of them (68%) had been conducted in the United States. The meta-analysis on 14 studies that provided information on the psychological effects and on the 12 studies which analyzed HbA_{1c} levels indicated a moderate positive effect of these educational interventions. — SR of RCT and observational studies 1++/2++

In terms of effectiveness in adults, an RCT[42] that assessed the effects of a structured outpatient education program, taught over four weeks by nurses, dieticians and people affected by DM1, showed significant benefit of these interventions on metabolic control and quality of life. — RCT 1+

A medium sized RCT[43] evaluated the effects of a monthly educational program with different educational aspects. After a year of education with this method, the HbA_{1c} levels were significantly reduced in the intervention group versus the control group in patients with DM1. — RCT 1 +

Following the NICE CPG 2004, two RS and two RCTs were published on this topic. In addition, the results of another RCT published in 2002 but which was not included in the NICE CPG 2004 have been incorporated.

The SR published by Couch *et al* [44] reviewed the effectiveness of educational programs on diabetes that included at least one of the following: information about the disease process and treatment options, nutritional management, physical activity, monitoring blood glucose and ketone bodies in urine using the results to improve glycaemic control, use of treatments, prevention, detection and treatment of acute complications, control of risk factors, detection and treatment of chronic complications, setting targets for health improvement; solving daily life problems, and psychosocial adjustment. — SR of RCT and observational studies 1++ /2++

Of the 12,756 items found, 80 studies, 53 randomized clinical trials or controlled clinical trials and 27 observational studies were included.

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$HbA_{1c:}$ Most studies (35/52) that examined the effect of educational intervention on HbA_{1c} found no evidence of greater effectiveness of the intervention regarding education than that provided with standard care. The interventions which achieved successful results were the cognitive behavioural therapy, family therapy, training in practical skills and training in diabetes in general.

Regarding children with poorly controlled diabetes, 13 studies examined the effects on HbA_{1C}: two high quality RCTs that studied diabetes education in general and family therapy concluded that the intervention had no impact on the level of HbA_{1C}. The results of the remaining studies were inconsistent.

These studies indicate that it is not so much that programs are structured as that they are taught and that all their educational content is assimilated, albeit in an unstructured way.

Use of health services: 11 studies assessed the impact of diabetes education on the use of health care services (length of stay, emergency admission or hospitalization for complications related or not to diabetes). Most studies showed a lower use of health services, although the result was statistically significant in less than half of them.

Acute complications: 15 studies examined the effects on acute complications, most related to severe hypoglycaemia and 6 studies about diabetic ketoacidosis. Of these studies, 10 analyzed children with diabetes in general, three newly diagnosed children and one child with poor metabolic control. The results of these studies were not conclusive, since two studies in children with diabetes showed significant improvements in terms of complications, but the rest found no significant effects.

Practical skills: 9 studies measured the effects of diabetes education in the development of practical skills, including self-monitoring of blood glucose, nutrition and diet-related and urinary analysis practices. The results were inconclusive.

Adhesion: 14 of 21 studies showed significant improvement in the results and showed that interventions that improved adherence were general diabetes education, cognitive behavioural therapy and family therapy.

Psychosocial: 39 studies examined one or more connections (family and social relationships, family and social support, social skills, coping, self-perception, self-efficacy, stress, depression and anxiety) and, in general, there was an improvement of various psychosocial outcomes; although it is not possible to draw firm conclusions because of the low quality and the heterogeneity of the studies.

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Another SR[45] included 33 studies of educational interventions conducted in adults with DM1. The results of this study indicated that these interventions improve significantly the quality of life of patients (as measured by the SF-36 survey) in aspects of physical function, pain, social function, mental health, vitality and limitation due to physical problems, which leads to positive changes in lifestyle, commitment with self-control and adherence to the treatment.

SR of RCT
1 + +

An RCT [46] with 78 children and adolescents with DM1 analyzed the effects of a structured program of education based on the family and showed that the effect depended on the number of sessions attended, as the families attending two or more sessions (up to four) had a significant and beneficial effect on metabolic control after 12 months. No significant effects on quality of life or level of family responsibility were found.

RCT
1+

Another RCT [47], conducted in 164 adult patients with DM1 with hypoglycaemia problems, showed that a structured and specific program for this complication obtained significant benefits in relation to awareness of hypoglycaemia, a significant increase in its detection threshold and a decrease in the number of undetected episodes.

RCT
1+

A multicenter RCT published in 2002[48], but not included in the CPG NICE 2004, examined the effects of a structured educational program based on five sessions aimed at improving skills in insulin management. This study showed a significant improvement in metabolic control and quality of life after six months.

RCT
1+

Summary of evidence

RCT 1+	Structured educational programs targeted at adults with diabetes mellitus type 1 improve their quality of life[42]
RCT 1+	Programs that include cognitive behavioural therapy and family therapy training in practical skills and diabetes improve metabolic control and reduce the risk of acute complications[44].
RCT 1+	Studies carried out with children suggest that the structured nature of the program does not seem as important as how these are taught and that they include all the educational content [44].
RCT 1+	There is evidence that specific education programs are effective in preventing hypoglycaemia complications and improve their management, and that specific education programs on insulin management improve metabolic control and quality of life [46, 47, 48].

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Recommendations

A	All patients with diabetes mellitus type 1 should have access to a diabetes education program delivered by a multidisciplinary team (doctors, nurse educators, psychologists, dieticians, etc.) with specific skills in diabetes, both in the diagnosis stage and subsequently, based on the patient's needs..
A	In cases of repeated hypoglycaemia, the patient with diabetes and their families should be offered a specific educational program.

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5.2. Education aimed at patients and family

Key question:

- Structured education aimed at families and people with diabetes mellitus type 1: when, how, by whom and with what content is it taught?

There is great diversity in relation to the content and characteristics of educational programs. Knowledge about aspects that increase the effectiveness of these educational interventions will optimize their application and improve their results on health.

Given the heterogeneity of the interventions examined in the available scientific evidence, the recommendations that have been made on this issue are based on consensus documents published by the following international organizations: Expert consensus

- *National Institute for Clinical Excellence* (NICE CPG 2004) devotes several paragraphs of its CPG on DM1 to identify the effectiveness of the elements of education and educational programs in diabetes, both in the case of adults and children and adolescents[7].
- *International Society for Paediatric and Adolescent Diabetes* (ISPAD)[49; 50].
- *National Standards for Diabetes Self-Management Education*. *Diabetes Care* (SRDS), issued by the working group of the American Diabetes Educators Association and the *American Diabetes Association* and representatives of the *American Dietetic Association, the Veteran's Health Administration, the Centres for Disease Control and Prevention, the Indian Health Service and the American Pharmaceutical Association* [51, 52]. These standards are reviewed approximately every five years based on available evidence and with expert consensus.
- *Teaching letters* prepared by the Study Group on Diabetes Education from the European Association for the Study of Diabetes (EASD), aimed at doctors and other professionals involved in the daily care of patients with diabetes, both type 1 and type 2[53; 54].

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Summary of evidence

Expert consensus 4	Given the heterogeneity of the interventions examined in the scientific evidence available the recommendations that have been made on this issue are based on the consensus of the GEG, which has taken into account the consensus documents published by the following international organizations: *National Institute for Clinical Excellence* (CPG NICE 2004)[7]. *International Society for Paediatric and Adolescent Diabetes* (ISPAD)[49,50], *National Standards for Diabetes Self-Management Education. Diabetes Care* (EAMD), issued by the working group of the American Association of Diabetes Educators and the *American Diabetes Association* and representatives from the *American Dietetic Association, the Veteran's Health Administration, the Centres for Disease Control and Prevention, the Indian Health Service and the American Pharmaceutical Association*[51,52]. *Teaching letters prepared* by the Study Group on Diabetes Education by the European Association for Study of Diabetes (EASD)[53,54].

Recommendations

D	**Structured diabetes education should be provided in the following circumstances:** • At the time of diagnosis (survival education). • In the period following diagnosis (deepening and reinforcement education). • In the long term: on periodic reviews on self-care and educational needs, depending on the achievement or not of the objectives agreed between the patient and the practitioner.
D	**Structured diabetes education should be provided to the following people:** • All patients diagnosed with diabetes mellitus type 1. • Parents and carers in cases where there is dependency because of age or disability. • The people who make up the school environment of children or adolescents: teachers, caregivers, etc.

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D	**Professionals who must provide structured diabetes education:** • Multidisciplinary teams: the members of these teams should have competencies and skills to convey information effectively. There must be enough professionals available to organize regulated educational programs for groups. The team should include, at least, specialists in endocrinology, paediatric endocrinology and diabetes nurse educators. It is also desirable that psychologists were included in these teams for people who many need them. • At extra sanitary level the associations of people with diabetes, who provide educational programs for specific groups, play a key role (camps for children, elderly patients, informative talks, gatherings, etc.) The members of the educational team should be characterized not only by their capacity for empathy, but also for their flexibility and ability to communicate.
D	**Methods and materials used to provide structured education on diabetes:** • Attendance-based training sessions using audiovisual media, food, and objects related to learning about food: games, plastic food, and descriptive flashcards to facilitate understanding. • Complementary methods: o Books and leaflets: a great effort should be made for the guidelines contained in these materials to be useful in the daily management of the disease. o Internet: due to the lack of standardized certifications about the origin, source and credibility of the online content, it is important to facilitate reliable reference website addresses and that the learner has a basic knowledge of the disease and its clinical management for proper interpretation of the information available. o Media: Newspapers, magazines, television and radio. o Cards, identification bracelets or necklaces and transport equipment for carrying and storing of insulin devices. o Data on associations of people with diabetes and other support groups. o Psychological counselling at the time of diagnosis of diabetes mellitus type 1. o Provide contact phone numbers in case of emergency. o Other information and communication technologies (telemedicine, blogs, etc.)

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	Aspects that structured diabetes education should include: **Level 1: Survival education.** • What is diabetes mellitus. Types of diabetes. • Symptoms of diabetes mellitus type 1. • What is insulin. Treatment with insulin. • What is glucose and blood glucose goals. • Basic dietary advice. • Acute complications (hypoglycaemia, hyperglycaemia and ketosis) • Special situations (diabetes mellitus type 1 in school, intercurrent diseases, gastronomic celebrations, events, travels, etc.). • Psychological impact of the disease, identification of prior beliefs, fears and expectations. • Techniques for the injection of insulin and glucagon. • Self-analysis of capillary blood glucose meter techniques. • Urine self-analysis technique, measurement of ketonuria, ketonemia and interpretation of results.
D	**Level 2: Advanced Education.** • Physiopathology, epidemiology and classification of diabetes. • Types of insulin: absorption, action profiles, variability and adjustments. • Food planning: qualitative and quantitative advice on immediate and fibre intakes, with special attention to carbohydrate intake. • Control objectives, including the concept of glycosylated haemoglobin. • Reinforcement of knowledge of acute complications. • Problem solving and adjustment of treatment. • Micro-and macrovascular complications: prevention and monitoring. • Adjustment of insulin patterns and feeding on special situations, such as exercising, holidays and travelling. • Tobacco, alcohol and other drugs. • Adjustment to work and driving. • Sexuality, contraception, teratogenic drugs, pregnancy and breast-feeding. • Updated research on diabetes mellitus type 1. • Continuous infusion pumps. • Foot care.

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D	**Methods for teaching structured education about diabetes:** Several methods have been used successfully in diabetes education. The choice of one or the other depends on the characteristics of the patient, the disease stage and the capacity of each team or health care centre. **Individualized education.** • An intensive individualized program should be provided to newly diagnosed diabetes mellitus type 1 patients and in the case of pregnancy. **Education groups.** • The groups should be organized according to age, socio-cultural background, etc. It is desirable that family members and friends of patients also participate in the groups. Group education should include the following aspects: o Structured training by explicative lectures. o Discussion groups, with analysis of the perceptions and experiences of all group members. o Identification of fears and anxieties. o Assessment of needs and expectations. o Manifestation of personal experiences regarding hypoglycaemia, physical activity, stress response, etc. o Audiovisual methods. o Support educational material, which the patient can read at home.
D	**Characteristics which structured education programs on diabetes must contain:** • Actively involve patients in all the stages of the educational program (design, implementation, evaluation), providing them with the tools to make the best decisions about their own health. • Set the benefits of learning new skills, including the daily monitoring of the treatment. • Assess the educational needs of each patient. • Assess patients' personal perceptions. • Be flexible so that the programs are adapted to the specific educational, social and cultural needs.

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D	• Have educational goals agreed with patients. The expectations of professionals and patients may differ, so it is important to agree on common objectives, which may vary over time and require continuous review. Any proposed therapeutic target should be achievable. • Have a syllabus and a fixed schedule. • Do not create a very concentrated program and schedule frequent breaks. • Schedule lectures that do not exceed 25% of the total time, and include a time for asking and answering questions. • Pay attention to the choice of words and expressions, avoiding an overly technical language. • Provide standardized and consistent information between different team members. • Plan meetings between the professionals involved, to exchange ideas, discuss cases and review the program and methods. • Facilitate that adults participate in their own health care by giving them the possibility to make judgments and choices about their own care. • It is advisable to establish a dynamic contact process with the patient, either through visits, group discussions between patients, telephone contact or computer systems.
D	**Other considerations:** • Discuss any changes that have taken place at biomedical level (new insulin requirements, glycaemia monitoring strategies, onset of ocular complications, etc.). • Evaluation: the educational program and the goals should be assessed by process and results indicators. • Provision should be done of all the information needed to enable the development of the therapeutic education program: space required, enough qualified personnel, necessary educational materials and work agendas and schedules.

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5.3. Community Support arrangements

Key question:

- How effective are the arrangements for community or extra sanitary support (schools, diabetes associations, etc.) aimed at people with diabetes mellitus type 1?

DM1 has a major impact on the lifestyle of patients as well as their self-esteem. Both the psychological characteristics of the individual and their social relationships affect the way to deal with this disease. DM1 patients and their families and caregivers, through contact and involvement with community support groups, can get information to address the needs and problems that can arise during the development of the disease.

The CPG NICE 2004[7] defines a support group as a group of people with DM1 that meets to provide support for themselves and others in their locality." In our context, associations of people with diabetes usually carry out this role.

While these forms of community support are considered positive in the evolution of the disease, it is important to know their effectiveness in terms of health.

In the CPG NICE 2004, the evidence comes from observational studies such as the DAWN study[55], which states that emotional support, along with family support are key factors in the control of diabetes, and that social networks are considered at least as important as medication regarding management of the disease. Several studies have determined the following benefits of support groups for patients and caregivers:

Observational studies
2 +

- Psychological and emotional benefits, including improvements in the ability to deal with stress.
- Decreased burden and stress on caregivers.
- Improved quality of life.
- Improved self-care strategies through the promotion of health.
- Improved access to health services.
- Decreased isolation, overcoming depression and of the loss of self-esteem.
- Better knowledge of the conditions, symptoms and health care systems through education and information.

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The CPG NICE 2004[7] affects the influence of psychosocial support in the acceptance of the disease, how to deal with it and the results in children and adolescents with DM1 and their families. However, the results found show a lack of good quality studies that assess the effectiveness of structured support in these patients.

RCT
1+

There is evidence on the effectiveness of the systems of behavioural family therapy in reducing family conflict related to diabetes and mentoring programs with social and educational activities in young patients with DM1.

Cohort studies
2+

One study[56] has evaluated the interventions based on the support within the family context of peers with good results in the relationship between blood sugar levels and the support received.

Cohort studies
2+

Another study[57] that examined the support of friends in an intervention program, found higher levels of knowledge of diabetes ($p < 0.0001$) and a higher proportion of support from friends/family ($p < 0.05$) compared to pre-intervention measures. The friends reported improvements in self-perception after intervention ($p < 0.0001$), and the parents a decrease regarding the conflicts related to diabetes at home ($p < 0.05$).

An SR[58] carried out by *The Task Force on Community Preventive Services* group studied the effectiveness of education for the self-management of diabetes developed outside the usual clinical settings (community assembly centres, home, workplace, recreational camps, school) reached the following conclusions:

SR of observational studies
2++

- Recreational camps improve knowledge of the disease and its management in children and adolescents with DM1.
- The evidence was insufficient to assess both the effectiveness of educational interventions in the workplace or in summer camps for DM1 patients, and to assess the effectiveness of education to co-workers and school personnel on diabetes.

Effectiveness of educational interventions in the workplace or in summer camps:

In a prospective study[59] in 25 patients who participated in a 7-day summer camp, the effectiveness of the educational activity conducted therein was assessed. There was a significant reduction of HbA_{1C} values after six and 12 months, with respect to the values before the camp, and an increase in knowledge about diabetes and self-control.

Descriptive study
3

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These results were confirmed in another study[60] during a five-day camp in 60 patients who were taught knowledge of diabetes and self-management education (DSME) and were followed for six months to assess their level of knowledge and levels of HbA_{1C}, showing that children in diabetes camps undergo a considerable blood glucose variability.

Descriptive study 3

A prospective cohort study[61] compared two groups of children with DM1 (34 who received a specific educational program on knowledge, behaviours, skills and psychological factors in a summer camp *vs*. 23 who received education and usual care). There were no significant changes in mean annual HbA_{1C}, levels, BMI, knowledge of diabetes, anxiety, medical visits, or in hospital admissions compared with those before the intervention. Only the adaptation to the school environment improved significantly. The control group increased significantly the BMI and HbA_{1c} levels.

Cohort studies 2+

A descriptive study was conducted on the basis of information contained in medical records[62] of adolescents with DM1 aged 12-18 years, comparing those who attended (n = 77) or not (n = 106) a camp for diabetes education. There was a decrease in HbA_{1c} levels in those attending the camp during the follow-up compared with the baseline [mean (SD): 8.6% (1.8) *vs*. 8.3% (1.8)] while it increased in those who did not attend the camp [mean (DE): 8.4% (2.1) *vs*. 8.9% (2.3), P <0.005]. Seven months after the camp, there were still significant differences in HbA_{1c} (p = 0.04) due to persistent improvement in girls, but not in boys. Adherence to treatment (p <0.05) and the adjustment (p <0.05) was higher among the children who attended the camp.

Descriptive study 3

Another descriptive study[63] examined the effects of an education program on self-management of diabetes taught to 60 patients in a 5-day camp. After training, the patients were divided into two groups based on the frequency of self-monitoring (<3 times/day *vs*. 3-4 times/day) and were monitored for a period of 6 months. The HbA_{1c} was significantly lower in the group with the highest self-monitoring frequency after 3 months, but not after 6 months. Although the duration of the camp was short, there was an improvement in knowledge and a better attitude towards diabetes among the participants.

Descriptive study 3

Summary of evidence

Cohort studies 2+	Social networks are key factors in controlling diabetes mellitus type 1[55]
RCT 1+	Methods of family therapy and tutoring programs with social and educational activities for young patients with diabetes mellitus type 1 are effective in reducing family conflicts related to diabetes[57].

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Cohort studies 2+	The support of friends and family in an intervention program aimed at children allows for higher levels of knowledge of diabetes and self-esteem[56, 57].
Cohort studies 2+	Summer camps are effective in improving adherence to the treatment and metabolic control[59, 60, 62, 63].

Recommendations

B (Adults)/ A (children)	Updated information should be provided to adults, children and adolescents with diabetes mellitus type 1 as well as to their families at the time of diagnosis, and periodically thereafter, on the existence of diabetes support groups, both locally and nationally and how to contact them. (Appendix 11.2.)
B	The diabetes care teams should be aware that a poor psychosocial support has a negative impact on various outcomes of diabetes mellitus type 1 in children and young patients, including glycaemic control and self-esteem.
A	Young patients with diabetes mellitus type 1 should be offered specific support strategies, such as tutoring on self-analysis supported by solution to problems, how to improve their self-esteem and glycaemic control, and retreats to exchange experiences, to reduce conflict related to diabetes among family members.
√	There is no formal relationship between the health care services and diabetes associations. This relationship can be beneficial as long as the performances are confluent. It would be advisable for a physician and/or diabetes nurse educator to participate in the diabetic associations in order to provide technical support for the activities to be developed.

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6. Feeding

6.1. Feeding specifications for people with diabetes mellitus type 1

It is important that the food intake of people with DM1 is balanced, varied and that it meets the caloric needs, and takes into account changes in glycaemic intakes and the relation with the insulin treatment. Young people and children with DM1 should acquire healthy eating habits to optimize their metabolic control. The food they eat should provide them enough energy and nutrients to ensure proper growth. In order to improve metabolic control and the prevention of complications, it is very important that people with this disease are aware and understand the close relationship between food and complications.

The evidence on nutrition in DM1 included in this CPG comes mainly from a high quality SR published in 2010[64], updated by subsequently published studies or studies not included in it.

6.1.1. Carbohydrates

Postprandial glucose levels mainly depend on the intake of carbohydrates (CH) and insulin available. Adequate intake of CH is therefore a key strategy to achieve a good glycaemic control.

Three studies[65, 66, 67] showed that even and regular distribution of carbohydrate intake during the day enhances metabolic control.	Observational studies 2 +
As for the strategy to adjust the insulin dose according to the planned intake of carbohydrates, 3 studies of patients with DM1[48, 68, 69] showed significant improvements in glycaemic control ($p < 0.0001$), in quality of life ($p < 0.01$) in the occurrence of severe hypoglycaemia, lipid profile, as well as stability in the weight.	RCT 1+
The prospective observational study of Lowe *et al*.[69], found benefits from the adjustment of the insulin dose and the planned intake of carbohydrates during a one year follow up: HbA_{1c} decreased from 8.7% to 8.1% ($p = 0.0002$), improved quality of life ($p < 0.05$) and problem solving skills ($p < 0.00001$).	Cohort studies 2+

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Five trials examining diets with different percentages of carbohydrates did not obtain conclusive results. In two of these studies, monounsaturated fats were replaced by carbohydrates obtaining heterogeneous results regarding glycaemia and lipids[70; 71]. Other two studies[66, 71] found benefits with diets low in carbohydrate percentage *vs*. diets high in carbohydrate percentages, while another study[72], however, showed benefits of a diet with a high percentage of carbohydrates (80%) *vs*. a standard diet

RCT 1+

The *Strong Health Study Study*[73] investigated the association between HbA_{1c} levels and macronutrient intake. The study included 1,284 American Indians with DM. This study found that a diet with less carbohydrate intake, along with higher consumption of total fat, saturated and monounsaturated fatty acids, was associated with poorer metabolic control.

Cohort studies 2+

In DM1 patients who received intensive treatment in the *Diabetes Control and Complication Trial* [74], a diet low in carbohydrates and high in total fat and saturated fatty acids was associated with poorer metabolic control, regardless of the level of exercise and the Body Mass Index.

RCT 1+

6.1.2. Sucrose (table sugar)

Fifteen studies examined the effect of sucrose intake on glycaemic control. Eleven of them lasted from 2 days to 4 months and used sucrose doses in the diet of between 19 and 42 g/day. There were no differences in metabolic control with the intake of carbohydrates in the form of sucrose or starch[75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85].

RCT 1+

In addition, three studies examined the effect of sucrose intake on plasma lipid levels. These studies found no significant consequence[75, 76, 84].

RCT 1+

However, one 15-day long study comparing two diets containing 16% and 1% of sucrose respectively, concluded that the addition of sucrose in the diet increases blood glucose and lipid levels[86].

RCT 1+

A prospective study carried out in 19 young patients with DM1[87] found that, after 4 months of follow-up, HbA_{1c} levels decreased ($p = 0.027$) and cholesterol and triglyceride levels were within normal ranges; thus it concluded that the sucrose consumption using the carbohydrates counting technique does not affect metabolic control in these patients with DM1.

Observational studies 2+

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6.1.3. Sweeteners

There are two types of substances that can sweeten foods according to their ability or inability to increase the glycaemia of the people taking it (Appendix 2):

- Non-caloric sweeteners (have no calories): saccharin, aspartame, cyclamate, acesulfame K, sucralose, etc.
- Caloric sweeteners (provide calories, raising blood sugar in a more or less abrupt way): glucose, sucrose (table sugar), fructose and polialcohols, such as sorbitol, maltitol, xylitol, mannitol, etc.

Eight studies examined the effect of artificial sweeteners (AS) in people with DM1.

Three studies[79, 88, 89] showed that the intake of artificial sweeteners has no effect on blood glucose and lipid levels. — RCT 1+

A single study[90] found a significant decrease of blood glucose levels using sucralose. — Observational study 3

An American cross-sectional study[91] found that adults and children with DM who consumed one or more *light* or diet drinks every day had higher HbA_{1c} levels than those who did not consume any drink. — Descriptive study 3+

Two studies examined the effect of stevioside and rebaudioside A[92, 93] sweeteners and none of them found significant effect on glycaemia, HbA_{1c} or blood pressure in people with DM1 — RCT 1+

Regarding the role of fructose as a sweetener, an SR[95] found that it produces a smaller increase in postprandial plasma glucose than other carbohydrates and, therefore, could be a useful dietary sweetener for diabetics. However, fructose diets with percentages between 15% and 20% can raise levels of *Low Density Lipoprotein* (LDL) and triglyceride levels in men with and without diabetes[96, 97] in the short-term. It was also considered that dietary fructose may foster weight gain and obesity, but there is no conclusive evidence on this matter. — SR of experimental and observational studies 1++ 2++

Within the Spanish health context, the Ministry of Health and the Diabetes Foundation published a consensus document on sweeteners and their effect on glycaemia, aimed at children with DM1. This information is available in the following web address: http://issuu.com/fundaciondiabetes/docs/alimentacion_ninos_diabetes08[94]. — Expert consensus 4

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6.1.4. Glycaemic Index

In 1981, Jenkins *et al*. defined the concept of *glycaemic index* (GI) to order the food containing carbohydrates according to their ability to raise blood glucose levels compared with a reference food or food pattern, usually sugar or white bread.

There is also the concept of *glycaemic load* (GL), which is calculated by multiplying the glycaemic index of a food by the amount of carbohydrates it contains, expressed in grams, and dividing the total by 100. The glycaemic load serves to simultaneously describe both the quality (IG) and the amount of carbon hydrates of a particular food or dietary daily planning.

Although the balance between carbohydrate intake and insulin available is the main determinant of postprandial glycaemia, it has been shown that there are other factors influencing the glycaemic response to food intake, such as the content and type of food fibre, fat content, the type of starch and the physical conditions of the food determined by the way it has been processed or cooked, temperature, etc.

12 studies that examined the relationship between the glycaemic index of foods and metabolic control in patients with DM1[67, 98] were found[99, 100, 101, 102, 103, 104, 105, 106, 107, 108].	RCT 1+
Of these 12 studies, an SR with meta-analysis[104], an SR[98] and 4 cohort studies[67, 100, 103, 105] showed a beneficial effect of a diet with low glycaemic index food for HbA_{1c}.	SR of experimental studies 1++
Two studies, however, did not find this beneficial effect[101, 102].	Cohort studies 2+ RCT 1+
A one day study[107,108] in young people with DM1 undergoing continuous glucose monitoring showed lower mean levels of glycaemia, but no differences in the mean levels of nocturnal glycaemia with a diet rich in low glycaemic index foods.	RCT 1+
In an attempt to clarify the effect of a low glycaemic index diet in people with DM1 and DM2, a review by Brand-Miller *et al*.[104] analyzed this aspect. Considering those studies included in this SR which is at least 6 weeks long, it compared low and high glycaemic index diets, and an average decrease of 0.35% (range: 0 to 0.7%) in HbA_{1c} levels was found[102].	SR of observational studies 2++

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6.1.5. Fibre

Five small RCTs compared a diet rich in fibre (40-60 g) with diet low in fibre (10-20 g) with a similar percentage of macronutrients and similar caloric content. Two of them found no significant difference between the two alternatives in relation to HbA_{1c} [109, 110] and 3 demonstrated a beneficial effect of a diet rich in fibre on metabolic control[111, 112, 113].

RCT
1+

Three studies examined the effect of fibre intake on fasting glucose, two of which found no significant effect[114, 115, 116], while one study found improvement in fasting glucose with a diet rich in fibre[117].

RCT
1+

A cross-sectional study found an inverse relationship between the amount of fibre intake and HbA_{1c} levels[118], while another[119] did not find this effect.

Descriptive study
3+

Studies carried out in the general population suggest that diets with high fibre content (over 25 g/day) were associated with a lower risk of cardiovascular diseases, due to the observed effect of a diet rich in total and soluble fibre in reducing the total plasma cholesterol by 2-3% and LDL-cholesterol by 7%[120].

SR of RCT/ observational studies
1++ 2++

6.1.6. Proteins

No direct evidence is available on the effect of protein intake in DM1 patients, as the 7 studies were performed with patients with DM2,[121, 122, 123, 124, 125, 126, 127].

SR of RCT
1++
RCT
1+

6.1.6.1. Proteins in patients with nephropathy

An SR Cochrane with meta-analysis on the low protein diet in diabetic nephropathy[128], which included 12 studies, analyzed the effect of a low protein intake defined as "all types of dietary regimens with reduced or protein modification (e.g., vegetable proteins rather than animal proteins) for a minimum period of four months" in patients with diabetic nephropathy. It showed a relative risk (RR) of end-stage renal disease (ESRD) or death of 0.23 (95% CI 0.07 to 0.72) for patients assigned to a low-protein diet, after adjustment to initial values due to the existence of cardiovascular diseases (p = 0.01), and no significant improvement in the glomerular filtration rate of 0.1 ml/min/month (95% CI: -0.1 to 0.3) within the same group. Regarding compliance, planned protein intake in the intervention groups ranged between 0.3 and 0.8 g/kg/day. The actual protein intake varied between 0.6 and 1.1 g/kg/day, what indicates a lack of compliance. As a recommendation, the authors proposed reducing protein intake to 1 g/kg/day or up to 0.8 g/kg/day in patients prepared to carry out this diet.

SR of RCT whit MA
1++

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Another SR[129] analyzed 8 studies with 519 participants for a period between 6 months and 4 years, comparing a low protein diet (0.91 g/kg/day) *vs*. a control group (1.27 g/kg/day). No significant differences were found between the two groups in the rate of glomerular filtration and creatinine clearance. The group with low protein diet showed a significant reduction in the level of HbA_{1c} in 7 of the 8 trials that analyzed it [WMD 0.31% (95% CI -0.53% to -0.09%)]. RCT 1+

Nine studies investigated the effects of a low protein diet (less than 0.8 g of vegetable and animal proteins/kg/day) in the progression of nephropathy in patients with DM1. Three of these studies analyzed this effect in patients with incipient nephropathy[130, 131, 132] and 5 with advanced nephropathy[128, 129, 133, 134, 135, 136]. RCT 1+

In patients with mild nephropathy (persistent microalbuminuria of 30-299 mg/24 hours or kidney failure in phases 1 and 2, defined as hyperfiltration with glomerular filtration rates of 60 ml/min/1, 73 m^2 of body surface), 2 studies compared dietary protein levels over 1 g/kg/day *vs*. 0.8 g/kg/day or less, proving that a poor protein intake decreases albuminuria, but has no effect on the glomerular filtration[130, 131]. RCT 1+

A study carried out in diabetic patients with incipient nephropathy showed no significant effects on the glomerular filtration rate or excretion rate with a low protein diet *vs*. a normal diet[132]. RCT 1+

In patients with advanced nephropathy (macroalbuminuria defined as more than 300 mg/24 hours, chronic kidney disease (CKD) stages 3-5, defined as glomerular filtration rate less than 60 ml/min/1, 73 m^2 of body surface area), two studies found that intake of 0.7 to 0.9 g/kg/day of protein improved the excretion rate *vs*. the intake of 1.2 to 1.4 g/kg/day of protein, but not the glomerular filtration rate [133, 136]. RCT 1+

Another study, however, showed no difference between the two diets[134]. RCT 1+

Moreover, hypoalbuminemia, the malnutrition marker, was associated with a protein intake of 0.7 g/kg/day and not with a protein intake of 0.9 g/kg/day[133, 136]. RCT 1+

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6.1.7. Diet for the prevention and treatment of cardiovascular disease

Five studies analyzed the effect of diet on augmented cardiovascular risk (CV) in patients with DM1[48, 137, 138, 139, 140, 141].

Studies examining the effects of the Mediterranean diet for at least one year[141], as well as adequate control of HbA_{1c} levels[137, 140], proved to reduce cardiovascular risk in patients with DM1.	Observational studies 2 +
Likewise, in patients with DM1 in the DCCT study[74] who received intensive treatment with a diet low in carbohydrates but rich in saturated and total fat showed a poorer glycaemic control (p = 0.01), a difference that remained significant after adjusting for level of exercise, plasma triglycerides and body mass index (BMI) (p = 0.02).	Observational studies 2 +

Summary of evidence

RCT 1+	The regular intake of carbohydrates has been shown to improve glycaemic control[65, 66, 67].
RCT 1+	Adjusting insulin doses based on the planned intake of carbohydrates improves metabolic control and the quality of life without producing side effects[48, 68, 69].
RCT 1+	The total intake of carbohydrates is the main determinant of the postprandial glucose levels, independently of the source being sucrose or starch[75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85].
RCT 1+	As to the effect of sucrose intake on plasma lipid levels, studies provide no conclusive data[75, 76, 84, 86, 87].
Observational studies 2+	The intake of artificial non-caloric sweeteners has no significant effects on short- term metabolic control in people with diabetes mellitus type 1[79, 88, 89, 92, 93].
SR of observational studies 2++	Fructose consumption in percentages between 15% and 20% of the caloric intake could produce a significant increase in the levels of LDL-cholesterol and plasma triglycerides in men with and without diabetes[95].
SR of RCT 1++ SR of observational 2++	The use of the glycaemic index and glycaemic load may provide a modest additional benefit to that provided by other interventions, such as carbohydrate counting. However, studies examining the effect of glycaemic index on metabolic control show great variability in the definition of glycaemic index and important confounding factors, so it is not possible to obtain conclusive information from them[64, 67, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108].

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RCT 1+	The available evidence on dietary fibre intake in people with diabetes mellitus type 1 presents no conclusive results regarding its effect on metabolic control[109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 117].
SR of RCT/ observational studies 1++/2++	A diet rich in total and soluble fibre is associated with lower cardiovascular risk due to its lowering effect on total plasma cholesterol by 2-3%, and LDL-cholesterol by 7%[120].
SR of RCT 1 + + RCT 1 +	No direct evidence is available on the effect of protein intake in patients with diabetes mellitus type 1, as the studies found include only patients with DM2[121, 122, 123, 124, 125, 126, 127].
SR of RCT 1 + + RCT 1 +	The dietary protein intake of less than 0.8 g/kg/day improves albuminuria in individuals with diabetic nephropathy, but has not shown any effect on glomerular filtration rates[128, 129, 131, 132, 133, 134, 135, 136].
Observational studies 2+	Cardioprotective nutritional interventions, such as reducing saturated fatty acids, trans fatty acids and dietary cholesterol, reduce cardiovascular risk and improve the prognosis of cardiovascular disease in patients with diabetes mellitus type 1[48, 137, 138, 139, 140, 141, 137, 140, 74].

Recommendations

General recommendations	
√	Nutrition recommendations for a healthy lifestyle valid among the general population are also appropriate for people with diabetes mellitus type 1. Currently, there are several insulin options available, allowing to adapt the best-suited insulin regimen to the taste preferences and food choices of people with diabetes mellitus type 1 in the context of a healthy diet.
√	The improvement in glycaemic control with insulin therapy is usually associated with increased body weight. As potential weight gain may adversely affect blood glucose, lipids, blood pressure and health in general, it is desirable to prevent it.
√	Although the carbohydrate content of food determines the insulin dose, special attention should also be given to the total intake of proteins and fats.
Carbohydrates	
A	The insulin dose should be adjusted to the carbohydrate intake in people with diabetes mellitus type 1. This recommendation should be accompanied by the support of health professionals through a comprehensive nutrition education.

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A	In patients with diabetes mellitus type 1, foods with table sugar can be replaced with foods containing other sources of carbohydrates.
√	If the patient eats food with high sugar content, its absorption should be slowed down by associating their food intake with fat or fibre.
Artificial sweeteners	
B	In patients with diabetes mellitus type 1 it is preferable to use artificial sweeteners which do not interfere with glycaemic increase (see Appendix 2).
B	It is recommended to prevent the abuse of drinks and foods sweetened with fructose. This recommendation should not be extended to the fructose contained in fruits and vegetables, as these are healthy foods that provide small amounts of fructose in a normal diet.
Glycaemic Index	
A	For patients with diabetes mellitus type 1 who are assessing dietary planning based solely on the glycaemic index of foods, health professionals should inform them about the lack of conclusive evidence regarding its benefits.
Fibre	
A	Recommendations for fibre intake in patients with diabetes mellitus type 1 are similar to those of the general population: therefore, a diet containing 25 to 30 g fibre/day, with special emphasis on the consumption of soluble fibre (7 to 13 g) is advisable.
Proteins in patients with nephropathy	
A	In people with diabetic nephropathy, a protein intake of less than 0.8 g/kg/day is recommended.
A	In people with advanced diabetic nephropathy (chronic renal failure in phases 3-5), a possible hypoalbuminemia should be monitored by modifying the protein and caloric intake to prevent malnutrition.
Diet for the prevention and treatment of cardiovascular disease	
B	Nutritional interventions should be implemented to improve metabolic control and lipid profile in the prevention and treatment of cardiovascular disease in patients with diabetes mellitus type 1.

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6.2. Eating plan recommended for patients with diabetes mellitus type 1

The recommendations regarding the diet of people with diabetes have undergone numerous fluctuations over time, from the complete removal of carbohydrates and plenty of fat and protein, to the current situation, where the word "diet", as synonym of bans and restrictions, has been banished for people with diabetes. In these people it is of paramount importance to determine a meal plan according to each individual, not only taking into account circumstances such as weight, age and sex, but also the type of work, habits, schedules, physical activity, religious beliefs or economic resources. It is, in short, to adapt the meal plan to the characteristics and circumstances of each person, without forgetting that the most outstanding feature of this plan is the successful food distribution of carbohydrates throughout the day, along with the proportion of the other macronutrients and observing its effect on weight.

There are many possibilities when planning food for people with DM1. The choice depends on the characteristics of each person and the availability of resources (material resources and experienced professionals) to choose one plan or another.

6.2.1. Menus based method (Appendix 4)

It is based on the use of predefined and adapted meal plans tailored to daily menus, whilst maintaining adequate nutritional parameters.

They are very useful for those people who find it difficult to organize themselves or are in the early stages of diabetes, a phase in which the patient or their family need simple and effective strategies.

6.2.2. Servings based method (Appendix 5)

It is based on a count of all the basic nutrients: the HC group, proteins group and lipids or fats group, thus contemplating their correct amount and distribution in the context of a healthy diet.

For an easier use there are 6 food groups based on the proportion of the most important nutrients that contain:

1. Dairy products (HC).
2. Farinaceous (HC).
3. Vegetables and salads (HC).
4. Fruits (HC).
5. Proteins.
6. Fats.

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The concept *serving*, used as quantitative terminology, is defined as the amount of food containing 10 grams of each of the primary nutrients. For example:

20 grams of bread contain 10 grams of carbohydrates = 1 serving

50 grams of meat contain 10 grams of protein = 1 serving

10 g of oil contain 10 grams of fat = 1 serving

It should be noted that other countries use different contents of carbohydrates per serving, which is important for bibliographic queries or recipes, for example, in Germany one serving is equivalent to 12 grams of carbohydrates and in the United States, to 15 g.

Based on this servings' method other systems have been developed to make meal plans easier.

6.2.3. Exchange and equivalents system (Appendix 6)

The system of exchange and equivalence is included as an extension of the method based on servings to create a list of foods grouped by similar nutrient values. This allows, within the prescribed plan, to exchange equivalent food, offering more choice and more freedom for the design and adaptation of the menu.

Proper application requires that the person shows willingness to learn and receive proper training.

6.2.4. System based on counting carbohydrate servings

It is based on the concept that the amount and distribution of carbohydrates in the food provided is the most influential factor in postprandial glycaemia, although it is also important to pay attention to proteins and fats.

Few studies attempt to assess the effectiveness of different types of diet in isolation. In fact, most studies assessed contain a specific method of diet included within complex and multidisciplinary education and intensive insulin therapy programs. Therefore, it is difficult to extract the effectiveness of the diet in isolation in the overall intervention.

A poor quality methodological SR[142] analyzed the dietary treatment in children and adolescents, based on studies published between 1990-2001 and found few consistent results among the 8 studies included, and concluded that the available evidence cannot determine the differences between the carbohydrate counting method (*carbohydrate counting*) and the unrestricted diet. SR 1-

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The Goksen and Kalergis *et al*.[143, 144] studies are the only studies that try to compare the HC counting method and the exchange system in isolation, outside the context of a structured program of education and intensive treatment. These studies showed no significant differences between the two methods in terms of the effects on HbA_{1c}, BMI and quality of life. RCT 1+

Summary of evidence

RCT 1 +	Evidence on the effectiveness of meal plans is limited and does not provide conclusive results regarding its effect on metabolic control and quality of life[142, 143, 144].

Recommendations

√	A meal plan must be set adjusted to age, insulin dosage, physical activity, weight and personal situation (pregnancy, hypercholesterolemia, etc.) of the patient and his/her ability to understand.

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7. Exercising

Performing regular physical activity is, along with a balanced diet, one of the mainstays of the treatment of DM.

Metabolic and hormonal changes in response to exercise depend on several factors: intensity and duration of the exercise, metabolic control, type and dose of insulin administered before exercise, injection sites and time between the administration of insulin and the last meal.

Variations of glycaemia in connection with the exercise depend on several factors:

- Glycaemia tends to decrease during moderate-intensity aerobic exercise if a proper insulin level has been administered, it lasts longer than 30-60 minutes or in the absence of intake before or during the exercise.
- On the contrary, glycaemia cannot be changed if the period is short and low or moderate in intensity and adequate intakes are performed before or during the exercise.
- Finally, glycaemia tends to rise when a there is a situation of hypoinsulinemia, very intense exercise or carbohydrate intake before or during exercise is excessive.
- It is important to note that children have a smaller muscular and hepatic glycogen store and are more sensitive to the effect of exercise.

In normal people, insulin secretion decreases during moderate exercise, offsetting the increased insulin sensitivity in the muscle. This is not possible when the administration of insulin is exogenous, as is the case for patients with DM1. Insulin reduces the normal increase of hepatic glucose production and induces its uptake by the muscle, and also prevents the normal ascent non-esterified fatty acids (NEFA) from the mobilization of fat stores. In cases of hypoinsulinemia, the production of hepatic glucose is increased and the muscle glucose uptake is reduced, and counterregulatory hormones (catecholamines, glucagon, cortisol and growth hormone) rise, and these changes are more prominent at higher exercise intensity. It also produces an increase in hepatic lipolysis and ketogenesis.

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7.1. Benefits of exercise in patients with DM1

Key question:

- What are the benefits of exercise for people with diabetes mellitus type 1?

The CPG NICE 2004[7] includes the following studies:

7.1.1. Children and adolescents

An RCT[145] compared the effect on metabolic control of a program of intense regular physical activity (30 minutes three times a week for 12 weeks) in 9 children with DM1 *vs*. 10 children who did not participate in the program. The intervention group showed significant improvement in HbA_{1c} levels [mean (SD): 11.3% (0.5) vs. 13.3% (0.5), p <0.05]. RCT 1+

Another RCT[146] with 32 children studied the effect of a program between workout once a week for three months and found no changes in HbA_{1c} levels, urine glucose or maximal oxygen consumption. RCT 1+

One before-after RCT evaluated the effect of three daily sessions of low intensity aerobic for two weeks (n = 20)[147] obtaining an improvement in HbA_{1c} levels [mean (SD): 8.28% (1.3) to 7.92% (1.42), P =0.023] after the intervention. RCT 1-

A cohort study[148] with 19 143 children and adolescents with DM1 aged 3 to 20 years, evaluated the effect of regular physical activity on glycaemic control, insulin doses and frequency of hypoglycaemia. Observational Studies 2 +

The HbA_{1c} levels were lower in the groups who practiced regular physical activity more frequently (p <0.001), this difference remaining in all age groups and in both sexes. A higher frequency of physical activity was associated with a greater effect on HbA_{1c}: exercise 1-2 times per week reduced HbA_{1c} levels by 30%, 3 or more times per week by 37%.

Children over 9 years who did not practice any physical activity required a higher daily dose of insulin than those who exercised 1-2 times per week (p <0.001).

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7.1.2. Adults

The CPG NICE 2004[7] includes the following studies:

A small sample of RCT[149] (n = 56) which studied the effect of a 16-week program of aerobic exercise in young men with DM1, identified no significant change in HbA_{1c} or glucose, although it did find significant differences regarding the maximum oxygen consumption (higher) and the total cholesterol level in blood (less) in the intervention group.	RCT 1+
A prospective non-randomized study[150] with a before-after design showed no significant change on HbA_{1c} or microalbuminuria, but did find significant decreases in total cholesterol and glucose compared to the starting point in the group that followed a supervised exercise program (at least 135 minutes/week) for three months compared with the group that did not perform any exercise.	Non-randomized CT 1-
A before-after designed test[151] found that an intervention consisting of a 10-hour educational module which included physical exercise three or four times a week, had no significant changes in the blood glucose or fasting cholesterol levels.	Non-randomized CT 1-
A small sample cross-sectional study[152] found no significant changes in blood pressure, lipid profile, HbA_{1c}, fructosamine or glycaemia, relative to baseline.	Descriptive study 3
The SR Conn *et al*.[153] included 24 studies (n = 1435 adults with DM1) evaluating the effects of educational interventions that included physical exercise. Despite the heterogeneity detected, it was found that interventions involving physical exercise improve metabolic control in adult patients with DM1 [Mean reduction of HbA_{1c} 0.33% (95% CI 0.26 to 1.28%)]. Besides these compared the effect of interventions that included only physical exercise *vs*. those which also included dietary and pharmacological measures (9 studies), proving that the latter had a greater effect on HbA_{1c}.	SR with MA of RCT 1++

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The Pedersen *et al*.[154] SR reviewed the effect of exercise in patients with DM1 and identified a protective effect on the development of cardiovascular diseases, a positive effect on the lipid profile (decreased LDL-cholesterol and triglycerides, increased HDL-cholesterol and the HDL-cholesterol/total cholesterol ratio). However, it did find inconsistent results on the impact of exercise on the endothelial function. The authors of this SR concluded that although there are few studies analyzing specifically the effect of exercise in patients with DM1, the results indicate that there are minor differences in the metabolic control of active and inactive adults[155, 156] or that there is no difference[149, 157, 158, 159]. However, they felt that physical activity has possibly a beneficial effect on lipid profile in people with DM1 by lowering LDL-cholesterol, triglycerides[149] levels, increasing HDL-cholesterol and the HDL-cholesterol/total cholesterol ratio[149, 158].

RT
1++/2++

An SR[160] examined the effect of exercise on different result measures (glycaemic control, insulin requirement and lipid profile) in people with DM1. No improvement was observed in terms of metabolic control through exercise, even if there was a reduction of insulin requirements, an improvement in lipid parameters, in blood pressure and on the endothelial function.

SR
1++

7.1.3. All age groups

An SR[161] made in Spain analyzed the impact of exercise on metabolic control and the development of chronic complications in patients with DM1. Different results regarding the benefits of physical activity on glycaemic control, regardless of the level of evidence were observed: an SR showed no significant changes[162] while another showed a significant improvement of 0.33% in HbA_{1c} levels in the group who did take up some exercise[153]. From 16 RCTs, 10 showed no change and 6 found some minor improvements and from three observational studies, two showed some effects on those you had practiced exercise. The authors of the SR concluded that most of the studies show that the practice of regular physical activity affects positively (or at least does not worsen) the metabolic control of patients with DM1. Regarding the results on the development and progression of chronic complications, there is not enough information on this matter.

SR of RCT
and
observational
studies
1++/2++

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Summary of evidence

SR 1++/2++ RCT 1 + Observational studies 2 +	In people with diabetes mellitus type 1, scientific evidence provides inconclusive results on the effect of regular exercise on metabolic control (HbA_{1c}) since some studies find beneficial effects in patients who do practice exercise[145, 147, 148, 153,] while others[149, 150, 152, 154, 160, 161] found no significant differences with people who do not practice regular physical activity.
RCT 1 + Observational studies 2 +	The analysis by age group has shown that the lack of studies in children and adolescents with diabetes mellitus type 1 show a beneficial effect of physical exercise on metabolic control[145, 147, 148, 163].
SR 1++/2++ RCT 1 +	Most studies show that physical exercise has a positive effect on the lipid profile, lowering LDL-cholesterol and the concentration of triglycerides, HDL cholesterol and increasing the HDL/total cholesterol ratio[149, 150, 154, 160]. However, other studies have shown no significant changes in lipid profile[151, 152].
SR 1++ Descriptive study 3	As for the effects on blood pressure, a systematic review shows that physical exercise does decrease it[160], nevertheless a descriptive study[152] found no significant change.
SR 1++/2++ SR 1++	Physical exercise leads to increased insulin sensitivity in patients with diabetes mellitus type 1, which is associated with a reduction in exogenous insulin intake[160], of about 5%[154].

Recommendations

A	Patients with diabetes mellitus type 1 are recommended to do physical exercise, especially for its positive effect on the lipid profile and on blood pressure.
A	Children and adolescents with diabetes mellitus type 1 should be highly recommended to do physical exercise as there is some evidence showing its benefits on metabolic control.

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7.2. Type, intensity and duration of physical exercise in people with diabetes mellitus type 1

Key question:

- What kind of physical exercise is recommended for people with diabetes mellitus type 1?

7.2.1. Children and adolescents

The CPG NICE[7] includes the following studies:

An RCT[145] that included 19 children with DM1 described the beneficial effect on metabolic control of an intensive regular exercise program carried out for 30 minutes three times a week.

RCT
1 +

Another RCT[146] with 32 children studied the effect of a once-a-week training program for three months, finding no changes in HbA_{1c} levels, urine glucose or maximal oxygen consumption.

RCT
1 +

A cohort study[148] with 19 143 children and adolescents with DM1 aged between 3 and 20 years found that the HbA_{1c} level was higher in the group with no regular physical activity (8.4% in the group with less frequency *vs*. 8.1% in the group with greater frequency, P <0.001). This effect was found in both sexes and in all age groups (p <0.001). A multiple regression analysis revealed that regular physical activity was one of the most important factors that influence the HbA_{1c} level. There was no association observed between the frequency of regular physical activity and the frequency of severe hypoglycaemia or hypoglycaemia with loss of consciousness or convulsions. The study authors concluded that the regular practice of physical activity in children and adolescents with diabetes mellitus type 1 should be recommended, being the recommended frequency 3 or more times a week. This study defined "regular physical activity" as physical activity systematically practiced at least once a week for at least 30 minutes, excluding sport practiced at school.

Observational studies
2 +

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7.2.2. Adults

The CPG NICE 2004[7] includes the following studies:

A prospective nonrandomized study[150] with a before-after design concluded that conducting a supervised exercise program of at least 135 minutes per week for a period of three months, produces significant benefits it decreases glucose levels and plasmatic cholesterol.

Non-randomized CT 1-

A before-after study[151] concluded that the practice of physical training three or four times a week, did not produce any significant metabolic response.

Observational study 2+

In an SR[154], it was recommended that people with DM1 should perform at least 30 minutes of moderate intensity physical activity every day or 3-4 hours a week in the form of light walk, cycling, swimming, rowing, golf, etc. In addition, it was advised to include periods of mild exercise for 5 to 10 minutes before and after training with an adjustment of hydrocarbon intake and take into account the presence of autonomic neuropathy to adjust the intensity of exercise.

SR 1++/2++

The Carral *et al*.[161] SR noted that two clinical trials which examined the effects of exercise training programs with strength and muscle resistance exercises showed no significant effects on the levels of HbA_{1c}[164, 165].

SR 1++/2++

Summary of evidence

2 + + Observational study 2 +	In children and adolescents with diabetes mellitus type 1, the practice of moderate to intense exercise three to five times a week for 20 to 60 minutes, produced a significanty improvement on metabolic control[145, 146, 148].
SR 2 + +	Moderate-intensity both aerobic and anaerobic exercise for 30 minutes a day or 3-4 hours a week, showed to have beneficial effects in adult patients with diabetes mellitus type 1[154].
Non-randomized CT 1 - Observational study 2 +	There is no clear relationship between the characteristics of physical exercise and the effects on metabolic control[150, 151, 161, 164, 165].

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Recommendations

A	People with diabetes mellitus type 1 should be encouraged to perform regular physical exercise.
A	People with diabetes mellitus type 1 should be recommended moderate physical exercise for at least 135 minutes a week, without being more than two consecutive days without doing physical exercise.
√	People with diabetes mellitus type 1 and their families should be informed that they can participate in all forms of exercise, providing they know how to perform the appropriate adjustments to the intake and insulin.
√	The people with diabetes mellitus type 1 who wish to participate in less common/or specific risk sports should be educated on this matter, however it is not advisable to perform these alone.
√	People with diabetes mellitus type 1 and their families should be encouraged to monitor blood glucose levels before and after exercise to learn about the glycaemic response in different conditions of exercise, and make the necessary adjustments before, during or after it.
√	People with diabetes mellitus type 1 and their families should be informed about late hypoglycaemia risk in situations of intense and/or prolonged exercise, to take the necessary precautions.
√	People with diabetes mellitus type 1 and their families should be informed that exercise is contraindicated if there are high levels of blood glucose and/or ketones in the blood or urine.
√	Young people and adults with diabetes mellitus type 1 who want to do intense physical exercise should consult a doctor to rule out microvascular complications that contraindicate it.

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8. Glycaemic Control

8.1. Glycosylated haemoglobin

Key question:

- What are the target values of glycosylated haemoglobin?
- What are the criteria for the standardization and presentation of glycosylated haemoglobin analytic results?

The risk of arterial disease and microvascular complications in people with diabetes is associated with inadequate metabolic control over time. Glycosylated haemoglobin (HbA_{1c}) has proved to be a good indicator of metabolic control, but since very strict control is associated with more episodes of hypoglycaemia, it is important to identify the optimal value of this parameter to guide the treatment of people with diabetes.

8.1.1. Glycosylated haemoglobin target figures

The CPG NICE 2004[7] includes the results of a randomized trial published by the *Diabetes Control and Complications Trial Research Group*[166] and the follow-up of that same cohort[167], which assessed the occurrence of microvascular complications, comparing a group of 638 insulin dependent patients with intensive therapy (mean HbA_{1c} levels of 7%) *vs*. another group of 638 diabetic patients treated with conventional therapy (mean HbA_{1c} levels of 8.8%). After 6.5 years of follow-up, it was observed that the group who underwent intensive therapy reduced the risk of retinopathy by 75%, and its progression by 54%, the risk of microalbuminuria decreased by 56%, the risk of neuropathy was reduced by 69% and its progression by 57%. However, there was three times the risk of hypoglycaemia and a higher rate of overweight in the intensive treatment group than in the conventional treatment group.

RCT
1

A medium-high quality SR from 8 RCTs (1,800 patients with DM1)[168] evaluated the effect of long-term glycaemic control on macrovascular complications in patients with DM1 and DM2, comparing intensive treatment *vs*. non-intensive treatment, with an average difference of 1.25% (-11 mmol/mol) of HbA_{1c} levels between the two groups. It was found that patients with DM1 and intensive treatment had lower risk of macrovascular events [RR of macrovascular events 0.38 (95% CI 0.26 to 0.56) and RR of cardiac events 0.41 (CI 95% CI 0.19 to 0.87), RR of peripheral vascular events 0.39 (95% CI: 0.25 to 0.62)].

SR of RCT
1 + +

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A high quality cohort study[169] studied 879 patients with DM1 with no cardiovascular or kidney disease at baseline. These patients were divided into 4 groups according to their mean levels of HbA_{1c} at baseline: group 1, HbA_{1c} = 5.6 - 9.4% (70 mmol/mol), group 2, HbA_{1c} = 9.5 - 10.5% (81 mmol/mol), group 3: HbA_{1c} = 10.6 - 12% (96 mmol/mol), group 4: HbA_{1c} = 12.1 to 19.5% (171 mmol/mol). After a 20-year follow-up, the incidence of cardiovascular and overall mortality was compared between the groups. Analyzing the HbA_{1c} as a continuous variable, it was observed that each HbA_{1c} unit increase was associated with a RR for death from all causes 1.16 (95% CI: 1.08 to 1.24) and RR for cardiovascular mortality 1.20. By analyzing the HbA_{1c} as a qualitative variable, it was observed that people with greater than or equal to 7% HbA_{1c} showed an RR for mortality from all causes 2.66 (95% CI: 1.16 to 6.11) and RR for cardiovascular mortality 3.50 (95% CI 1.09 to 11.23).

Cohort studies 2+

A cross-sectional descriptive study[170] reported a positive correlation (r = 0.427, p <0.001) between HbA_{1c} levels and severity of coronary disease, as measured by the Gensini scale.

Descriptive study 3

8.1.2. Criteria for the standardization and presentation of glycosylated haemoglobin analytical results

Considering the variability of how analytical results are expressed in HbA_{1c} in Spain in 2002 (70% expressed in units JDS/JSCC and 30% in units NGSP/DCCT), a paper from expert consensus has been published in Spain to recommend a series of measures for the harmonization in stating the HbA_{1c} results[171].

Expert consensus 4

The points agreed upon were as follows:

1. Laboratories shall use traceable methods to the IFCC reference method.

2. Following international recommendations[172], it is agreed to issue HbA_{1c} results in two types of simultaneous units in all laboratory reports: NGSP/DCCT % units (with a decimal) and IFCC (mmol/mol) (no decimals).

3. The publications and clinical guidelines developed from the date of the agreement include the two units in their texts.

4. The transformation into units NGSP/DCCT (%) will be performed through different conversion equations, using the information technology systems of each laboratory:

- If working with calibration JDS/JSCC (Japan): NGSP (%) = 0.985 × JDS/JSCC % + 0.46.
- If working with Mono-Sweden calibration (Sweden): NGSP (%) = 0.923 × Mono – Sweden % + 1.34.
- If working with IFCC calibration (%): NGSP (%) = 0.915% + 2.15 × IFCC.

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- To calculate the equivalent in IFCC units (mmol/mol) starting from NGSP/DCCT (%) units: IFCC (mmol/mol) = (NGSP % - 2.15/0.915) × 10.

5. The methods used should have an imprecision (coefficient of variation) of less than 4%, but the ultimate goal should be to achieve an accuracy of less than 2%.

6. In transient situations, such as the current use of JDS/JSCC (%), it is recommended to inform, if necessary, during a transitional period (12-14 months) in both units JDS/JSCC (%) and NGSP/DCCT (%) units.

7. The societies that underwrite this document will undertake to implement education and outreach programs for its members.

8. Including estimated mean glucose (eAG) with glucose and HbA_{1c} in glycaemic status reports is not based on enough scientific evidence to allow its use in the clinic. To determine the actual role it could play in the clinical practice, further research is required in all groups of diabetic patients, including paediatric patients, pregnant women and elderly, as well as the various ethnic groups.

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Summary of evidence

RCT 1 +	Intensive therapy with medium HbA_{1c} levels of 7% reduces the microvascular complications risk but increases the risk of hypoglycaemia[166, 167, 168, 169].
SR of RCT 1 + +	HbA_{1c} levels greater than 7% increase cardiovascular and death due to all causes risk[168, 169, 170].

Recommendations

A	It is recommended to inform people with diabetes mellitus type 1 and their families of the benefits of a long-term metabolic control with HbA_{1c} levels below 7% (46 mmol/mol) without disabling hypoglycaemia, therefore the care measures must be designed to achieve these aims.
√	The aims of the treatment should be individualized and agreed with the patient, assessing the risks and benefits.
√	The goals should be less demanding in people with a history of severe hypoglycaemia, no recognition of hypoglycaemia, patients with limited life expectancies, young children and patients with chronic concomitant diseases.
D	The HbA_{1c} results should be issued in two types of units simultaneously on all laboratory reports: NGSP/DCCT % units (with a decimal) and IFCC (mmol/mol) (no decimals) units.

8.2. Systems of Continuous Glucose Monitoring

Key question:

- Do the continuous glucose monitoring systems improve metabolic control?

In people with diabetes mellitus type 1 it is considered appropriate to assess blood glucose levels in different times during the day: before and after meals, before, during and after exercise, and occasionally overnight. However, intermittent measurements by capillary glucose do not always provide enough information about the time when the glucose changes, and, if it does, how fast it does so and in what direction. To overcome these limitations, systems have been developed that allow continuous glucose monitoring (CGM) in interstitial fluid for more than 50 years.

On the one hand, non-invasive continuous monitoring systems have been searched for: enzyme electrochemical sensors, spectroscopy, infrared or other, although currently most are under development[173, 174, 175].

The MCG systems marketed today are invasive and measure the amount of glucose within the interstitial fluid using a subcutaneous electrochemical enzyme sensor (Dexcom ®, Medtronic ®, Navigator ® systems), or by obtaining samples of interstitial fluid by microdialysis techniques (Menarini ®)[176, 177]. These devices require capillary glucose measurements for calibration[178].

Moreover, one must distinguish two types of MCGs according to the way the reading of the data is performed: with retrospective or real time reading.

In systems with retrospective reading, the information is downloaded after use, allowing adjustments in the therapy of patients with diabetes. Initially, the reading period was 72 hours, now it reaches up to a week.

In real-time systems a computer program, providing an interstitial glucose reading every few minutes, allowing adjustments of the real-time therapy, processes the information. In addition, these systems allow analyzing trends and set alarms for hypoglycaemia and hyperglycaemia and predictive alarms. The duration of the real-time sensor currently marketed is approximately one week. The technological evolution of the MCG is fast and constantly evolving, thus leading to the improvements of the monitoring systems.

The recommendations of the CPG NICE 2004[7] do not apply to this guide as technological developments in terms of comfort, applicability and capacity of monitoring devices in real time in recent years cannot compare the results of the current devices with those existing years ago. Therefore, only the evidence published in the last 7 years has been taken into account.

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8.2.1. Retrospective monitoring

Two meta-analysis[179,180] which included 7 and 5 randomized trials, respectively, including the one conducted by Chico *et al*.[181] in Spain, concluded that using retrospective continuous monitoring systems is not associated with significant reductions in HbA_{1c} compared to frequent capillary blood self-analyses [HbA_{1c} reduction difference 0.22% (95% CI -0.439 to 0.004), P = 0.055]. — Descriptive study 3

For continuous monitoring during pregnancy, a study of patients with DM1 and DM2 has demonstrated an improvement in HbA_{1c} levels and lower macrosomia rates using retrospective MCG[182]. 71 pregnant women with diabetes were studied, 46 of them with DM1, comparing the use of MCG (n = 38) versus standard 0glycaemic controls (n = 33), with treatment adjustments based on the results observed. The women with MCG had lower HbA_{1c} levels during the last weeks of pregnancy [mean (SD): 5.8% (0.6)] than the group without MCG [mean (SD): 6.4% (0.7)]. The children of mothers with MCG had lower standard deviation values regarding birth weight [0.9 *vs*. 1.6, (95% CI: 0.0 to 1.3)]; smaller mean weight percentiles (69 *vs*. 93), and, above all, a reduced risk of macrosomia [OR 0.36 (95% CI 0.13 to 0.98)] compared to children of mothers with standard control. — RCT 1+

8.2.2. Real-time monitoring

The STAR1[183] study performed a prospective trial with an integrated insulin pump and continuous glucose sensor system (Paradigm Real Time ®). 146 patients with DM1 and HbA_{1c} > 7.5% were randomized in 2 comparison groups: continuous infusion pumps and real-time MCG *vs*. infusion pump and frequent self-analysis in capillary blood. After 6 months of follow-up, no significant differences were found in HbA_{1c} levels between the two groups. — RCT 1+

The *Juvenile Diabetes Research Foundation* (JDRF) published a study in 2008[184] that included 322 patients, randomly assigned to real time MCG (n = 165) or conventional monitoring via frequent capillary blood self-analysis (n = 156), and were evaluated for 6 months. Most patients used CSII (67-84%, depending on the groups) and measured their blood glucose levels more than 5 times a day with a capillary blood glucometer. 87% of the sample had an average HbA_{1c} level which was less than or equal to 8% (56 mmol/mol). In patients older than 25 it was found that the average HbA_{1c} level was lower and statistically significant in the MCG group [difference -0.53% (95% CI: -0.71 to -0.35), P <0.001]. — RCT 1+

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Regarding side effects, the differences were not statistically significant. The authors of this RCT concluded that the effect of MCG was strongly correlated with age and that these devices can help motivated adults who are able to improve their glycaemic control.

This same group[185] conducted a 26-week study with 126 patients with DM1 and good metabolic control (HbA_{1c} <7%). The group with MCG maintained its HbA_{1c} levels, while the group without MCG showed a 0.3% deterioration in HbA_{1c} levels (p <0.001). No differences were found in the number of hypoglycaemias between the two groups, which was the study's primary endpoint. RCT 1+

Another study published by the JDRF[185] evaluated the effectiveness of the continuous glucose monitoring system (CGM) used on a daily basis in patients with DM1. Patients who were assigned to the control group (n = 299), showed a decrease in the use of the monitoring system over time, although it was significantly lower in those over 25 years (p <0.001). Regarding glycaemic control, a significant decrease in HbA_{1c} levels (p = 0.01) was observed. RCT 1+

Summary of evidence

RCT 1 +	The continuous glucose monitoring systems (both retrospective and real time) developed in recent years have shown a slight improvement after a one year follow up of metabolic control in adult patients with diabetes mellitus type 1 [179, 180, 181, 182, 183, 184, 185].

Recommendations

A	Although continuous glucose monitoring can be an instrument to improve or maintain metabolic control in patients motivated and trained in intensive care, if it is used continuously, its universal use is not recommended for people with diabetes mellitus type 1.

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8.3. Inpatient or outpatient clinical management of patients with diabetes mellitus type 1 at the time of diagnosis

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Key question:

- What are the benefits and drawbacks of the management of patients with diabetes mellitus type 1 in the hospital at the time of diagnosis, compared with outpatient level management?

Traditionally in our health context, when a person is diagnosed with diabetes mellitus type 1, he/she was admitted into hospital in order to normalize blood sugar levels and control the symptoms and complications of the disease. During his/her stay in hospital, the patient and his/her family were educated about the disease. It is interesting to analyze the effectiveness of interventions performed in other health care settings, such as outpatient or home treatment, which, in the case of showing its usefulness, could arise as alternatives to hospitalization and therefore avoid the stress associated with hospitalization.

The CPG NICE 2004[7] analyzed the results of 13 trials and concluded that home care *(home-based)* carried out by a local clinical group specialised in diabetes management including permanent telephone contact, is as safe and effective as hospital management, and therefore recommends that at the time of diagnosis of DM1 children and adolescents should be offered home or hospital care according to their clinical circumstances and the wishes of the family, and the proximity of the home to the hospital (strength of recommendation A).

CPG
1+

The SR of Clar *et al*.[186] includes seven studies that provide evidence for the following outcome measures:

Metabolic Control

Four studies assessed HbA_{1c} levels relative to inpatient or outpatient management of patients with DM1 at the onset of the disease [187, 188, 189, 190]. Two of the studies [187, 189] found no differences in HbA_{1c} levels (1, 2 and 5 years follow-up) between the two options, while in a third study188, HbA_{1c} values were lower in the group of ambulatory or home based patients than those treated in the hospital: 0.7% less after 2 years ($p < 0.05$) and 3 years ($p < 0.02$) of follow-up.

SR of RCT
1+ +

Psychosocial and behavioural measures

- **Knowledge of diabetes**
  The three studies that measured parental knowledge about diabetes[188, 190, 191] found no significant differences between the comparison groups in any of the points in time evaluated.

- **Adherence to the treatment**
  Dougherty et al. found no differences between the comparison groups regarding adherence to the treatment after one month, 12 months, or 24 months, according to what parents or adolescents reported. The reported adherence ranged from 66% to 86% [188].

  On the contrary, Galatzer et al reported higher adherence rates in the out-patient/home based group than the hospital group (85% *vs*. 65.5%, P <0.001), but this effect is due to the behaviour of the group with a higher socioeconomic status[192].

  Siminerio *et al*. found no significant differences in the adherence of the subscales regarding food and exercise regulation, while the group treated in the hospital scored significantly higher on the subscale of glucose regulation (p <0.01)[191].

- **Family Impact**
  In the study by Dougherty *et al*., no differences were observed between the groups in the scores on the *Family Assessment Scale* after one month, 12 months and 24 months [188].

  Galatzer *et al*. found higher rates of positive adaptation in the family relationship in the outpatient or home group (84% *vs*. 68%, p <0.02), but again, this result was observed in the socioeconomically higher group and was not evident in the lower socioeconomic group [192].

  Siminerio *et al*, with the *Family Assessment Device* found no significant differences between groups in the subscales on general functioning, problem solving, communication, affective involvement and affective response in any of the points in time evaluated. However, the outpatient group scored better in the behavioural control (p <0.005) and in the subscales roles (p <0.05) a month after the onset of the disease. No significant differences were found between the groups of outpatients and inpatients in the share of responsibilities regarding diabetes care for children and their families [191].

  Srinivasan *et al*. [190] found no significant differences between the two groups with the scale *Parent Emotional Adjustment to Diabetes Scale or the Diabetes Responsibility and Conflict Scale* after 6 or 12 months.

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- **Coping and Stress**
  The Dougherty and Siminerio *et al* studies [188, 191] showed no significant differences between the two groups in the stress scales perceived when evaluating the parents after a month, 12 months or 24 months.

- **Satisfaction with the treatment and quality of life**
  The Dougherty and Siminerio *et al* studies [188, 191]showed no significant differences between the groups in the scales of satisfaction and quality of life in the assessments carried out after a month, 12 months or 24 months [188, 191].

- **Truancy and performance at school or work**
  Neither the Galatzer et al. nor the Dougherty et al. studies found any significant differences between the groups in performance at school or work or school absences, respectively [188, 192].

Complications

- **Need for hospital admissions or emergency unit visits**
  The studies that analyzed this outcome[187, 190, 191] found no significant differences between the comparison groups in hospitalization, nor visits to the emergency units related to diabetes.

- **Acute complications**
  None of the four studies that analyzed severe hypoglycaemia, hyperglycaemia and ketosis, diabetic ketoacidosis or chronic hyperglycaemia [187, 188, 190, 193] showed significant differences between the two comparison groups for more than 5 years.

Summary of evidence

SR 1 + +	Ambulatory education at the onset of diabetes mellitus type 1 is as effective as hospitalization, provided that the patient is clinically well, his/her home is near the hospital and there is a hospital sanitary organization (12 hour day hospital and 24 hour telephone contact)[7, 186, 187, 188, 189, 190, 191, 192, 193].

Recommendations

A	At the time of diagnosis of diabetes mellitus type 1 outpatient care and education can be offered versus hospital management, according to the clinical needs, circumstances and wishes of the patient and the patient's home proximity to the health services, provided that there are no acute complications and that enough sanitary infrastructure can be guaranteed to ensure adequate health care quality.

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8.4. Preparations of insulin in the treatment of patients with diabetes mellitus type 1

Key question:

- What is the effectiveness and safety of the different insulin preparations?

Since the eighties new forms of insulin, called "insulin analogues" synthesized with genetic recombination techniques are available. The fast acting analogues have fewer tendencies to be combined in hexamer complexes than human insulin and are absorbed more easily, so its onset of action is faster, its peak of action is higher and its duration is shorter. Currently, in the Spanish market there are three products with these features: lispro, aspart and glulisine.

Slow acting analogues (glargine) produce a more prolonged release of insulin and no peaks, with a lower risk of hypoglycaemia.

Insulin analogues have sought to imitate the physiological profile of basal insulin secretion, improve the pharmacokinetic profile of conventional insulins to overcome the limitations they had.

8.4.1. Fast acting analogues *vs*. human insulin

8.4.1.1. Adults. Fast acting analogues *vs*. human insulin

The CPG NICE 2004[7] analyzed a total of 20 good quality RCTs that compared fast-acting insulin analogues with soluble human insulin.

Eleven of these studies used a parallel design (2,425 patients were treated with an analogue treatment of fast acting insulin, 1821, with soluble insulin)[194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204]. In these studies, the levels of HbA_{1c} were lower [WMD -0.14% (95% CI -0.19 to 0.08%)] in patients using fast acting insulin analogues, compared with those treated with soluble human insulin. RCT 1+

These results were confirmed in the analysis for each insulin analogue. Thus the results of 8 RCTs comparing lispro insulin *vs*. soluble human insulin[194, 195, 196, 197, 198, 199, 200, 201] showed a lower level of HbA_{1c} [WMD -0.13% (95% CI -0.24 to -0.02%)] in the group that continued the treatment with fast acting insulin analogues. RCT 1+

In addition, 3 RCTs comparing aspart insulin *vs*. soluble human insulin obtained a similar result [WMD -0.14% (95% CI: -0.20 to -0.07%)][202, 203, 204]. RCT 1+

Twelve RCTs using a crossover design[194, 205, 206, 207, 208, 209, 210, 211, 212] showed no significant differences in HbA_{1c} levels in the treatment with fast acting insulin analogues *vs*. soluble human insulin (WMD 0% (95% CI -0.09 to 0.08%)]. RCT 1+

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Seven systematic reviews that have examined the effectiveness and safety of fast acting analogues *vs*. human insulin [213, 214, 215, 216, 217, 218, 219] have been located. In this guide, for the update of the CPG NICE 2004, the Cochrane review of Siebenhofer *et al* [214] will be used, due to its rigorous methodology regarding the definition of the disease, have a longer follow-up period (minimum 4 weeks) and include more recent studies. Although there is a review with a publication date later than that of Siebenhofer *et al*. [213], with a review period, which is very similar to the previous one and very similar results and conclusions, it applies less rigorous inclusion criteria, so the GEG has decided to disregard it.

SR of RCT
1++

Metabolic Control

In the Cochrane review of Siebenhofer et al. [214] were 20 RCTs were analyzed, the WMD of HbA_{1c} was statistically significant in favour of the insulin analogue compared with human insulin [WMD -0.1% (95% CI: - 0.2% to -0.1%)]. However, in the sensitivity analysis carried out, the higher quality tests showed no better HbA_{1c} levels with insulin analogues, therefore the above results should be considered with caution.

SR of RCT
1++

Sixteen RCTs compared lispro *vs*. human insulin and found no significant differences HbA_{1c} [WMD -0.1% (95% CI: -0.2% to 0%)].

Six RCTs compared aspart with human insulin and found no significant differences [WMD -0.1% (95% CI: -0.2% to 0%)].

No studies specifically designed to investigate the possible long-term effects were found.

In the study by Chen *et al*. [220] the HbA_{1c} levels measured after 12 weeks of treatment were better in the insulin aspart group than in the group with human insulin [geometric mean (range) 8.2 (6.7 to 9.5) *vs*. 8.7 (7.4 to 11.4), P <0.05].

RCT
1+

An SR with meta-analysis[221] that compared insulin analogues *vs*. human insulin included 68 RCTs and found a slightly greater reduction of HbA_{1c} with lispro [WMD -0.09% (95% CI -0.16 to -0.02), P <0.05] and with aspart [DMP -0.13 (95% CI: -0.20 to -0.07) p <0.05] than with human insulin.

SR of RCT
1++

Hypoglycaemia

In 10 of the studies included in the review of Siebenhofer *et al*.[194, 195, 208, 212, 222, 223, 224, 225, 226, 227], with a total of 4266 patients, there were fewer hypoglycaemic episodes with insulin analogues than with human insulin [Weighted mean difference (WMD) of mean overall hypoglycaemic episodes per patient per month -0.2 (95% CI -1.1 to 0.7)].

SR of RCT
1++

An SR [219] observed that in 13 of the 27 studies with fast acting insulin analogues a significant reduction in the number of episodes of hypoglycaemia per patient per month [mean (SD) 14.0 (3.7) p <0.05] took place.

SR of RCT
1++

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An RS with meta-analysis [221] compared insulin analogues *vs*. human insulin included 68 RCTs and found that use of insulin lispro led to a lower risk of severe hypoglycaemia [RR 0.80 (95% CI: 0.67 - 0.96)] and a lower rate of nocturnal hypoglycaemia [RR 0, 5 (95% CI 0.42 to 0.62)]. SR of RCT 1+

Quality of Life

Twelve studies[202, 205, 207, 208, 209, 226, 227, 228, 229, 230, 231, 232, 233, 234] analyzed aspects related to quality of life, but there was great heterogeneity in terms of the instruments and measurement scales used. Assessing quality of life with the most used instrument, the *Diabetes Treatment Satisfaction Questionnaire*, showed no significant differences between the treatment used in 3 studies, while 4 studies found improvement in the group treated with insulin analogues in relation to the convenience, flexibility and continuation of the treatment. RCT 1+

In an SR[219] the quality of life in 13 of the 27 studies with insulin analogues *vs*. human insulin was assessed; 11 of which showed improvement and 2 showed no significant changes. SR of RCT 1+

Summary of evidence

SR of RCT 1 + +	In adult patients with diabetes mellitus type 1, treatment with fast acting insulin analogues produces a slight improvement in glycaemic control, (overall less than 0.1% of HbA_{1c})[220, 221, 235] and less hypoglycaemic episodes, [194, 195, 208, 212, 222, 223, 224, 225, 226, 227] than the treatment with human insulin. Some studies indicate that the treatment with analogues could improve the quality of life of patients, although the results are not consistent[202, 205, 207, 208, 209, 226, 227, 228, 229, 230, 231, 232, 233, 234, 219]. It is not known how this treatment affects the development and evolution of microvascular complications, as there are no long-term data.

Recommendations for adults

A	In adults with diabetes, type 1 fast acting insulin analogues cannot be recommended in a generalised way, as they have similar effectiveness to human insulin and there is no evidence to ensure its long-term safety. However, as these provide greater flexibility in their administration, patients are more satisfied, which may improve adherence to the treatment. It is therefore advisable to make an individualized assessment of the treatment.

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8.4.1.2. Children and adolescents. Fast acting analogues *vs*. human insulin

The CPG NICE 2004[7] included 3 RCTs in children and adolescents that compared fast-acting analogues vs. human insulin[207, 236, 237] and found no significant differences in the metabolic control assessed based on the HbA_{1c} levels [WMD -0.03% (95% CI -0.21 to 0.14%)].

Metabolic Control

Two RCTs carried out in prepubertal children[233, 238] assessed the difference between lispro and human insulin and found no significant difference in the HbA_{1c} levels between the two drugs. — RCT 1+

A subsequent study[239] carried out with 26 children aged between 2 and 7 showed little difference between the treatment with aspart or human insulin. — RCT 1+

Two studies carried out in adolescents, Holcombe *et al*.[240, 241,] found no significant differences in metabolic control in this population group using fast acting analogues or human insulin. — RCT 1+

An SR with meta-analysis[221] that compared insulin analogues *vs*. human insulin and included 68 RCTs found no significant difference in HbA_{1c} levels between lispro and human insulin.

Hypoglycaemia

The trials that examined the incidence of hypoglycaemia in prepubertal patients[236, 238] and adolescents[240] found no significant differences in the type of insulin used. Neither showed differences in the rate of severe hypoglycaemia in prepubertal children[237]. — RCT 1+

The results of the studies were not consistent in the number of nocturnal hypoglycaemic episodes in children before puberty: of the three studies examining the rate of overall nocturnal hypoglycaemic episodes, two found no significant differences[237, 238] and one identified differences statistically significant in favour of the treatment with analogues[240].

An SR with meta-analysis[221] which compared insulin analogues *vs*. human insulin included 68 RCTs and found only significant differences in the risk of nocturnal hypoglycaemia in adolescents with lispro insulin versus human insulin [RR 0.61 (95% CI 0.57 to 0.64)]. — SR of RCT 1++

Growth

The study by Mortensen *et al*.[241] found lower increase in BMI in adolescents treated with aspart *vs*. those patients using human insulin; the difference was statistically significant only in men [mean (SD) -0.13 kg/m^2 (0.16) vs. 0.41 kg/m^2 (0.18), $P = 0.007$]. — RCT 1+

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Summary of evidence

SR 1 + +	In children and adolescents with diabetes mellitus type 1, treatment with fast acting insulin analogues has not shown differences in glycaemic control or incidence of hypoglycaemic episodes compared with the results obtained with human insulin[221; 236; 237; 233; 238; 240; 241, 221, 236, 237, 233, 238, 240, 241].

Recommendations for children and adolescents

A	In children and adolescents with type 1 diabetes, the widespread use of fast acting insulin analogues cannot be recommended, since they have similar effectiveness to human insulin and there is no evidence to ensure their long-term safety. However, as they do provide greater flexibility in their administration, patient's satisfaction increases, thus it may improve adherence to the treatment. It is therefore advisable to make an individualized assessment of the treatment.

8.4.1.3. Pregnant. Fast acting analogues *vs*. human insulin

Metabolic control

Two trials carried out in pregnant women[242, 243] found a similar HbA_{1c} reduction in the group treated with lispro insulin analogue and the group treated with human insulin.

SR of RCT
1++

An SR[244] assessed the effectiveness of fast acting insulin analogues in pregnancy. The authors believe these drugs to be very helpful during pregnancy, as they reduce postprandial hyperglycaemia better than human insulin.

SR of RCT
1++

Hypoglycaemia

Regarding the risk of undergoing hypoglycaemic episodes, the Persson *et al*.[242] study found that the rates of biochemical hypoglycaemias were significantly higher in the gro up of analogues compared with the group of human insulin (5.5% vs. 3.9%, P <0.05), while the study by the *Insulin Aspart Pregnancy Study Group*[243] found no significant differences between the two treatments.

RCT
1+

Regarding severe hypoglycaemic episodes, in the first study, 2 women who were treated with human insulin had 4 severe hypoglycaemic episodes *vs*. no episode in any patient in the group with insulin analogues. Meanwhile, the study of Mathiesen *et al*. [243] showed no significant differences.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

In an SR[244] the authors considered interesting the use of fast acting insulin analogues, since they can reduce episodes of pre-prandial hypoglycaemia. SR of RCT 1++

Adverse Effects

Two trials[243, 245] found no significant difference between the treatments in relation to the number of cases of live births, foetal loss or congenital malformations. RCT 1+

An SR[246] examined the effectiveness and safety of analogues during pregnancy and concluded that, although there are only studies on lispro and aspart during pregnancy available, studies show that teratogenicity, antigenicity and autoantibodies placental transport of these drugs is similar to human insulin. SR of RCT 1++

Summary of evidence

SR of RCT 1++	In pregnant women with diabetes mellitus type 1, the results of the studies in terms of metabolic control, hypoglycaemia and adverse effects on the foetus of fast acting analogues vs. human insulin are not consistent[242; 243; 244; 245; 246.242, 243, 244, 245, 246].

Recommendations in pregnant

A	In pregnant women with diabetes type 1, the use of human insulin is recommended by its demonstrated efficacy and its greater safety against the use of analogues.

8.4.2. Slow-acting analogues vs. human insulin

8.4.2.1. Glargine *vs*. retarded human insulin (NPH)

8.4.2.1.1. *Adults*

The CPG NICE 2004[7] does not include studies that provide evidence on this matter.

Metabolic Control

In an SR[247], 11 studies (n = 3279) examined the effects of glargine on metabolic control. The results were inconclusive, because only 5 studies demonstrated statistically significant results in favour of glargine compared to human insulin (NPH) and the differences found were not clinically relevant (less than 1%). SR of RCT 1++

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

Another SR[248] compared NPH insulin preparations *vs*. slow acting analogues for basal insulin replacement in patients with DM1, administered subcutaneously once a day or more. 23 randomized controlled trials were identified. A total of 3,872 patients were analyzed in the intervention and 2915 in the control group. The weighted mean difference (WMD) for the level of HbA_{1c} was -0.08 (95% CI -0.12 to -0.04) in favour of slow-acting analogues. The WMD between the groups in plasma glucose levels and fasting blood was -0.63 (95% CI: -0.86 to -0.40) and -0.86 (95% CI: -1.00 to -0.72) in favour of the analogues. The weight gain was more significant in the control group. No differences were found in the number or acuteness of severe adverse events or deaths.

SR of RCT
1++

A high quality SR with meta-analysis[249] assessed differences in HbA_{1c}, the incidence of hypoglycaemias and weight gain between the treatment with human insulin and slow acting insulin analogues in adults with DM1. A total of 20 RCTs comparing NPH human insulin (2486 patients) with slow insulin analogues (detemir or glargine) (3693 patients) were selected. 7 of the 20 studies showed a significant improvement in HbA_{1c} levels in patients treated with analogues (no differences in the remaining 13); in total there was a significant reduction in HbA_{1c} levels with analogues [-0.07 % (95% CI -0.13 to -0.1), P = 0.026]. In terms of weight, 9 studies found a significantly lower gain with detemir *vs*. NPH, with differences in BMI [0.26 kg/m ^{2} (95% CI 0.06 to 0.47), P = 0.012]. However, no differences were found in the BMI when comparing insulin glargine with NPH insulin.

SR of RCT
1++

An SR with meta-analysis[221] which compared insulin analogues *vs*. human insulin and included 49 RCTs with slow-acting insulin analogues, reported a small decrease in HbA_{1c}, but statistically significant [WMD -0.11% (95% CI -0.21 to -0.02)], with insulin glargine *vs*. NPH insulin.

SR of RCT
1++

Hypoglycaemias

The review of Tran *et al*.[247] showed no significant differences in terms of overall, severe or nocturnal hypoglycaemias.

SR of RCT
1++

Another SR[248] found no significant differences in the risk of hypoglycaemias in patients treated with slow-acting analogues [OR 0.93 (95% CI 0.8 to 1.08)] *vs*. patients treated with NPH insulin. However, the differences were significant for severe and nocturnal hypoglycaemic episodes: [OR 0.73 (95% CI 0.61 to 0.87) *vs*. 0.70 (95% CI: 0.63 to 0.79)] respectively. The WMD between the NPH insulin groups and slow-acting analogues for hypoglycaemic events was not significant [WMD -0.77 (95% CI: -0.89 to -0.65)].

SR of RCT
1++

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

An SR with meta-analysis[249] of 16 studies compared the use of analogues (n = 264) *vs*. NPH (n = 225). With respect to hypoglycaemia and nocturnal hypoglycaemia, the risk was significantly lower with slow acting insulin analogues [OR 0.73 (CI 95% 0.60 to 0.89), P = 0.002) and OR 0.69 (95% CI: 0.55 to 0.86), p = 0.001, respectively]. Comparing the analogues, detemir was associated with significantly fewer episodes of hypoglycaemia and nocturnal hypoglycaemia than NPH.

SR of RCT
1++

A meta-analysis SR[221] that compared insulin analogues *vs*. human insulin, included 49 RCTs with slow-acting insulin analogues. No significant differences were found between the groups of insulin glargine and NPH insulin using equivalent doses in both groups.

SR of RCT
1++

Quality of Life

The study by Kudva *et al*.[250] found no statistically significant differences regarding the score on the *Fear of Hypoglycaemia Questionnaire* scale among glargine users, but did find statistically significant differences in a lower score on the scale of concern among the glargine users.

RCT
1+

Another study[251] found a better score in glargine users for all areas of the *Diabetes Treatment Satisfaction Questionnaire* (DTSQ), which assesses satisfaction, usability, flexibility and willingness to continue with the treatment. Meanwhile, with the Well-Being Questionnaire (WBQ) found no significant differences between the treatments in relation to the presence of depression, anxiety, energy and wellbeing.

RCT
1+

Safety

Four studies [252, 253, 254, 255] have suggested a relationship between the use of insulin glargine and cancer development, which has led the Committee for Medicinal Products for Human Use of the European Medicines Agency to conduct an assessment whose findings are not yet available.

(http://www.ema.europa.eu/humandocs/PDFs/EPAR/Lantus/40847409en.pdf).

Cohort Studies
2+

Summary of evidence

SR 1++ RCT 1+ Cohort studies 2+	In adults with diabetes mellitus type 1, glargine offers slight advantages versus NPH insulin in respect to metabolic control and occurrence of hypoglycaemia. As for the effects on the quality, the results are not conclusive[221; 247; 248, 249, 250, 251, 252, 253, 254, 255].

More than 5 years have passed since the publication of the Clinical Practice Guideline, and its validity has not been reviewed

Recommendations

B	The use of glargine versus NPH can be recommended in adults, although the lack of data on long-term safety should be noted.
√	Regarding the current safety of glargine, it is recommended not to take any regulatory action or instruct a change of treatment to the patients using insulin glargine until the results of the evaluation of the Committee for Medicinal Products for Human Use (CHMP) of the EMEA are published.

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

8.4.2.1.2. *Children and adolescents*

Metabolic Control

An RCT found statistically significant differences in favour of glargine in HbA_{1c} [256]: in 14 children aged 6 to 12 years. On the contrary, another study[257], carried out with 42 young people aged between 6 to 21 years, found no significant differences in HbA_{1c} levels.

SR of RCT 1+

An SR with meta-analysis [221], which compared insulin analogues *vs*. human insulin in 49 RCTs with slow acting insulin analogues, showed no significant differences in metabolic control in children or adolescents.

SR of RCT 1++

Hypoglycaemia

Schober *et al*.[258] found no significant differences between the intervention group with glargine and the group treated with NPH insulin, either in severe hypoglycaemia (23% *vs*. 29%), or severe nocturnal hypoglycaemia (13% vs. 18%).

RCT 1+

The SR by Singh *et al*.[221] found no significant differences between glargine *vs*. human insulin in severe hypoglycaemias and nocturnal hypoglycaemias in children.

SR of RCT 1++

Ketoacidosis

A prospective observational study[259] analyzed 10,682 patients under 20 years with DM1 with at least 2 years of evolution of the disease, and a seven-year follow-up. The total rate of ketoacidosis episodes which required admittance to hospital /100 patients per year was on average (SD) 5.1 (0.2). While patients using insulin glargine or detemir (n = 5317) had a higher incidence of ketoacidosis episodes than those using NPH insulin. This difference remained significant after the adjustment for age at diagnosis of DM1, HbA_{1c}, insulin dose, sex, and history of emigration [OR 1.357; (95% CI: 1.062 to 1.734)].

Observational study 2+

Quality of Life

Regarding quality of life, the study by Hassan *et al*. [257] found no significant differences between the two treatments. RCT 1+

Adverse Effects

The study by Schober *et al*. [258] found less severe adverse effects (reactions at the site of injection, antibody formation and ocular reactions) with glargine ($p < 0.02$), while Hassan *et al*. [257] found no significant differences between the treatments. RCT 1+

Summary of evidence

RCT 1 +	In children older than 6 years, no significant differences have been found between the treatment with glargine vs. NPH human insulin in terms of metabolic control, hypoglycaemia and quality of life [221, 256, 257, 258]. A higher rate of episodes of ketoacidosis with insulin glargine than with NPH insulin was found [259].

Recommendations

B	The widespread use of glargine is not recommended in children with diabetes mellitus type 1 over 6 years, since no benefit has been demonstrated for the use of NPH. It is therefore recommended to individualize treatment based on the preferences and circumstances of each patient.
√	The treatment with glargine is not recommended in children with diabetes mellitus type 1, aged 6 years or less, since there is no evidence to compare glargine vs. NPH in this age group and there is already an effective and safe therapeutic alternative.

8.4.2.1.3. *Pregnant women*

Summary of evidence

SR of observational studies 2 + +	An SR[246] analyzed the safety of analogues during pregnancy. The results show a similar rate of congenital malformations with insulin glargine as with human insulin.

More than 5 years have passed since the publication of the Clinical Practice Guideline, and its validity has not been reviewed

Recommendations

B	For the time being and waiting for new evidence on the safety of glargine, the use of NPH as basal insulin during pregnancy is recommended. Individually, its use could be considered in cases of significant worsening of metabolic control with NPH or in the presence of hypoglycaemias.

8.4.2.2. Detemir *vs*. human insulin.

8.4.2.2.1 *Adults*

Metabolic Control

In the review by Tran *et al*.[247], in which the levels of HbA_{1c} in 2937 patients with DM1 we analyzed, no statistically significant differences were found between detemir and human insulin [WMD -0.05 (95% CI -0.12 to 0.03)]. SR of RCT 1++

Another RS[248] compared patients with NPH insulin *vs*. slow-acting analogues basal for insulin replacement in DM1 patients administered subcutaneously once a day or more. 23 were identified in randomized controlled trials. A total of 3,872 and 2,915 participants in the intervention and control groups, respectively were analyzed. The WMD for HbA_{1c} was -0.08 (95% CI -0.12 to -0.04) in favour of slow-acting analogues. The WMD between the 2 groups in fasting glycaemic levels was -0.63 (95% CI: -0.86 to -0.40) and -0.86 (95% CI: -1 to -0.72) in favour of the analogues. The weight gain was more significant in the control group. No differences in the number or characteristics of severe adverse events or deaths were found. SR of RCT 1++

Hypoglycaemias

In the review by Tran *et al*.[247] no differences between treatments related to overall hypoglycaemia [RR 0.99 (95% CI 0.97 to 1.02)] were found, but there were in terms of nocturnal hypoglycaemia [RR 0.89 (95% CI 0.82 to 0.97)] and severe hypoglycaemia [RR 0.75 (95% CI 0.59 to 0.95)] in favour of detemir users. For severe hypoglycaemia significant differences were found in studies that used bolus insulin analogue (aspart) [RR 0.70 (95% CI 0.52 to 0.95)], but not for those using human insulin bolus [RR 0.83, (95% CI 0.56 to 1.22)]. SR of RCT 1++

In the SR by Vardi *et al*. [248], the number of patients experiencing at least one episode of severe or nocturnal hypoglycaemia was lower in the group using detemir and glargine, but the number of total events did not differ. Detemir insulin had a greater influence on this parameter, with lower heterogeneity. The number of episodes was lower both with detemir and with glargine for total and nocturnal events, but not for serious episodes. SR of RCT 1++

More than 5 years have passed since the publication of this clinical practice Guideline and its validity has not been reviewed

Summary of evidence

SR 1 + +	In adult patients with diabetes mellitus type 1, detemir provides better metabolic control and lower rates of hypoglycaemia than NPH retarded human insulin[247; 248].

Recommendations

A	The use of detemir vs. NPH in adults with diabetes mellitus type 1 can be recommended, although the lack of data on long-term safety of this insulin should be noted.

8.4.2.2.2. *Children and adolescents*

Only one unblinded 26-week long RCT of parallel design has been located[260], comparing detemir vs. human insulin, both combined with aspart insulin in 140 prepubertal children (6 to 11 years) and 207 pubertal (12 to 17 years). RCT 1+

Metabolic Control

No significant differences in HbA_{1c} levels were found between the treatment groups [WMD -0.1% (95% CI: -0.1 to 0.3)] [260]. RCT 1+

Hypoglycaemias

No significant differences were found in overall hypoglycaemia [RR 0.89 (95% CI 0.69 to 1.14)], or daytime hypoglycaemia [RR 0.92 (95% CI 0.71 to 1.18)]. Regarding the risk of nocturnal hypoglycaemia, the differences are statistically significant in favour of detemir [RR 0.74 (95% CI 0.55 to 0.99), P = 0.041] [260]. RCT 1+

Summary of evidence

RCT 1 +	The limited available evidence shows no benefits of detemir compared with NPH insulin in children with diabetes mellitus type 1, in terms of glycaemic control and daytime hypoglycaemia, although detemir could be used as an alternative in case of nocturnal hypoglycaemias[260].

Recommendations

A	The widespread use of detemir cannot be recommended in children with diabetes mellitus type 1, although this therapy should be considered in children with nocturnal hypoglycaemia or threat thereof.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

8.4.2.3. Glargine *vs*. detemir

Pieber *et al*.[261] in an unblinded RCT of parallel design, with 320 patients, compared detemir vs. glargine in people receiving aspart before meals. The decrease in HbA_{1c} levels was similar in both groups: 8.8 to 8.2% (64 to 58 mmol/mol) in the detemir group and from 8.7 to 8.2% (63 to 58 mmol/mol) in the glargine group. RCT 1+

The overall risk of hypoglycaemia was similar with both treatments, whereas the risk of severe and nocturnal hypoglycaemia was less among the detemir users.

An RCT[262] compared the efficacy of both drugs in 443 patients with DM1 adults and at least after one year from the time of diagnosis. After 52 weeks of follow-up these showed no significant difference in the estimated HbA_{1c} mean between the detemir and glargine groups (7.57% and 7.56%, respectively [Mean difference 0.01% (95% CI: -0, 13 to 0.16)] or in the proportion who achieved HbA_{1c} levels below 7% without severe hypoglycaemias (31.9% and 28.9%, respectively). RCT 1+

Regarding the pharmacokinetics of these drugs, an RCT[263] studied 24 patients with DM1: mean age (SD) 38 years (10), BMI 22.4 kg/m ^{2} (1.6), and HbA_{1C} 7.2% (0.7) to compare the pharmacokinetics and pharmacodynamics of insulin analogues glargine and detemir. After two weeks of treatment with glargine or detemir insulin administered once a day (randomized, double blind, crossover), in patients treated with glargine, the plasma glucose remained as mean (SD) 103 mg/dl (3.6) up to 24 hours, and all the participants completed the study. Blood glucose levels increased progressively after 16 hours of treatment with detemir insulin, and only 8 participants (33%) completed the study with blood glucose less than 180 mg/dl. Detemir has effects similar to those of insulin glargine during the first 12 hours after administration, but the effects are lower for 12 to 24 hours after administration. RCT 1+

Summary of evidence

RCT 1 +	Analogues glargine and detemir have not shown significant differences between them in terms of metabolic control and the overall risk of hypoglycaemia, although detemir appears to have a lower risk of severe and nocturnal hypoglycaemia than glargine. The most relevant clinical distinction between glargine and detemir, is the necessity of having 2 doses in the case of some patients using detemir, something that affects the quality of life [261, 262, 263].

Recommendations

A	Both detemir and insulin glargine have similar effects in adults with diabetes mellitus type 1 in terms of metabolic control and hypoglycaemia, being insulin glargine that which can provide a higher quality of life for patients as detemir insulin should be administered in some cases twice a day.

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8.5. Indications of the continuous subcutaneous insulin infusion pump (insulin pump or CSII)

In order to improve metabolic control, people with type 1 diabetes must inject different types of insulin several times a day (multiple dose insulin injection therapy or MDI) and determine their blood glucose levels at least 4 times a day. The aim of therapy with continuous subcutaneous insulin infusion pump (CSII or insulin pump) is to provide an accurate, continuous and controlled insulin input, and in pulses that can be regulated by the user to meet their objectives of glycaemic control. Different to the MDI therapy, the CSII offers patients the possibility of maintaining optimal metabolic control without insulin injections several times a day but, in return, require a lot of responsibility, discipline, training, education and dedication.

It is interesting to assess the aspects that influence the effectiveness and safety of the insulin pump therapy in order to establish the criteria for its indication.

8.5.1. Adults

The CPG NICE 2004[7] recommends the CSII as an option for people with DM1, provided that the treatment with MDI (including, where appropriate, the use of insulin glargine) has failed and provided that the people receiving treatment are responsible and competent.

CPG 1++

The updated NICE guideline on insulin pumps 9 based on the systematic review by Cumminns *et al*.[264] considered that, in comparison to the optimized MDI therapy, the CSII therapy achieved a slight improvement in HbA_{1c}, levels, although its main value may be in reducing other problems such as hypoglycaemia and the "dawn phenomenon" and on improving the quality of life by allowing greater flexibility in the treatment.

CPG 1++

Metabolic Control

The meta-analysis by Jeitler *et al*.[235] included 12 RCTs that examined the level of HbA_{1c} at the end of the treatment, comparing the efficacy and safety of CSII *vs*. MDI on a daily basis.

SR of RCT 1 + +

The pooled analysis of 6 RCTs showed better metabolic control with the CSII therapy as measured by the level of HbA_{1c} [WMD -0.43% (95% CI: -0.65 to -0.20)], but in the studies measuring overall HbA_{1c}, the difference was not statistically significant [WMD -0.60% (95% CI -1.34 to -0.14)].

The meta-analysis which combined data from studies that lasted less than 6 months found a WMD in the level of HbA_{1c} of -0.4% (95% CI: -0.82 to -0.01). The studies which lasted 6 months or more, showed a difference of -0.7% (95% CI: -1.24 to -0.19).

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

In studies of parallel design, the WMD in the level of HbA_{1c} was -0.9 [(95% CI: -1.64 to -0.10) I^2 = 85%] in favour of CSII, with a reduction of 1.2%. In studies of crossover design, this difference was -0.4% units [WMD -0.4 (95% CI: -0.68 to -0.07) I^2 = 52%].

On the other hand, the meta-analysis by Cummins *et al*.[264] found no significant differences in the control of HbA_{1c} in users of the CSII therapy *vs*. MDI users, being the WMD -0.64% (-1.28 to 0.01) after 4 months, -0.26% (-0.57 to 0.05) after 6 months, and -0.61% (-1.29 to 0.07) after 12 months. — SR of RCT 1++

A more recent review[265] presented a meta-analysis of studies in adults and identified an HbA_{1c} level slightly lower in CSII users than with MDI [WMD -0.18% (95% CI: -0.27 to -0.10)]. — SR of RCT 1++

In another SR[266], in studies that included participants aged above 18 years[267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280] the mean difference of HbA_{1c} was -0.3% (95% CI: -0.5 to -0.1) in favour of CSII compared with MDI. — SR of RCT 1++

A before and after designed study carried out within our health environment[281], which included 20 patients with DM1 analyzed the effect after CSII therapy *vs*. the previous situation, where they received intensive therapy, found a better metabolic control (reduction in the incidence of symptomatic hypoglycaemia, improvements in HbA_{1c} levels [mean (SD) 7.99 (0.76) *vs*. 7.19 (0.51), p = 0.001], and improved lipid profile without changes in weight and with less insulin requirements. The patients' satisfaction was higher with CSII. — Quasi-experimental study 1-

A multicentre, controlled and randomized study[282] analyzed the effectiveness of the CSII therapy with sensors (n = 244) *vs*. MDI (n = 241) and found, after a one year follow-up, a significant decrease from an 83% of HbA_{1c} at basal level in both groups to 7.5% in the pump therapy group and 8.1% in the MDI group. — RCT 1+

Total insulin requirements

The meta-analysis by Cummins *et al*.[264], with data from 4 studies found a significant reduction in mean insulin dose in CSII users compared to MDI [WMD UI -11.90 (-18.16 to -5, 63)]; a statistically significant difference. — SR of RCT 1++

In the meta-analysis by Reitler *et al*.[235] of the 14 studies that examined the effects of CSII on insulin requirements, 7 found that these were significantly lower in patients treated with CSII than with MDI on a daily basis. — SR of RCT 1++

An RCT[283] found that the total insulin requirement at the end of the study was lower in the CSII group than in the MDI group [mean (SD) 36.2 (11.5) IU/day *vs*. 42.6 (15.5) IU/day]. — RCT 1+

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

Hypoglycaemias

In the meta-analysis by Jeitler *et al*.[235] the number of overall hypoglycaemia events was similar: range from 0.9 to 3.1 episodes/patient/week in the group treated with CSII, and 1.1 to 3.3 in the group treated with MDI; the median weekly episodes was 1.9 and 1.7, respectively. SR of RCT 1++

Cummins *et al*.[264] found 8 RCTs published between 2002 and 2007 that examined the number of episodes of hypoglycaemia. The RCT by Doyle *et. al* [284] found a statistically significant difference in favour of the group treated with CSII *vs*. the group treated with MDI. SR of RCT 1++

A systematic review[265] with meta-analysis found no significant differences in severe hypoglycaemia [OR 0.48 (95% CI: 0.23 to 1)], nocturnal hypoglycaemia [OR 0.82 (95% CI 0.33 to 2.03)] or mild hypoglycaemia [OR -0.08 (95% CI -0.21 to 0.06)]. SR of RCT 1++

In another SR[266] 23 studies that randomized 976 participants with DM1of all ages to treatment with CSII or MDI were included. No obvious differences were observed between the interventions in relation to non-severe hypoglycaemia, but severe hypoglycaemia seemed to be reduced among patients assigned to the treatment with CSII. SR of RCT 1++

Other adverse effects

The available evidence on the adverse effects of CSII is generally scarce and of poor quality.

In reviewing Jeitler *et al*.[235], only 4 of the 22 studies included information on serious adverse effects other than hypoglycaemia and not related to diabetes or its treatment. Incidence rates were generally low: in 2 studies[279; 285] no serious adverse effects were observed and in another study[286] only one severe adverse event (ketoacidosis) was reported in the intervention group with CSII. Another team[287] reported 15 severe adverse events (ketoacidosis) in the group treated with MDI, as compared to 20 events in the CSII group. SR of RCT 1++

Of 10 studies that provided information on episodes of ketoacidosis, only one[274] found a significant difference between the treatments, with the highest incidence of ketoacidosis in the group using MDI. The methodological quality of this study was low, so the results should be considered with caution.

Four studies[278, 285, 287, 275] analyzed the problems at the site of injection, which were more frequent in patients treated with CSII.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

Quality of Life

The systematic review by Barnard *et al*.[288] analyzed the effect of the use of CSII in the quality of life of patients with DM1. Of the two RCTs involving adult patients, one study found moderate gains in quality of life[268], although there was a high dropout rate and the other study found no significant differences[280].

SR of RCT 1++

Cummins *et al*. found two studies published between 2002 and 2007[284, 289]; none of them showed significant differences in quality of life between the treatments.

SR of RCT 1++

In the SR by Misso *et al*.[266], the measures of quality of life showed better results with CSII than with MDI.

SR of RCT 1++

Costs

According to a study carried out in the Spanish context[290], the average cost of the treatment with CSII was € 25,523 per treated patient, considering data from 2005. A cost-utility analysis indicates that although the CSII is a more expensive technology than MDI, it is a bit more effective than MDI (assuming a gain control base of HbA_{1c} of -0.51% in favour of the CSII therapies) with a cost/utility incremental ratio of 29,947 €/QALY.

Economic evaluation (cost-utility analysis)

Summary of evidence

Adults

SR of RCT 1 + + RCT 1 +	For adults with diabetes mellitus type 1, four systematic reviews[235; 265; 266; 291], an RCT[282] and a quasi-experimental study[281] found a significant improvement of metabolic control with the continuous subcutaneous insulin infusion pump therapy (CSII or insulin pump) *vs*. the multiple dose insulin injection therapy. However, a systematic review[264] has not shown significant differences between the treatments.
SR of RCT 1 + + RCT 1 +	The treatment with continuous subcutaneous insulin infusion pump (CSII or insulin pump) decreases the total requirements of insulin compared to the multiple dose insulin injection therapy in adults with diabetes mellitus type 1[235, 264, 283].
SR of RCT 1 + +	The rate of hypoglycaemia is similar using the continuous subcutaneous insulin infusion pump therapy (CSII or insulin pump) or the multiple dose insulin injection therapy in adults with diabetes mellitus type 1[235, 264, 265, 266, 267, 284].
SR of RCT 1 + +	The evidence comparing the quality of life of the treatment with continuous subcutaneous infusion insulin pump (CSII or insulin pump) vs. the multiple dose insulin injection therapy does not provide conclusive results in adults with diabetes mellitus type 1[266, 284, 289].

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

8.5.2. Children and adolescents

Metabolic Control

An RCT[292] (n = 30), which compared the efficacy of CSII *vs*. the therapy with MDI in children and adolescents with newly diagnosed DM1, found lower levels of HbA_{1c} with the CSII therapy after 2 years of follow up. RCT 1+

Another RCT[293] compared the effectiveness CSII *vs*. MDI once a day, in 14 young people with newly diagnosed DM1 during the first 28 to 62 days of treatment. During the intervention period, the treatment with CSII was associated with lower levels of HbA_{1c} [mean (SD) 10.9 (0.6%) *vs*. 14.6 (0.7%), P <0.005], lower fasting blood glucose levels and glycosuria, but at the end of the intervention period this difference persisted only statistically significant in HbA_{1c} levels. RCT 1+

In an RCT with young people aged 13 to 19 years [294] no differences in HbA_{1c} levels were found 1 year after the onset of the treatment with CSII, compared with the insulin injection therapy 1 or 2 times a day (n = 14). RCT 1+

The meta-analysis by Fatourechi *et al*.[265] did not find, in children, a statistically significant difference in the levels of HbA_{1c} [WMD -0.20% (95% CI: -0.43 to 0.03)] between those using CSII or MDI. SR of RCT 1++

In the RCT by Doyle *et al*.[284], no significant differences were found in HbA_{1c} levels [8.1% *vs*. 7.2% (p <0.05)] between the group treated with CSII *vs*. the group treated with MDI. RCT 1+

The Opipari-Arrigan *et al*.[295] study in children aged around 4.5 years, found no significant differences between the group treated with CSII *vs*. the group treated with MDI. RCT 1+

An RCT in young children with an average age of 4 years[296] found that HbA_{1c} levels were not different in children treated with CSII *vs*. those children receiving the MDI therapy (7.9 *vs*. 7.7%). RCT 1+

In an SR[266], from studies that included participants under 18 years[284, 297, 298, 299, 300, 301, 302], the mean difference in HbA_{1c} levels was -0.2% (95% CI: -0.4 to -0.03) in favour of the CSII therapy, compared with MDI. SR of RCT 1++

Insulin requirements

Three studies [284, 303, 296] found that insulin requirements were lower in patients treated with CSII; the result was statistically significant in two of them, including adolescent patients. RCT 1+

Hypoglycaemia

The review by Fatourechi *et al*.[265] performed a meta-analysis of parallel designed RCTs in children and found a significantly higher rate in CSII users [WMD 0.68 (95% CI: 0.16 to 1.20), p = 0, 03)]. SR of RCT 1++

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

A meta-analysis of RCTs of crossover design, in adolescents and adults[267], showed no significant differences in episodes of mild hypoglycaemia per week among CSII and MDI users. SR of RCT 1++

Quality of Life

Three RCTs carried out in children found no significant differences between the treatments[296, 304, 305], while 2 RCTs[271;301] did find significant differences in favour of the CSII therapy. RCT 1+

Summary of evidence

Children and adolescents

SR of RCT 1 + + RCT 1 +	The results of studies in children and adolescents with diabetes mellitus type 1 do not provide conclusive information on the effects of the treatment with continuous subcutaneous insulin infusion pump in relation to metabolic control, hypoglycaemias and quality of life compared with the multiple daily insulin injections treatment[265, 266, 284, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302].

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

8.5.3. Pregnant women

Three systematic reviews examined the use of CSII *vs*. the conventional intensive therapy in pregnant women: a review by Farrar *et al*.[306], the Nosari *et al*.[307] study, which included 31 women with DM1 (32 pregnancies) and the Card *et al*.[308] study, which included 15 women with DM1 and 14 with DM2.

SR of RCT
1++

The SR by Farrar *et al*.[306], which included two systematic reviews indicated that no significant differences have been demonstrated in perinatal mortality [RR 2 (95% CI 0.20 to 19.91)], in foetal abnormalities [RR 1.07 (95% CI 0.07 to 15.54)], in maternal hypoglycaemia [RR 3 (95% CI 0.35 to 25.87)] or maternal hyperglycaemia [RR 7 (95% CI 0.39 to 125.44)].

Summary of evidence

SR of RCT 1 + +	In pregnant women with diabetes mellitus type 1, the available evidence shows no differences between the treatment with continuous subcutaneous insulin infusion pump (CSII or insulin pump) *vs*. multiple daily insulin injections regarding perinatal mortality [RR 2 (95% CI: 0.20 to 19.91)], foetal abnormalities [RR 1.07 (95% CI 0.07 to 15.54)], maternal hypoglycaemia [RR 3 (95% CI 0.35 to 25.87)], maternal hyperglycaemia [RR 7 (95% CI 0.39 to 125.44)], or macrosomia rate [RR 3.20 (95% CI 0.14 to 72.62)][306, 307, 308].

Recommendations

√	The treatment with continuous subcutaneous insulin infusion pump is not a universal option for all patients with diabetes mellitus type 1, as candidates for this treatment must have a high level of diabetes education and have the support of a health team expert in this type of therapy. Therefore, to achieve greater profitability of the treatment, a proper selection of the candidate patients should be carried out, taking into account the metabolic control, the risk of acute complications acute and the higher cost.
A	The use of insulin pumps in patients with poor glycaemic control or disabling hypoglycaemias which have made invalid other conventional treatments (multiple dose insulin therapy) and which are able to achieve good adherence to the treatment, is recommended.
√	The HbA_{1c} level is not the only criterion to be considered when recommending the use of CSII treatment in pregnancy. This treatment option should be considered when a target less than 7% of HbA_{1c} level has not been achieved, after previously having optimized other aspects, integrating data from metabolic control, presence of difficult to manage hypoglycaemia, the quality of life of patients and the availability of the resource in the workplace.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

8.6. Methods of insulin administration in patients with diabetes mellitus type 1

The usual route of administration is subcutaneous insulin (SC), except in the case of diabetic decompensation, when intravenous (IV) is generally used with fast acting insulin and with less frequency, intramuscularly (IM). Administration may be by disposable syringes or pre-filled pens.

It is of interest to know whether the use of these methods of administration may result in different health outcomes and to examine the patients' preferences regarding these alternatives.

8.6.1. Disposable syringe *vs*. pre-filled pen

8.6.1.1. Adults

The CPG NICE 2004[7] provides the following evidence:

Metabolic Control

Five RCTs carried out with adult patients with DM1[309, 310, 311, 312, 313] found no significant differences between patients using disposable syringes or pre-filled pens, in relation to HbA_{1c}, glucose profiles (except in blood glucose levels before dinner, which were significantly lower in the group with the pen in the study by Murray *et al*.), or in relation to the episodes of hypoglycaemia.

RCT
1+

Acceptability and patient preferences

The CPG NICE 2004[7] included 6 RCTs of crossover design[310, 311, 312, 313, 314], which analyzed the patients' preferences regarding injection techniques and found greater preference for prefilled pens vs. disposable syringes (range of percentage of patients who preferred prefilled pens: 96-74%).

RCT
1 +

Two RCTs[315, 316] and an SR[317] confirmed the patients' preference for pre-filled pens *vs*. disposable syringes, with values of 82%, 70% and 75% of patients, respectively.

RCT
1 +
SR of RCT
1 + +

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

Another SR[318], which included 5 studies analyzed patients' adherence to insulin prefilled pens *vs*. insulin disposable syringes; hypoglycaemic episodes, visits to the emergency unit due to hypoglycaemia, and the costs associated with diabetes and health care. The results stated that there was greater adherence to the treatment with insulin pre-filled pens than with syringes. In addition, with the use of pen devices, the consumption of healthcare resources and costs decreased.

SR of RCT
1++

A study carried out with 79 patients who had difficulties to self-administer insulin[315] found a higher percentage of patients who could self-administer insulin without help from caregivers or nurses with prefilled pens than syringes (53% *vs*. 20%).

RCT
1+

Costs

An economic evaluation conducted in the Spanish context[319] carried out an analysis on how to minimise costs by assuming that the 3 systems compared (syringe, prefilled pen and prefilled syringe) were equally effective in controlling the level of blood sugar. The estimated average cost for insulin injection was € 0.383 with syringe, € 0.341 with pre-filled pen, and € 0.329 with prefilled syringe, resulting prefilled pens and syringes more efficient than syringes.

Economic analysis

A study in people with difficulties to self-administer [315] found that use of prefilled pens supposed savings because less insulin was wasted than with conventional syringes and assumed a lower cost associated with the time spent by nurses.

Economic analysis

8.6.1.2. Children and adolescents

The CPG NICE 2004[7] provides the following evidence:

Metabolic Control

The CPG NICE 2004[7] included an RCT[320] comparing prefilled pens *vs*. conventional syringes in 113 children and adolescents with DM1, aged between 8 and 18. This study showed no differences between the two systems in HbA_{1c} levels [mean (SD) 10.58 (2.4%) *vs*. 10.27 (2.6%)], in hypoglycaemic episodes or unacceptably high levels of blood glucose.

RCT
1+

Another study carried out with 20 children and adolescents with DM1, and aged between 8 and 19 years[321], compared some specific prefilled pens (Novopen II ®) *vs*. standard syringes, and found no differences between the treatments regarding the risk of nocturnal hypoglycaemia.

RCT
1+

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

Acceptability and patient preferences

The CPG NICE 2004[7] included an RCT[320] that compared the preferences of children with DM1 between using the conventional syringe and the prefilled pen, and found that 99.5% of the participants in the study preferred the prefilled pens versus the conventional syringe. RCT 1+

In another study[321] all participating children (n = 20) showed preference for the prefilled pen against the conventional syringe. RCT 1+

8.6.2. Comparison of pre-filled pens

In the unblinded study of crossover design by Valk *et al*.[322], prefilled pens were compared for 6 months (Innovo ® and NovoPen 3 ®) and no significant differences were found between the two options in terms of HbA_{1c} levels, blood glucose levels, hypoglycaemia episodes or adverse effects. RCT 1+

Summary of evidence

RCT 1 +	The available evidence shows no differences in effectiveness or safety between the prefilled pens and syringes in children and adults with diabetes mellitus type 1 [309, 310, 311, 312, 313, 320, 321]. From the perspective of the patient preferences, evidence shows a greater predilection of patients for the pens rather than syringes[187, 311, 312, 313, 314, 320, 321].

Recommendations

A	The use of pre-filled pens is recommended because they can encourage adherence to the treatment, but it will be the patient who decides on the administration system used.

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8.7. Insulin administration techniques

There is consensus regarding the best route of administration of insulin being the subcutaneous (SC). However, many factors can affect the subcutaneous absorption of insulin: type of insulin, patient gender, body mass index, morphology and abdominal fat distribution, site of injection, subcutaneous tissue thickness of the target area and the injection technique. Other factors to consider are the presence or absence of lipodystrophy, insulin injection volume, temperature of the site of injection, taking vasoconstrictor or vasodilator medication and the existence of muscle contraction underlying the injection area[323].

8.7.1. Administration site: injection site

The systematic review conducted for the CPG NICE 2004[7] included several RCTs[324, 325, 326, 327] that analyzed the relationship between the injection site of insulin and its effects. All these studies were carried out in adults; no study was found in children, adolescents and pregnant women. — SR of RCT 1++

A working group composed of 127 experts from around the world[328, 329] developed an SR that included 157 experimental and observational studies, with recommendations on injection in diabetic patients — SR of RCT 1++/2++

Results on insulin absorption

A small observational study (n = 7)[325] found a significantly higher rate of insulin absorption and speed of insulin absorption in injections administered in the abdomen, intermediate in the arm, and lower in the thigh against arm or thigh, in this order. — Observational study 2+

Results on glycaemic control

Three studies examined blood glucose levels and found that levels were lower when the injection was made in the abdomen[325, 326, 327]. — RCT 1+

An RCT with 35 adults who were followed up for 3 months[324] observed that there were variations of glycaemia and episodes of nocturnal hypoglycaemia significantly more common in people who were administered insulin in the thigh *vs*. those who had been administered insulin in the abdomen. — RCT 1+

A group of 40 experts[330] proposed, based on the evidence from observational studies, the following recommendations for the administration of insulin, depending on the type of insulin and the timing of administration: — Observational studies 2+

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Table 3. Site of subcutaneous administration of insulin according to the type and timing of insulin administration [330]

Insulin type	When	Where	Why
NPH, lente or ultralente	Anytime	Thigh or buttock	Longer and more stable action
Fast-acting insulin	Anytime	Abdomen	Faster action
Combination of regular and NPH insulin (or slow or ultralente)	In the morning	Abdomen	Increased importance of regular insulin action
Combination of regular and NPH insulin (or slow or ultralente)	In the afternoon or evening	Thigh or buttock	Increased importance of the action of long-acting insulin

Summary of evidence

Observational study 2 +	Insulin absorption speed varies depending on the injection site, being faster in the abdomen, intermediate in the arm and slower in the thigh[325].
Observational study 2 +	The percent of insulin absorption is greater in the abdomen than in other injection sites[326, 327, 325, 326, 327].

Recommendations

B	In patients with diabetes mellitus type 1 fast acting insulin injection is recommended in the abdomen in order to promote fast absorption, especially in cases of hyperglycaemic decompensation.

8.7.2. Rotation of injection points

An RCT of crossover design[326], which compared the administration of insulin by rotation of the injection sites (arm, abdomen and thigh) vs. injections only in the abdomen, in 12 patients with DM1, found higher mean levels of glucose [mean (SD) 66.6 (5.4) *vs.* 48.6 (3.6) mg/dl, p <0.001) and higher mean variation in the levels of blood glucose [mean (SD) 313.2 (29.6) *vs.* 165.6 (18) mg/dl, p <0.001) in patients who rotated the injection sites than those who injected only in the abdomen. RCT 1+

An RCT[331] found that the rotation of the injection site is a good method to avoid lipodystrophy and hypertrophy, which may limit the absorption of insulin. RCT 1+

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Summary of evidence

RCT 1 +	The rotation of the insulin injection sites results in increased plasma glucose levels and higher mean change in plasma glucose level than having the injection always in the abdomen[326].
RCT 1 +	The rotation of the insulin injection site is a good way to keep the skin in good condition[326, 328, 329, 331].

Recommendations

A	Rotation in the insulin injection sites is recommended to prevent lipodystrophy.
A	It is recommended to change the insulin injections' area if the current site is affected by lipodystrophy, inflammation, oedema or infection.
√	Patients should be taught a rotation scheme of the different injection sites.
√	It is recommended to divide the area into quadrants and change the quadrant clockwise weekly.
√	The injections in each quadrant are to be spaced at least 1 cm in order to avoid repetition of tissue trauma.
√	The clinician should verify in each visit that the rotation scheme is being followed and advice should be offered when needed.

8.7.3. Injection technique (injection angle and skin fold)

A descriptive study[332] carried out in 14 patients with DM1 assessed the average thickness of subcutaneous fat and found great variability depending on the body areas and the people: in the abdomen the average thickness is 14 mm (range: 9.74 to 18, 26), in the lateral thigh the average thickness is 6 mm (range 2-19), in the upper thigh the average thickness is 8 mm (range 3-15 mm) and in the medial thigh the average thickness is 14 mm (range 4-25 mm).

Descriptive study 3

A descriptive study[330] indicated a reduced risk of injection into the muscle, and therefore of hypoglycaemia, if skin fold was performed with the thumb and index finger *vs*. the fold being performed with all the fingers.

Descriptive study 3

An RCT [333], which included 28 adults who were injected with insulin pre-filled pens and skin fold injection, compared the injection with 45° *vs*. 90º injection angles. No significant differences were found in levels of HbA_{1c}, fructosamine, in fasting insulin doses administered or the number of episodes of moderate and severe hypoglycaemia.

RCT 1+

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The Birkenbaek *et al* study[334] analyzed in 21 children (16 males) and 32 adults (23 males) the risk of intramuscular injection with 4 mm and 6 mm needles in thin patients. It was determined that it to inject in the subcutaneous tissue was achieved more frequently using 4 mm needles than 6 mm needles in the abdomen ($p = 0.032$) and thigh ($p = 0.001$), without using skin fold. The authors suggest that in the cases using 6 mm needles, a skin fold is made and used at an angle of 45°.

RCT 1+

Another study in thin men (BMI <25 kg/m^2)[335] determined that the injection angle of 90° with an 8 mm needle into the thigh often reaches muscle tissue. The injection applied perpendicular to the skin and without folds, with a 4 mm needle favours the subcutaneous administration of insulin.

RCT 1+

A trial in 72 children with DM1[336] assessed the injection in the abdomen and thigh with a 6 mm needle and skin fold and compared the angle at 90° vs. an angle of 45° With perpendicular injection and skin fold, muscle tissue was reached in 32% of individuals and in 22% in muscular fascia; with an injection at 45º and skin fold, insulin administration was always subcutaneous.

RCT 1+

Summary of evidence

RCT 1 +	In adult patients with diabetes mellitus type 1 metabolic control showed no differences if insulin injection is performed at 45º or 90º [333].
RCT 1 +	Thin people should use 4 mm needles, perpendicular to the skin and without skin fold to facilitate subcutaneous administration of insulin [334, 335]. When using 6 mm needle, it is better to use skin fold and at an angle of 45° [334].
RCT 1 +	In children with diabetes mellitus type 1, if using a 6 mm needle, the injection at an angle of 45º and skin fold favours the subcutaneous administration of insulin[336].

Recommendations

√	It is important to consider the preferences of patients with diabetes mellitus type 1 when assessing the most appropriate injection technique as this aspect can improve adherence to the treatment.
C	The skin fold must be made by grasping the thumb and forefinger in a clamp.
B	In thin people, when the injection is performed on limbs or abdomen with 4mm needles, it is advised not to use skin fold injecting perpendicularly in order to prevent potential intramuscular injections. If the needles are longer, it is advisable to inject with skin fold and at an angle of 45°.

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B	In thin people, injections with 6 mm needles have to be performed properly with skin fold and at an angle of 45°.
B	Adult patients with diabetes mellitus type 1 using 8 mm needles or greater have to raise a skin fold or apply a tilt angle of 45ºto avoid intramuscular injections.
A	In children and adolescents that use 6 mm needles, the injection is to be applied at an angle of 45° and with skin fold.
B	In children and adolescents that use 4 mm needles, the injection has to be applied at an inclination of 90°, without skin fold. For really thin people, skin fold may also be required.
√	If children or adolescents have only 8 mm needles (as is the case of those using syringes), the injection must be applied with skin fold and with an inclination of 45°.

8.7.4. Reusing needles

No RCTs or systematic reviews have been found on this topic.

Recommendations

√	It is recommended to change the needle at least every 3 or 4 uses, unless the user's skill allows using it more often without any pain.

8.7.5. Injection through the clothes

An RCT[337] compared the effect of the injection through clothing (with one layer of different tissues) *vs*. direct subcutaneous injection. This 20 week-long trial of crossover design, included 42 adults between 23 and 63 years of age and analyzed a total of 13,720 injections. The results showed no differences in HbA_{1c} levels, or in the frequency of problems during insulin administration between the two forms of injection. There were no cases of erythema, induration or abscess at the injection sites. The benefits reported by patients in the injection through the clothes were of greater convenience and time saving.

RCT
1+

Summary of evidence

RCT 1 +	The injection of insulin through clothing was not associated with an increased frequency of adverse effects or worse results in metabolic control than the direct subcutaneous injection[337].

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Recommendations

A	Although not considered optimal practice since it does not allow the correct elevation of skin fold or to visualize the site of injection, injecting insulin through a layer of fabric is not ruled out in specific situations.

8.7.6. Needle Size

A study in obese adult patients (BMI ≥ 30 kg/m^2) compared[338] the abdominal injection with short needles (31 gauge × 6 mm) *vs*. long needles (29 gauge × 12.7 mm) and found no differences in metabolic control [HbA_{1c} final mean (SD) 7.6% (1.20) for the short needles *vs*. 7.9% (1.54) for the long needles]. Regarding patients' preferences, short needles scored significantly better than the long ones. No differences were found regarding adverse effects.

RCT
1+

A trial published in 2010[339] compared the use of 4mm needles *vs*. 5 mm and 8 mm needles, in 168 adult patients with DM1 (37%) and DM2, and found no significant differences between both groups in terms of changes in fructosamine levels ($p = 0.878$) and HbA_{1c} ($p = 0.927$), or the occurrence of adverse effects. Patients with less pain reported to feel less pain with 4mm needles ($p < 0.005$) and preferred the 4mm needles rather than the 5 mm or 8 mm ones.

RCT
1+

Another study investigated the metabolic control[340], safety and patient preferences depending on the length of the needles in 52 patients. The patients of a first group used 5 mm needles during 13 weeks and then changed to longer needles (8 mm or 12 mm) during the same period. The second group followed the reverse order. The first group underwent a slight increase in the HbA_{1c} levels after changing from a short needle to a long one (baseline 7.67% 7.65% 13 weeks, 26 weeks 7.87%, $p < 0.05$). The second group showed no significant changes. No changes were found in the amounts of insulin administered, frequency or severity of hypoglycaemia, insulin or overflow between groups. 5 mm needles were significantly associated with less bleeding, erosion and pain ($p < 0.05$) and the patients reported a preference for them ($p < 0.05$).

RCT
1+

In order to assess the effects on glycaemic control when changing from a 12.7 mm needle to an 8 mm one in obese and non-obese patients, a prospective study was carried out in 106 patients[341] and found that obese patients, when changing the needle size from 12.7 mm to 8 mm suffered less pain. No significant differences were found between obese and non-obese patients in terms of metabolic control or insulin overflow.

Observational study
2+

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A trial[334] carried out in 56 patients with DM1 and slender build (21 children and 36 adults) compared the use of 4 mm needles *vs*. 6 mm needles for insulin injection in the abdomen and thigh injection without perpendicular skin fold. It was verified that a significantly higher number of patients who were injected with 4 mm needles did so in the subcutaneous tissue in the abdomen ($p < 0.032$) and thigh ($p < 0.001$), there were no differences in the frequency of insulin overflow.

RCT
1+

In normal weight children, 12.7 mm needles were compared with 8 mm needles and demonstrated that 8 mm needles reduce the risk of intramuscular injection by 58%, with no significant differences in insulin overflow[342].

RCT
1+

Summary of evidence

RCT 1 +	The 5 mm and 6 mm needles have proven effectiveness, safety and tolerability similar to the 8 mm and 12.7 mm ones, even in obese patients with diabetes mellitus type 1[334, 338, 339, 340, 341, 342].
RCT 1 +	There is no consistent evidence indicating more insulin leakage or worse metabolic control with short needles (4 mm, 5 mm, 6 mm)[340]. Moreover, they have been shown to produce less pain and are better accepted by patients with diabetes mellitus type 1[339].

Recommendations

A	In adults with diabetes mellitus type 1 4, 5 and 6 mm needles can be used even by people who are obese and do not generally require skin fold, in particular when using 4mm needles.
B	The is no medical reason to recommend needles longer than 8 mm. Initial therapy must begin with needles which are as short as possible.
A	The children and adolescents with diabetes mellitus type 1 have to use 4, 5 or 6 mm needles. Thin people or that are injected into a limp, have to increase skin fold, especially when using needles which are longer than 4 mm.
B	There are no medical reasons to recommend needles, which are longer than 6 mm in children and adolescents with diabetes mellitus type 1.
A	Children with normal weight using 8 mm needles must inject with skin fold and at an angle of 45°.

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8.8. Indications for the treatment with metformin added to insulin in adolescents with diabetes mellitus type 1

Metformin, biguanide used for over 40 years in the treatment of diabetes, mainly acts to reduce hepatic glucose production as well as insulin resistance in peripheral tissues. In adolescents with DM1, metabolic control is difficult, due to insulin resistance, eating habits, exercising, lower adherence to measurement and to dose adjustments.

Metabolic Control

In two RCTs with 27[343] and 26 patients respectively with DM1[344], a 2,000 mg/day coadjutant to insulin dose of metformin was administered. After 3 months of intervention, the decrease in HbA_{1c} levels was 0.9% in absolute terms in the Hamilton study and 0.6% in the Samblad study, versus placebo, in favour of the group treated with metformin.

RCT
1+

An SR[345] which included nine studies in which metformin was added to the insulin therapy compared with placebo or other treatment showed a reduction in insulin requirements (5.7 to 10.1 U/day in 6 of 7 studies) HbA_{1c} (0.6-0.9% in 4 of 6 studies), weight (1.7 to 6.0 kg in 3 of 6 studies and total cholesterol (0.3 to 0.41 mmol/l in 3 of 7 studies). Metformin treatment was well tolerated, although it showed more episodes of hypoglycaemia in these patients.

SR of RCT
1+

A medium quality SR that included two RCTs (60 adolescents with DM1)[346] indicated that metformin reduces HbA_{1c} in adolescents with DM1 with poor metabolic control.

SR of RCT
1++

Adverse Effects

In the study by Hamilton *et al*.[343], no significant differences were found in the occurrence of severe hypoglycaemia and gastrointestinal disturbances. Mild hypoglycaemia was more frequent in the metformin group than in the placebo group after 3 months of treatment [mean events per patient per week (DE) 1.75 (0.8) *vs*. 0.9 (0.4), P = 0.03].

RCT
1+

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

Summary of evidence

SR of RCT 1 + +	Although there are some studies in adolescents with diabetes mellitus type 1 and poor metabolic control that add metformin to the insulin treatment, and which show improved metabolic control, stronger evidence provided by larger studies is required to recommend this option[343, 344, 345, 346].

Recommendations

√	The widespread use of metformin associated to the insulin treatment in adolescent patients, although its use in some patients may improve glycaemic control, cannot be recommended.

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8.9. Pancreas and islet transplantation

The transplantation of pancreatic tissue, both the whole organ as well as isolated pancreatic islets, has become a therapeutic option to consider when treating patients with DM1.

8.9.1. Pancreas Transplantation

Mortality and graft survival

While mortality data vary depending on the surgical technique used and the patients' characteristics, as published in 2006[347], the survival rate after a pancreas transplant is between 95% and 97% per year, between 91 % and 92% after 3 years, and between 84% and 88% after 5 years. Most of the deaths are due to cardiovascular disease and usually occur within 3 years after discharge.

Descriptive Studies 3

The graft survival rates (defined as complete independence from insulin therapy with normal fasting glucose and normal or slightly high levels of HbA_{1c}) for simultaneous kidney and pancreas transplant are of 86% per year and 54% after 10 years. For isolated pancreatic transplantation, the rates are 80% per year and 27% after 10 years.

A retrospective cohort study[348] that included 11,572 participants showed no difference in mortality rates between the two groups[349, 350].

Cohort studies 2+

Metabolic Control

According to data provided by several observational studies[351, 352, 353, 354, 355, 356, 357, 358] pancreas transplants performed successfully restore the pancreatic function and lead to the independence of exogenous insulin therapy, normal blood sugar levels and normal or near-normal levels of HbA_{1c}. Patients with normally functioning grafts have normal responses to oral glucose overload and stimulation with intravenous glucagon.

Cohort studies 2+

The hormonal response to hypoglycaemia improves after a pancreas transplantation.[353, 359, 360].

Cohort studies 2+

Another observational study[360] stated that the recognition of symptoms of hypoglycaemia also improves after transplantation.

Cohort studies 2+

Studies as those carried out by Cottrell *et al*.[361] have described hypoglycaemia as a complication of pancreatic transplantation, but these episodes are usually mild[362].

Cohort studies 2+

Prospective and crossover studies have shown that improved metabolic control is maintained over many years. Several centres reported a persistent improvement over 15 years[356, 363, 364].

Descriptive studies 3

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Microvascular complications

After a simultaneous pancreas and kidney transplant, renal structure is normalized as shown by the decrease in mesangial mass in patients receiving kidney and pancreas transplantation *vs*. patients with kidney transplant alone[365, 366]. One study[367] described an improvement in non-transplant kidney structure after 10 years of follow up.

Cohort studies
2+

Several studies have described an improvement of driving speed in motor and sensory nerves and stabilization of the evolution of neuropathy[358, 368, 369, 370, 371, 372, 373].

Cohort studies
2+

Macrovascular

Combined pancreas and kidney transplant in patients with DM1 produces a greater reduction in cardiovascular risk than kidney transplant alone, which is associated with significantly better changes in metabolic control in postprandial levels of homocysteine and lower levels of the von Willebrand factor[374].

Descriptive
study
3

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

8.9.2 Pancreatic islet transplantation

Four SRs have analyzed the results of effectiveness and safety of pancreatic islet transplantation[129, 375, 376, 377]. This CPG will take into account the latest revision by Guo *et al*.[129], as it includes the three latest versions. This review includes 11 series of cases[378, 379, 380; 381, 382, 383, 384, 385, 386, 387, 388], with a total of 208 patients (mean age, 33-50 years), with follow-up periods ranging from 1 to 5 or 6 years.

SR of RCT
1++

Insulin independence: the percentage of people with good metabolic control without insulin in the 11 studies ranged from 30% above to 69% in the first year, from 14% to 33% in the second year and up to 7.5 %, five years after transplantation.

Case series
3

In the study by Edmonton with 7 patients with DM1[389] who were treated with transplantation and immunosuppressive drugs, all patients had normal HbA_{1c} levels without exogenous insulin after 1 year of follow-up.

In a 5-year follow-up of 65 patients with DM1[381] from the Edmonton program, 47 patients (72%) achieved insulin independence. The median of this independence was 15 months and only 10% remained insulin independent after 5 years. However, 80% showed C-peptide secretion and required half the dose of insulin they took before transplantation and showed lower blood glucose liability.

Hypoglycaemia: nine studies analyzed results for hypoglycaemia. All insulin independent patients were fully free of hypoglycaemia episodes. The hypoglycaemic episodes of insulin dependent patients were mild episodes.

Quality of life: Only two studies[388, 390] looked at the quality of life outcomes. Both studies showed reduced fear of hypoglycaemia after transplantation. However, the results were inconsistent in terms of total quality of life related to health.

Adverse effects: Islet transplantation is associated with complications related to the procedure and immunosuppression. None of these studies reported any preoperative or postoperative death as a direct result of the procedure.

However, there were 38 serious adverse events in 36 patients and 18 of them required hospitalization. Complications related to the procedure were mainly intraperitoneal bleeding (9% as mean, 23% in the study of Edmonton); the portal vein thrombosis, which in most cases was partial (described in 6 of the 11 studies percentages ranging between 6 and 17%) and liver abnormalities (described in 8 of the 11 studies, ranging from 10 to 100%).

Case series
3

More than 5 years have passed since the publication of the Clinical Practice Guideline, and its validity has not been reviewed

As for the adverse effects of immunosuppressive therapy, 7 of the 11 studies reported impairment of renal function from 17% to 50% of the patients, forcing regime change in immunosuppression between 10% and 37 % of the cases.

Other complications observed in an international multicenter study[227] were mouth sores (92%), anaemia (81%), leukopenia (75%), diarrhoea (64%), headache (56%), neutropenia (53%), nausea (50 %), vomiting (42%), and acne (39%).

8.9.3. Islet transplantation *vs*. intensive insulin therapy

A prospective observational study[391] the metabolic control of 44 patients who received intensive insulin therapy *vs*. 21 patients who received islet transplantation compared for 29 months, finding HbA_{1c} levels being significantly lower in the transplant group.

Observational studies 2+

8.9.4. Pancreatic islet transplantation *vs*. pancreas transplantation

In a retrospective case series[392] islet transplantation was compared with whole organ transplantation. In that study, 30 patients received pancreas transplantation and 13 patients islet transplantation; however, both groups were comparable in terms of poorly renal function (pancreas transplant group: 73% history of renal dialysis; islet transplantation group: 0%). There was no significant difference in survival between the two groups. Pancreas transplantation performed better in terms of C-peptide levels, HbA_{1c} and insulin requirement, but in this group negative results were also observed, such as longer hospital stays, higher readmission rates and increased postoperative morbidity.

Case series 3

Summary of evidence

Cohort study 2 +	The isolated pancreas transplantation and the simultaneous kidney and pancreas transplantation are effective for restoring endogenous insulin secretion, maintaining long-term glycaemic homeostasis and thereby prevent acute and chronic complications of diabetes, which improves the quality of life for people with diabetes mellitus type 1 relating to the fear of hypoglycaemia[351, 352, 353, 354, 355, 356, 357, 358].
Case series 3	Although islet transplantation appears to reduce short-term insulin needs, long-term effectiveness and its effects on diabetic complications[392] have not actually been proven.

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

Recommendations

B	Simultaneous transplantation of pancreas and kidney should be offered to young patients with diabetes mellitus type 1 (under 45), who are well informed and motivated, with ESRD and without cardiovascular risk factors.
B	The criteria for isolated pancreatic transplantation are: • Persistent failure in the insulin treatment in relation to glycaemic control and the prevention of complications. • Incapacitating clinical and emotional problems for insulin treatment.
C	Nowadays, islet transplantation is only recommended in the context of controlled trials.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

9. Management of diabetes mellitus type 1 in special situations

9.1. Insulin treatment guidelines during hospitalization of patients with diabetes mellitus type 1

Key question:

- What are the patterns of insulin therapy during hospitalization of patients with diabetes mellitus type 1: surgical patient, critically ill patient and stable patient?

Individuals with diabetes are a significant percentage of hospitalized patients, as they make up 30-40% of patients seen in emergency units, 25% of inpatients in both medical and surgical areas, and about 30 % of patients undergoing aorto-coronary bypass. This follows the increase in the prevalence of DM and associated comorbidity and diagnostic and therapeutic procedures that require hospitalization. In addition, patients with diabetes stay in the hospital an average of 1-3 days more than non-diabetics, and patients with hyperglycaemia on admission are more likely to require the use of the ICU.

Insulin requirements to keep blood sugar within acceptable limits during hospitalization vary markedly according to the changes in nutrient inputs (fasting or nutrient reduction, glucose IV, enteral or parenteral nutrition), counterregulatory hormone release in response to stress, or the use of drugs with hyperglycaemic effect. In critically ill patients, there is a metabolic overload situation by releasing a number of counter-regulatory hormones in response to stress, hyperglycaemia generating and activate metabolic pathways releasing amino acids and fatty acids, increasing the resistance of peripheral tissues to the action of insulin. Furthermore, in intensive care units these effects are enhanced by the administration of exogenous glucocorticoid adrenergic drugs. Moreover, critically ill patients have impaired ability to detect the symptoms of hypoglycaemia, which is especially dangerous.

In DM1 patients requiring hospitalization glycaemic control can be altered among other causes by the underlying disease that has led to the hospitalization, dietary and schedule changes, forced periods of fasting, testing, the at least partial immobilization, drugs with hyperglycaemic potential, psychological stress and the absolute loss of control over the administration of insulin. The latter can be variable depending on the area of hospitalization and how often staff deal with patients with DM1 and their knowledge. Not infrequently, is the insulinization pattern on demand, depending on glucose levels before each meal or every 4-6-8 hours (always below their previous requirements) and the inadequate supply of carbohydrates that cause large swings in blood glucose levels, prolonged stays and place patients at increased risk of infection. Therefore, it is essential to start up protocols for stable patients with treatment regimens depending on the most frequent variables, so that hospitalization for itself is not an added risk of diabetes control.

More than 5 years have passed since the publication of the Clinical Practice Guideline, and its validity has not been reviewed

9.1.1. Surgical Patient

The CPG NICE 2004[7] provides the following evidence in adult patients:

A cohort study[393] on patients with diabetes showed that blood glucose levels the same day of the operation and three days after surgery, were significantly lower ($p < 0.0001$) with the continuous intravenous infusion (IV) insulin compared with the subcutaneous insulin injection (SC). — Cohort Study 2+

Two trials compared IV insulin with the subcutaneous injection in minor[394] and major[395] surgical procedures and found that the median glucose may be reduced during the first day after surgery with the administration of IV insulin. Furthermore, the insulin/glucose ratio and the number of doses adjustments required were significantly lower in those receiving IV insulin compared with the group that used the subcutaneous route of insulin. — RCT 1+

Another study[396] compared two regimens of intravenous insulin in 58 consecutive patients requiring preoperative insulin infusions. Patients were randomized to an infusion of glucose-insulin-potassium (GIK) or a more complex protocol that required two insulin infusion pumps. Both methods gave similar results in terms of glycaemic control. However, the dual pump system had a higher percentage of patients with glycaemia within target ranges, both preoperatively (47.4% *vs*. 60.1%) as well as postoperative (52.0% *vs*. 66.4%). The length of stay (15 *vs*. 16 days), duration of infusion (15 *vs*. 16 hours) were similar for both groups. — RCT 1+

In a prospective cohort study[397] 3554 patients with hyperglycaemia who underwent cardiac surgery (coronary bypass graft) and who had been treated with either subcutaneous insulin or continuous infusion, were evaluated. The expected and observed mortality was compared using multivariate analysis models, showing a significantly lower mortality in patients with continuous infusion (2.5%) than those receiving subcutaneous insulin (5.3%, $P < 0.0001$). Glycaemic control was significantly better in the group with continuous infusion [mean (SD) 177 mg/dL (30) *vs*. 213 mg/dL (41), $P < 0.0001$]. — Cohort Study 2+

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SR of RCT
1++

The SR and meta-analysis by Gandhi *et al*.[398] evaluated the effects of insulin preoperative morbidity and mortality. 34 RCTs that assessed the effects of insulin infusion preoperatively in patients undergoing any surgery were included. The treatment groups were able to receive any type of intravenous insulin infusion (GIK, glucose and insulin, insulin alone). The control groups could receive insulin infusion, subcutaneous insulin therapy or other forms of standard glucose-specific value as long as this value was greater than that required for these interventions in the treatment group. This SR indicates that insulin infusion reduces mortality preoperative hypoglycaemia and increases in surgical patients. Total available mortality data represents only 40% of the optimal size of information required to identify a possible treatment effect. In the 14 RCTs that assessed mortality there were 68 deaths in 2,192 patients assigned to insulin infusion compared with 98 deaths in 2163 patients in the control group [RR 0.69 (95% CI: 0.51 to 0.94)] The risk of hypoglycaemia was higher in the intensive treatment group [RR 2.07 (95% CI 1.29 to 3.32)]. However, this study had methodological problems that weaken the inference of these results.

Summary of evidence

Cohort study 2 +	The continuous insulin infusion during and after surgery is related with lower blood sugar levels and lower mortality than the subcutaneous insulin injection[393 397, 398].
RCT 1 +	The administration of intravenous insulin in major and minor surgery allows achieving a lower insulin/glucose ratio and fewer adjustment doses in comparison with the subcutaneous[394, 395].

Recommendations

A	The system of continuous intravenous infusions of insulin is the ideal method to achieve good metabolic control and prevent complications such as metabolic acidosis or hypoglycaemia in patients with diabetes mellitus type 1 who are to undergo major and minor surgery.
√	Hospitals should ensure the existence of an appropriate protocol for surgery in patients with insulin-dependent diabetes. This protocol must ensure the maintenance of normoglycsemia levels through frequent glucose measurements that allow the adjustment of IV insulin without the risk of acute complications.

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9.1.2. Critical patient

The CPG NICE 2004[7] includes the following evidence on the management of critically ill patients with DM1:

An RCT conducted in 620 patients who had suffered an acute myocardial infarction (AMI), of which 20% had DM1[399], contrasted the effect of IV insulin and glucose infusion compared to a control group with conventional therapy. This study showed a lower incidence of cardiac death and reinfarction in patients receiving IV glucose-insulin infusion compared to controls after 3 months, one year and 3 and a half years of follow up. The HbA_{1C} levels decreased significantly in both groups, but this decrease was more significant in the group with IV insulin infusion after 3 months ($p < 0.0001$) and even after 3 years ($p < 0.05$).

RCT
1+

A randomized controlled trial in an elderly population with diabetes (19% DM1) who had suffered an AMI[400] compared IV insulin infusion during the first 24 hours of admission with conventional treatment, which allowed to observe a significant decrease in glucose levels in the IV infusion treatment group compared to the group with conventional treatment [mean (SD) 262.8 mg/dl (52.2) to 165.6 mg/dl (52.2) *vs*. 284.4 mg/dl (77.4) to 216 mg/dl (79.2) respectively, $p < 0.001$). Regarding the adverse effects in the IV infusion group, 28 patients (17%) experienced an episode of hypoglycaemia (glucose <54 mg/dl), whereas no patients in the control group underwent any experience ($p < 0.001$).

RCT
1+

Another RCT[401] carried out in patients with DM1 and DM2, compared IV insulin infusion following predefined decision algorithms against an undefined logical method. The latter method allows obtaining a lowering of blood glucose (below 180 mg/dl) in less time [mean (SD) 7. 8 hours (0.7) *vs*. 13.2 hours (1.5) $p < 0.02$] than the IV infusion one, probably by a greater number of dose adjustments.

RCT
1+

An RCT[402] conducted in 763 critically ill patients (4% with DM1 in the conventional treatment group and 5% in the intensive treatment group) showed that tight control of glucose (between 80 and 110 mg/dl) was associated with lower mortality 4.6% *vs*. 8% ($p < 0.05$) than in the group with conventional control. The morning blood glucose remained lower in the intensive treatment group than in the conventional treatment group [mean (SD) 103 (19) mg/dl *vs*. 153 (33) mg/dl, $P < 0.001$]. The difference in hypoglycaemic episodes was not significant.

RCT
1+

An observational study[403] found that the application of a protocol aimed to maintain blood glucose below 140 mg/dl in critically ill patients was associated with a reduction in mortality of 29.3% ($p < 0.02$) and reduced ICU stay of 10.3% ($p < 0.01$) without a significant increase in the risk of hypoglycaemia.

Prospective observational study
2+

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An SR with meta-analysis[404] analyzed 29 RCTs with a total of 8342 patients admitted to the ICU with different pathologies, which varied widely between the percentages of patients with diabetes. Hospital mortality remained unchanged in the control group with strict blood glucose *vs*. the group receiving usual care [21.6% *vs*. 23.3% (RR 95% CI: 0.85 to 1.03)]. No significant differences were observed when the glucose objectives were very strict (up to 110 mg/dl) or moderately strict (up to 150 mg/dl), or if the treatment was performed in a surgical, medical or surgical-medical ICU. Strict control was associated with a decreased risk of septicaemia [10.9% *vs*. 13.4% (RR 95% CI 0.59 to 0.97) and a significantly increased risk of hypoglycaemia (RR 95% CI: 4. 09 to 6.43).

SR of RCT
1+

In the NICE-SUGAR study[405], 3015 patients (50 of them with DM1) were treated with intensive IV insulin therapy with a glycaemic control target between 81 and 108 mg/dl and 3014 (42 of them with DM1) with conventional treatment, with a blood glucose target less than or equal to 180 mg/dl. In the control group, insulin was administered only in the case of blood glucose above 180 mg/dl, and the infusion was stopped if the glycaemia fell below 144 mg/dl. Mortality was significantly higher in the intensively treated group [OR 1.14 (95% CI: 1.02 to 1.28)], both in postsurgical patients as those with medical pathology. However, patients with DM1 showed no difference in mortality after 90 days. Severe hypoglycaemia (<40 mg/dl) occurred in 6.8% of patients treated intensively compared with 0.5% of those treated conservatively.

RCT
1+

Summary of evidence

SR of RCT 1 + + RCT 1 +	Preliminary studies in critically ill patients with diabetes mellitus type 1 showed greater glycaemic control resulted in better health outcomes[397, 402, 406]. However, subsequent studies have failed to reproduce these results and found that intensive insulin therapy to achieve normoglycaemia increases the risk of hypoglycaemia, whose appearance is an independent predictor of mortality[404, 407, 408]. In a clinical trial with a before and after design[403] found that the application of a protocol aimed at maintaining blood glucose between 80 and 110 mg/dl in critically ill patients was associated with a reduction in mortality, morbidity and ICU stay with no significant increase in the risk of hypoglycaemia.

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

Recommendations

A	In the case of critical patients with persistent hyperglycaemia, the treatment must start with a threshold of no greater than 180 mg/dl (10 mmol/l). Once treatment has begun, glycaemic targets must be set in a range between 140-180 mg/dl (7.8 to 10 mmol/l) for the most critically ill patients.
√	It is necessary to establish a safe and effective protocol to achieve an adequate blood glucose range without an increase in severe hypoglycaemic episodes.

9.1.3. Stable patient

The CPG NICE 2004[7] provides no evidence on this issue.

In the RABBIT 2 study[409] the use of a basal-bolus regimen achieved better glycaemic control than the *sliding scale* or fast acting insulin scale administered every 6 hours in patients without previous insulin treatment. In this study, the mean blood glucose during hospitalization was lower [mean (SD): 166 (32) *vs*. 193 (54) mg/dl] and the percentage of patients achieving the blood glucose target less than 140 mg/dl was higher (66 *vs*. 38%) with the basal-bolus regimen than with the standard *sliding scale*, without increasing the incidence of hypoglycaemia (p <0.05). This study was conducted in patients with type 2 diabetes and has been taken into account in this CPG as a source of indirect evidence for patients with DM1.

RCT
1+

During hospitalization of a stable patient, the *American Diabetes Association*[410] considers reasonable basal glucose targets under 128 mg/dl and postprandial glucose less than 180-200 mg/dl if achieved safely.

CPG
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The consensus document of the SED[411] recommends that, while waiting for further evidence, the blood glucose target during hospitalization should be that of normoglycaemia.

Expert consensus
4

Summary of evidence

Expert consensus 4	During hospitalization of stable patients with DM1, the targets for glycaemia should be similar to those of patients with diabetes who are not hospitalized[409, 410, 411].
RCT 1 +	The use of a basal-bolus regimen achieved better glycaemic control than the *sliding scale* or fast acting insulin regimens administered every 6 hours in patients without previous insulin treatment[409].

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Recommendations

√	All patients with diabetes admitted to a health centre should have this diagnosis clearly identified in their medical history.
√	All patients with diabetes should have blood glucose levels monitored and this information should be available to the healthcare team.
B	Monitoring should be initiated in any known non-diabetic patient who is administered any treatment with a high risk of hyperglycaemia, including high doses of glucocorticoids, initiation of enteral or parenteral nutrition or other medications such as octreotide or immunosuppresives.
√	If hyperglycaemia is identified and persistent, treatment is needed. These patients should be treated with the same glycaemic targets as those applied for patients with known diabetes.
√	A hypoglycaemia treatment plan should be set out for each patient. All episodes of hypoglycaemia in the hospital should be registered.
√	All patients admitted to hospital have an HbA$_{1c}$ level determination if data is not available for the 2-3 months prior to admission.
√	Patients with hyperglycaemia in the hospital with no prior accurate diagnosis of diabetes should have a protocol for diagnosis and monitoring of care at discharge.

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9.2. Preventive and treatment measures in the case of outpatient acute intercurrent diseases in patients with diabetes mellitus type 1

Key question:

- What are the preventive measures and treatment for outpatient acute intercurrent diseases?

Intercurrent diseases in DM1 patients can affect insulin requirements because they may be associated with a lower caloric intake due to decreased appetite, loss of nutrients by vomiting and/or diarrhoea and a variable increase of the counterregulatory hormones caused by the stress of the disease.

The diseases associated with fever tend to increase glucose levels due to the hormones stress level, causing an increase to insulin resistance and an increase in glycogenolysis and gluconeogenesis, which increases the risk of ketoacidosis. Associated diseases that present vomiting and diarrhoea may result in reducing blood glucose levels and thus in an increased risk of hypoglycaemia.

Decreasing calories by decreasing input (anorexia) or increased losses (vomiting) may cause hypoglycaemia. In older children, especially at puberty, a stressful disease is characterized by a relative insulin and hyperglycaemia deficiency.

Adults

The CPG NICE 2004[7] provides no evidence on this issue but has published recommendations based on consensus, just as the document of the *American Diabetes Association*[51] and the CPG of the Australian Government[412].

Expert consensus 4

While the most common problems in patients with diabetes mellitus type 1 associated with intercurrent diseases are hyperglycaemia and risk of ketoacidotic decompensation, found no relevant studies about adults. The evidence refers primarily to the management of hypoglycaemia and this is summarized in the corresponding section of this CPG.

Children and adolescents

The CPG NICE 2004[7] provides no evidence on this issue.

The ISPAD consensus guide from year 2009[413] offers the following recommendations:

CPG consensus 4

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

- The medical team responsible for the patient must provide patients and families clear recommendations on the management of the disease when there are intercurrent diseases in order to avoid complications such as:
    - Ketoacidosis.
    - Dehydration.
    - Uncontrolled or symptomatic hyperglycaemia.
    - Hypoglycaemia.
- Must never cease the administration of insulin.
- The dose of insulin is to be increased or decreased depending on the requirements.
- When a child with diabetes vomits, this must always be considered an insulin deficiency until proven otherwise.
- A child with intercurrent disease must be requested with urgent health consultation in the following cases:
    - When the underlying condition is not clear.
    - When weight loss continuous, suggesting a worsening in dehydration.
    - When the vomiting persists for two hours (especially in small children).
    - When glucose continues to increase despite the extra administration of insulin.
    - When parents are unable to maintain blood glucose above 60 mg/dl (3.5 mmol/l).
    - When ketonuria increases or continues being high or when the ketonemia is> 1 to 1.5 mmol/l.
    - When the child is very tired, confused, hypervigilant, dehydrated or has abdominal pain.
    - When the child is very young (under 2 or 3 years) or has an illness other than diabetes.
    - When patients or relatives are exhausted, for example, by the night waking.
    - When language problems make it difficult to communicate with the family, the possibility of going to the hospital emergency unit should be considered if the situation does not improve quickly or if professional advice can be provided.
    - When the level of ketonemia is 3 mmol/l there is an immediate risk of ketoacidosis, being therefore insulin treatment urgently required and a consultation with the emergency services should be considered.

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An Australian CPG[412] has proposed the following recommendations: CPG

- Families must be informed that intercurrent diseases can cause very high or very low blood glucose levels [Strength of recommendation: D].
- All families are to receive education about managing diabetes in days of disease and must have at reach the kit including fast/ultra-fast acting insulin, glucose test capillary strips, lancets, glucose test strips or urine ketones or blood ketone test strips, telephone of the doctor or reference hospital, refreshments/juice fruit/lemonade or other similar beverages, glucagon, emergency guides or diabetes manuals, thermometer, and paracetamol or ibuprofen [Strength of recommendation: D].
- Insulin is never to be omitted, even if the patient is not able to eat [Strength of recommendation: D].
- Blood glucose and ketones are to be monitored regularly [D].
- Any disease that is identified, should be treated immediately to [Strength of recommendation: D].
- Taking additional oral fluids should be encouraged, especially if the blood glucose is high or ketones are present [Strength of recommendation: D].
- Additional boluses of rapid/ultra-fast acting insulin should be provided in an amount equal or greater than 10-20% of the total daily dose, every 2-4 hours if blood glucose level is high or ketones are present [Strength of recommendation: D].
- Parents/caregivers must offer assistance immediately if, after administering the extra insulin boluses, blood glucose stays high, ketones persist, nausea, vomiting or abdominal pain appear [Strength of recommendation: D].
- Severe hypoglycaemia is to be treated with intravenous dextrose (in the hospital setting)[414, 415] [Strength of recommendation: A].
- If venous access is difficult or if the patient is outside the hospital setting, intramuscular glucagon is to be used to treat severe hypoglycaemia [Strength of recommendation: D].
- Under the supervision of a physician or a diabetes educator, small doses of subcutaneous glucagon can be administered to prevent or treat mean hypoglycaemia within outpatient settings[416] [Strength of recommendation: B].

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Document from the *American Diabetes Association*[417]

- The goals of disease management are the prevention and early treatment of hypoglycaemia, significant hyperglycaemia, ketosis and the prevention of acute ketoacidosis.
- The management of the days of disease requires frequent blood glucose and ketone levels in urine (or blood) monitoring, food and fluids intake monitoring and supervision by an adult.
- A child can never be left in charge of the management of a day of disease, thus being the implication of parents necessary and providing a contact telephone with the doctor.
- The child's primary care physician must assess not only diabetes but also intercurrent diseases.
- The effects of the disease on insulin requirements are variable. The lack of appetite represents a decrease of calories intake, and in addition, the presence of vomits or diarrhoea may lead to a reduction of insulin needs. Furthermore, the stress of the disease can lead to increased counterregulatory hormones, resulting in an increased need for insulin. In very small children (<6 years), in which the fast regulatory responses may not be well developed, the decrease in calories intake and the excess of the action of insulin may cause hypoglycaemia. However, in older children, particularly at puberty, a stressful disease is characterized by a relative insulin and hyperglycaemia deficiency.
- Regular monitoring can help to determine the action to be preformed. Ketones have to be monitored regardless of the level of blood glucose, as acidosis can occur without elevated glucose levels, especially if oral intake is poor.
- Children with nauseas or vomits, may take sugary liquids and small doses of glucagon. If vomits persist, and if treatment at home fails to correct hypoglycaemia, hyperglycaemia or significant ketoacidosis, it will be necessary to go to the emergency unit.

Consensus
CPG
4

Summary of evidence

Expert consensus 4	No scientific evidence has been found related to the management of diabetes mellitus type 1 with intercurrent diseases. The recommendations are based primarily on consensus of leading scientific institutions.

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Recommendations

D	People with diabetes mellitus type 1 and/or their families or carers should be informed that intercurrent diseases could cause hyperglycaemia. They can also lead to ketosis and hypoglycaemia, the latter being more common in children under 6 years.
D	All people with diabetes mellitus type 1 and/or their families or carers have to be educated about disease management in case of intercurrent disease and should have at reach fast acting insulin, glucose test strips, blood glucose test strips, lancets, strips and meters for the measurement of ketones in the blood or urine, refreshments/fruit juice/lemonade or other drinks alike, know how to use glucagon, a thermometer, paracetamol or ibuprofen, emergency guides or diabetes manuals and a contact telephone of their doctor or the hospital.
D	The administration of insulin should never be omitted, even if the patient is not able to eat.
D	Blood glucose and ketone bodies in urine (ketonuria) or blood (ketonemia) must be monitored frequently.
D	Any illness must be treated immediately.
D	Oral intake of extra liquids should be encouraged, especially if blood glucose is high or there are ketones.
D	Additional fast acting insulin boluses should be provided in an amount, which is the same or greater than 10-20% of the total daily dose, every 2-4 hours if the blood glucose is high or ketones are present.
D	Patients/carers must immediately seek medical help if after the extra insulin boluses, blood glucose stays high, ketone bodies persist, nausea or vomiting or abdominal pain appear.
D	Small children may be administered small subcutaneous doses of glucagon to prevent or treat hypoglycaemia. For severe hypoglycaemia, intramuscular glucagon is recommended. Treatment with intravenous glucose should be performed within the hospital setting.

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9.3. Psychological disorders in patients with diabetes mellitus type 1

Key question:

- Are psychological disorders more common in people with diabetes mellitus type 1?

Diabetes is considered a possible trigger of psychological disorders. It is interesting to determine the prevalence of these problems in patients with DM1 in order to improve their health.

9.3.1. Affective disorders

The CPG NICE 2004 provides the following evidence[7]:

In a case-control study[418], a significantly higher number of patients with DM (12.8%) than those without DM (7.4%) were treated with antidepressants during the 12 months preceding the study [OR 1.59 (95% CI 1.43 to 1.76)].	Case control study 2+
In a prevalence study SR[419] the presence of depression in patients with DM1 recorded was 21.7% compared to 8.6% in non-diabetic control patients [OR 2.9 (95% CI: 1.6 to 5, 5)].	SR of descriptive studies 3
Barnard *et al*. 420 conducted a prevalence study SR in adults that included 14 studies. The prevalence of depression found in the studies with the control group was 12% in people with DM1 and 3.2% in the people without diabetes.	SR of descriptive studies 3
The *Kaneer et al*. SR[421] included four observational studies in children and adolescents, indicating that the prevalence of depressive symptom pathology is higher in people with DM1 compared with a control group with a prevalence of 12% in children aged 8-12 years and 18% in adolescents that is 2-3 times higher than in people of the same age without DM.	SR of descriptive studies 3
Kessing *et al*.[422] compared the risk of developing depression in a sample of individuals with DM1 and DM2 (n = 91,507) versus a group of patients with other chronic diseases such as osteoarthritis (n = 108,407). No significant differences were demonstrated in the risk of developing severe forms of depression between both chronic diseases (p = 0.07).	Descriptive study 3

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Other descriptive studies found significant differences among people with diabetes compared to the general population, although there was variability in the prevalence rates of depression found: 5.8% *vs*. 2.7% (p = 0.003) 423; moderate/severe depressive symptoms 6% *vs*. 3% (p = 0.04) 424; 12.6% *vs*. clinical depression 6.3% 425, in the Al-Ghamdi study426 34% *vs*. 13% (p = 0.04) and in the Khamseh study 427 64% *vs*. 36% (p = 0.0001).

Descriptive study 3

The retrospective study by Ali *et al*.[428] aimed to examine the prevalence of depression in people with diabetes and the differences among ethnic groups in risk factors for depression diagnosis using multivariate logistic regression. The results showed that among people with DM1 (n = 1405) the prevalence of depression was 7.3 to 11.3%, and found no significant differences between ethnic groups (10% of South-Asians *vs*. 7.9%, of Europeans, P = 0.355), which is consistent with previous literature showing similar prevalence rates. Furthermore, the prevalence rate was higher in women (females 11% *vs*. males 5.8%, P <0.001), also consistent with previous literature. Similarly, the prevalence was significantly higher in patients with other comorbidities (12% *vs*. 6.6% without them, P = 0.02) and in those patients who had complications associated with diabetes (9.4% *vs*. 6%; p = 0.021). There were no significant differences in age (up to 59 years 7.8% *vs*. over 60 years 9%, P = 0.460); years of diabetes duration (between 0 and 5 years: 8.8%, between 6 and 14 years: 6.9% over 15 years: 8.1%, P = 0.663) or by HbA_{1c} levels (HbA_{1c} > 7%: 8.6%; HbA_{1c} < 7%: 5.1 %, P = 0.101).

Descriptive study 3

Summary of evidence

Descriptive studies 3	DM1 is associated with higher rates of depressions than among the general population, regardless of age, race and the evolution of DM1, but not higher than other populations with chronic diseases[420; 421, 423, 424, 425, 426, 427].
Descriptive study 3	The presence of depression is associated with the presence of other diseases and the presence of diabetes-associated complications[422].

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9.3.2. Anxiety disorders

A descriptive study[423] showed no significant differences in the prevalence of anxiety in newly diagnosed patients compared to a reference population (7.7% *vs*. 9.5%, P = 0.513).	Descriptive study 3
Hermanns *et al*.[425] compared a group of DM1 or DM2 patients (n = 420) with a sample obtained from the general population. The prevalence of anxiety disorders observed were 5.9% versus 9% in people without DM.	Descriptive study 3
An observational study[424] compared a group of patients with DM1 with another population without diabetes and found no difference in the prevalence rate of anxiety disorders among them (p = 0.31).	Case and control studies 2+
A cross-sectional study[429] with no control group noted that 35.5% of young adults with DM1 related stress, without any differences in gender, age or duration of diabetes being found. The use of CSII pumps is significantly associated with higher scores on stress measured by the Achenbach scale (p = 0.01).	Descriptive study 3
Other descriptive studies indicated that the use of CSII is associated with higher levels of anxiety[429]. However, neither the duration of the disease, nor age seem to have a significant effect on this disorder[425, 429].	Descriptive study 3

Summary of evidence

Case control study 2 + Descriptive studies 3	Anxiety is not related to the fact of suffering from diabetes mellitus type 1[423, 424; 425, 429], but the use of continuous subcutaneous infusion pumps for insulin is associated with an increased level of anxiety in patients[425, 429].

Recommendations

B	Professionals involved in the care of patients with diabetes mellitus type 1 should be alert to the possible emergence of depressive and/or anxious symptoms, especially when the person reports to have self-care problems.
√	Health professionals should have the necessary skills for the detection and management of non-severe forms of psychological disorders and be familiar with counselling techniques and the administration of psychotropic drugs.
√	Moderate to severe cases should be referred to mental health specialists.

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9.3.3. Eating disorders

The CPG NICE 2004[7] includes the following studies related to this issue:

A prospective study[430] compared possible eating disorders, weight changes or misuse of insulin in patients with and without diabetes, and found no increased incidence of eating disorders (ED), although higher BMI and greater concern on weight was observed among people with diabetes than among people without diabetes of the same age.

Descriptive study 3

A review of cross-sectional studies[431] found a higher prevalence of bulimia in women with DM1 than in the general population [OR 2.9 (95% CI 1.03 to 8.4)]. Misuse of insulin was increased when the ED coexisted with DM1 [OR 12.6 (95% CI: 7.8, 21.1)].

SR of descriptive studies 3

In a descriptive study, a rate of 5.3% ED was identified in patients with DM1[432].

Descriptive study 3

In a case-control study[433] 356 women with DM1 were compared to 1,098 controls, finding higher prevalence (10% *vs*. 4%) of ED in the group with diabetes ($p < 0.001$).

Case-control study 2+

According to the results of a study involving 91 young women with DM1[434], those with eating disorders had worse metabolic control than those not suffering from these ($p < 0.001$): baseline HbA_{1C} in the group with severe ED: mean (SD) 11.1% (1.2) in the group with mild ED mean (SD) 8.9% (1.7), and without ED mean (SD) 8.7% (1.6). The ED at the beginning of the study were associated with the presence of retinopathy four years later ($p = 0.004$), occurring in 86% of women with severe eating disorders, 43% of those with mild disorders and 24% without ED.

Cohort studies 2+

A cohort study[435], which included 234 women, detected insulin constraints in 30% of them. This was related to the presence of ED ($p < 0.05$), higher mortality ($p < 0.05$), early mortality (45 *vs*. 58 years, $p < 0.01$) and increased risk of nephropathy and foot diabetes during a 28-year follow-up.

Cohort studies 2+

Petrack *et al*.[423] compared a group of newly diagnosed DM1 patients (n = 313) with a reference group of general population (n = 2046) and found no significant differences in the prevalence of eating disorders at the time of diagnosis (1% *vs*. 0.3%).

Descriptive study 2

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Grylli *et al*.[436] conducted a study in 199 adolescents with DM1 (103 men/93 women) and found a higher prevalence of eating disorders in women than in men during this stage of life: 11.5% of women compared to 1% in males. The most common EDs were bulimia nervosa and non-specific eating disorders, with a very low incidence of cases of anorexia nervosa.

Descriptive study 3

Another comparative study[437] indicated that the prevalence of eating disorders in patients with DM1 is four times higher than in the general population ($p < 0.001$). The most commonly found weight control behaviour was dietary restriction (75%) and insulin management (40%).

Descriptive study 3

Summary of evidence

Descriptive studies 3	Eating disorders appear to be more frequent in patients with diabetes mellitus type 1 than in the general population[423, 437, 436] especially in teenage girls.
Cohort studies 2 +	People with diabetes mellitus type 1 who have eating disorders in adolescence have more medium-term microvascular complications[434, 435] and increased long-term mortality[435] than those who do not have these disorders.

Recommendations

C	The professional team members involved in the care of patients with diabetes mellitus type 1 should be alert about the possibility of occurrence of bulimia nervosa, anorexia nervosa and insulin management, especially in patients who express concern about their weight or body image, have a low body mass index or poor glycaemic control.
D	Given the risk of increased morbidity and mortality associated with poor metabolic control in people with eating disorders, it is recommended that in case of suspicion, the relevant diagnostic tasks are carried out and the department of psychiatry is contacted to apply the appropriate therapy.
B	Qualified health professionals should provide information on healthy lifestyles and particularly on diet regularly to patients with diabetes mellitus type 1, especially in the teenage years.

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9.4. Risk of decompensation of diabetes mellitus type 1 during adolescence

Key question:

- Does adolescence pose a risk for decompensation in diabetes mellitus type 1?

Adolescence is a period involving significant physical, psychological and social changes. These changes may have risks for adolescents with diabetes and provoke important metabolic decompensation, which may have long-term consequences on health, including kidney disease, cardiovascular risk, retinopathy, etc.[438].

In this chapter, the following aspects have been analyzed:

1. Risk of decompensation during adolescence.
2. Psychological factors that influence metabolic control during adolescence.
3. Adherence to the treatment during adolescence.

9.4.1. Risk of diabetic decompensation during adolescence

The CPG NICE 2004[7] includes the following studies:

A cohort study carried out in 42 children and adolescents with DM1 (mean age 12.9 years) examined whether pubertal development had an effect on metabolic control and adaptation to diabetes over four years[439]. Good control of the disease correlated with family cohesion ($r = 0.38$, $p < 0.01$). In prepubertal young patients, family cohesion correlated well with the variable peer relationships ($p = 0.008$), the attitude towards diabetes ($p = 0.03$), and body image concerns ($p = 0.05$) in comparison with other adolescents.

Cohort studies 2+

A study carried out in young patients with DM1 aged between 11 and 18 examined the effect of the psychological, behavioural and self-esteem on glycaemic control through an 8-year follow-up[430]. Behavioural problems in adolescence were significantly associated with higher levels of HbA_{1c}. The psychological state during the follow-up was a significant predictor of recurrent diabetic ketoacidosis admittance into hospital.

Descriptive study 3

In another descriptive study[56] a positive association was found between the knowledge that the family has about DM1, the good family relationships and the younger age of the adolescent with good compliance with insulin regimen.

Descriptive study 3

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

In a prospective observational study conducted on 15,967 young patients with DM1[440] with a mean of 15.8 years, nine deaths related to diabetes during adolescence (6 due to acute complications and 3 due to neuropathy) were identified. The risk of death was higher in adolescence than in childhood [RR 3.90 (95% CI 1.14 to 13.39)].

Observational study 2+

9.4.2. Psychological factors influencing metabolic control during adolescence

The CPG NICE 2004[7] includes the following studies:

A cohort study[441] showed that patients aged between 14 and 16 years with depressive symptoms had significantly higher mean levels of HbA_{1c} than patients without depressive symptoms [mean (SD): 9.0% (0.85) *vs*. 8.3% (1.4), P = 0.03].

Cohort studies 2+

In a small descriptive study[442] (n = 16) of young patients with DM1 (age range: 15-18 years) depression was positively correlated with the deterioration of glycaemic control (r = 0.51, p <0.05).

Descriptive study 3

A cross-sectional study with no control group[443] showed that depressive symptoms in adolescent girls and older, predicts poor adherence to the treatment (p <0.01).

Descriptive study 3

A multicenter cross-sectional study[444] showed that depressive symptoms were associated with higher levels of HbA_{1C} and more visits to the emergency unit, while no significant relationship was stated regarding the number of hospitalizations, the number of episodes of hypoglycaemia, and/or ketoacidosis.

Descriptive study 3

A longitudinal observational study[445] revealed that the presence of depressive symptoms at the beginning of the study predicted risk of hospitalization during the next 24 months [OR 2.58 (95% CI: 1.12 to 5.98)].

Longitudinal observational study 2+

The study by Pinar *et al*.[437] shows that the presence of ED predicts worse glycaemic control (p <0.001).

Descriptive study 3

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

9.4.3. Adherence to the treatment

The CPG NICE 2004[7] includes the following studies:

A study in Scotland[446] showed that people aged between 10 and 20 years old had significantly higher levels of HbA_{1c} ($p = 0.01$) and lower adherence to the insulin treatment ($p < 0.001$) than the younger or older age group. — Descriptive study 3

A longitudinal study[445] found that data reported by patients with DM1 regarding HbA_{1c} is the best predictor of HbA_{1c}, explaining the 30% of the variance in the case of adolescents and the 19% in the case of parents. The correlation between the referred self-care and glycaemic control was significant ($p < 0.01$). — Descriptive study 3

Naar-King *et al*.[447] examined the relationship between adherence and metabolic control, taking into account the role of the presence of psychological disorders. The presence of anxiety symptoms and behavioural problems were associated with poorer adherence, but ultimately only behaviour problems predicted worse metabolic control ($p < 0.01$). — Descriptive study 3

Summary of evidence

Descriptive study 3	Adolescence is associated with poorer metabolic control in patients with diabetes mellitus type 1[446] especially if associated with behaviour problems[430; 439].
Descriptive study 3	Good control of the disease correlates with family cohesion and its knowledge about diabetes mellitus type 1[56]
Descriptive study 3	Patients aged between 14 and 16 with depressive symptoms have significantly higher HbA_{1C} levels than those patients without depressive symptoms[441, 442, 443, 444, 445].
Descriptive study 3	The presence of eating disorders predicts worse glycaemic control ($p < 0.001$)[437].
Descriptive study 3	People aged between 10 and 20 have significantly higher HbA_{1C} levels ($p = 0.01$) and lower adherence to the insulin treatment ($p < 0.001$) than the younger or older age group[446].
Descriptive study 3	The presence of anxiety symptoms and behavioural problems are associated with poorer adherence, but ultimately only behaviour problems predicted worse metabolic control ($p < 0.01$)[447].

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Recommendations

C	Adherence to the treatment is a key factor in managing diabetes, so it is important to work on this aspect with the adolescent patient together with his family, and analyze barriers, which may impede an adequate adhesion (anxiety, depression, eating disorders and behavioural problems).
C	The professionals in charge of children and adolescents with diabetes mellitus type 1 should be aware they might develop depression and/or anxiety disorders, particularly when there are difficulties in controlling the disease or if the disease is long lasting.
√	In children and adolescents with persistent poor glycaemic control, the level of anxiety and depression should be assessed.
√	Children and adolescents suspected to suffer anxiety or depression disorders should be referred to mental health professionals.
C	Given the high prevalence of eating disorders in adolescents with diabetes, especially among women, it is advised to be alert about the presence of symptoms that may indicate the presence of an eating disorder or insulin managing. In case of suspicion, the department of psychiatry for diagnosis and appropriate therapy should be contacted and worked with.
√	It is recommended to address the issue of alcohol, smoking and other drugs with the teenager with diabetes mellitus type 1 to avoid its consumption and provide strategies to prevent episodes of hypoglycaemia.

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9.5. Pregnancy planning

Key question:

- Is it important to plan pregnancy in women with diabetes mellitus type 1?

Diabetes may favour the occurrence of certain events in pregnant women (urinary infections, vaginal candidiasis, polyhydramnios, hypertensive pregnancy and prematurity disorders) and in the foetus or newborn infant (malformations and/or abortions, retarded intrauterine growth, macrosomia, hypertrophic cardiomyopathy and foetal immaturity). In addition, pregnancy can affect glycaemic control in women with diabetes, increasing the frequency of hypoglycaemia and its inadvertence, or hyperglycaemia by increased placental lactogen especially after 20 weeks of gestation. The progression of certain complications of diabetes, especially diabetic retinopathy and nephropathy, may also be affected during this period.

It is considered of interest to analyze the benefits pregnancy planning can have in women with DM1, in terms of reduction of adverse perinatal outcomes (abortions, foetal malformations, eclampsia, perinatal death or other complications).

Planning pregnancy in pregnant women with DM1 is to use contraception to decide the most appropriate time for it to occur. This requires determining, based on maternal complications secondary to DM, the risk involved in a pregnancy, and reduce the maternal and foetal complications with adequate metabolic control and medical monitoring before conception. This is done by informing the couple of the mutual impact between DM and pregnancy, as well as of the methods to prevent potential complications.

The CPG NICE on pregnancy 2008[9] includes the following studies:

A study[449] conducted in 442 pregnant women with DM (73% with DM1) found an association between the lack of information about foetal risks before pregnancy and the risk of caesarean delivery [OR 2.9 (95% CI: 1, 1 to 8.2)] and increased neonatal mortality adjusted for maternal age and lower social status [OR 2.4 (95% CI: 1.0 to 5.8)].

Descriptive study
3

An SR with meta-analysis of 16 observational studies[450] evaluated the influence of preconception care programs (PCP) in women with diabetes in reducing the risk of major congenital anomalies. The PCP consisted of glycaemic control planning before pregnancy. The results obtained indicate that from the 2104 births, the weighted rate of major and minor anomalies was 2.4% for women included in the PCP compared with 7.7% for the group without PCP. The relatively low values of HbA_{1c} during the first trimester in the group with PCP suggest that glycaemic control during the first weeks of pregnancy probably plays an important role in preventing birth malformations.

SR of observational studies
2++

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The cohort study by McElvy *et al*.[451] evaluated the impact of a preconception care program made for 5 years in three stages (PPG I, II PPG, PPG III). During the period before the first program (PPG I) (1973-1978) n = 79 revealed a perinatal mortality rate of 7% and a congenital malformation rate of 14%. The perinatal mortality rate dropped from 3% in the PPG I and 2% with the PPG II, to 0% in the PPG III. The rate of congenital malformations decreased to a minimum of 2.2% by PPG III.

Cohort study
2+

In one trial[452] 84 women with DM (68% DM1) were trained for 17 weeks before and during pregnancy on concepts related to glucose monitoring, diet and exercise, insulin dose adjustments and complications of diabetes and they were compared with a group of 110 women (60% DM1) that was trained only during pregnancy. In the group that received the preconception education, a failure rate of 1.2% was found compared to the 10.9% found in the group that had only received education during the postconceptional period (p = 0.01).

RCT
1+

A prospective cohort study conducted in 160 women with DM1[453] analyzed the glycaemic control and the frequency of severe hypoglycaemia based on pregnancy planning. The results of the study were the following:

Cohort studies
2+

- 68.8% of pregnancies were planned *vs*. 33.8%, which were unplanned.
- 29.4% of women with DM1 had severe hypoglycaemia during pregnancy, 21.9% in the first trimester, 18.1% in the second trimester and 10.6% in the third trimester.
- The duration of diabetes was associated to an increased risk of severe hypoglycaemia during pregnancy (p = 0.012).
- The duration of diabetes was correlated with the total number of episodes of severe hypoglycaemia during pregnancy (r = 0.191, P = 0.017) and during the first trimester (r = 0.16, p = 0.05). The duration of diabetes in women who had an episode of severe hypoglycaemia was on average (SD) 19.2 years (7.2).
- The total number of episodes of severe hypoglycaemia during pregnancy is associated with the average HbA_{1c} level in the first trimester (r = 0.17, p = 0.043).
- 56% of U.S. women used 4 or more injections per day during periods before pregnancy, increasing to 77% and 83% in trimesters 1 and 3 respectively and this was not associated to an increase in hypoglycaemia.
- Women who achieved HbA_{1c} levels less than 6.5% (n = 41) during the first trimester were less likely to experience severe hypoglycaemia in the second trimester (7.3 *vs*. 25%; p = 0.019) and in the third trimester (0 *vs*. 16%, P = 0.003) than women with higher HbA_{1c} levels in the first trimester. These women had a lower mean duration of diabetes, although this difference is not significant.

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- The reduction in HbA_{1c} levels between the period before pregnancy and the first trimester was not associated with severe hypoglycaemia in the first trimester. However, a higher reduction of HbA_{1c} levels between the first and second trimesters was correlated with the number of episodes of severe hypoglycaemia in the second trimester (r = 0.194, P = 0.021).
- A significant difference was found in HbA_{1c} levels between planned and unplanned pregnancies. In addition, among planned pregnancies there were more numbers of severe hypoglycaemia than in the unplanned ones (p = 0.047).
- No significant differences were found in glycaemic control or the risk of severe hypoglycaemia among women using insulin analogues and those who did not take them during pregnancy, although there was a trend to significance in the third trimester (HbA_{1c} 6.4 *vs*. 6.7%, P = 0.06).
- The fall in the average HbA_{1c} levels between pre-pregnancy and the first trimester was significantly higher (1.0 *vs*. 0.5%) in women who used insulin analogues (n = 43, p = 0.005), but without noticing an increase in the number of severe hypoglycaemia.

Women smokers (n = 40) and those with retinopathy before pregnancy (n = 36) were 3 times more likely to suffer an episode of severe hypoglycaemia in the third trimester (p = 0.029, p = 0.03). Although those with retinopathy before pregnancy had a duration of diabetes (19.8 *vs*. 12.3 years, p = 0.001), the duration of diabetes was not associated with severe hypoglycaemia in the third trimester.

A cohort study[454], which included 46 women with DM1 and nephropathy before pregnancy, analyzed the complications during pregnancy including abortion in the first trimester, preeclampsia, premature delivery, baby weight and length, admission to the NICU and foetal loss. As results, these showed that 31 women (67%) had at least one complication during pregnancy. BMI was the only parameter with a significant difference between the groups, being higher in women with a complicated pregnancy compared to those who had no complications [mean (SD) 27 (9) *vs*. 24 (3), P = 0.027]. No differences were found between the groups in relation to preconception counselling (60% *vs*. 67%), the pre-pregnancy glycaemic control (HbA_{1c} 7.5 *vs*. 7.1%), the prevalence of patients who had an adequate glycaemic control (44% *vs*. 42%), weight gain during pregnancy (12.4 *vs*. 10.6 kg), duration of DM (18 *vs*. 19.7 years) and the proportion of patients treated with ACEi before pregnancy (26 *vs*. 33%). The authors concluded that overweight is associated with poor pregnancy outcomes in patients with DM1 and different degrees of nephropathy.

Cohort studies
2+

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An SR with meta-analysis[455] that included one RCT and 19 observational studies in patients with DM1 and DM2, analyzed the effects of glycaemic control with fasting glucose levels ≤ 5.7 mmol/l or postprandial glucose levels ≤ 7.8 mmol/l and/or HbA_{1c} levels ≤ 7.0%, counselling or education about diabetes, contraceptive use to optimize glycaemic control, multivitamin use and/or folic acid in the preconception period on complications during pregnancy. The results of the meta-analysis suggest that preconception care is effective in reducing birth defects, [RR 0.25 (95% CI: 0.15 to 0.42)], [NNT 17 (95% CI: 14-24)], preterm birth [RR 0.70 (95% CI 0.55 to 0.90)], [NNT 8 (95% CI 5-23)] and perinatal mortality [RR 0.35 (95% CI: 0.15 to 0.82)], [NNT 32 (95% CI 19-109)]. In these patients, the preconception care decreased HbA_{1C} levels in the first trimester of pregnancy by an average of 2.43% (95% CI: 2.27 to 2.58).

SR of RCT and Observational studies 2++

Summary of evidence

Cohort studies 2 +	In women with diabetes mellitus type 1 planned pregnancies have a better metabolic control and an increased risk of hypoglycaemia[453].
RCT 1 + Cohort studies 2 + SR of observational studies 2++	Preconception care is effective in reducing congenital malformations[450, 454, 455, 455] and in preterm delivery[455] and perinatal mortality[449, 451 452].
SR of observational studies 2 + +	Preconception care decreases HbA_{1C} levels in the first trimester of pregnancy[455].
Cohort study 2 +	Being overweight is associated with poor pregnancy outcomes in patients with DM1 and different degrees of nephropathy[454].

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Recommendations

B	As all patients diagnosed with diabetes mellitus type 1, adolescents and women of childbearing age should participate in diabetes education programs in order to facilitate the control of their disease and promote self-care. These programs should include specific ideas about the importance of control before conception and general recommendations for pregnancy (vitamin supplements, suppression of teratogenic drugs, etc.). It is convenient to remind these patients about these points in all the visits to the health centre to ensure a pregnancy in optimal conditions.
B	In women planning to become pregnant, it is considered relevant performing a pre-conceptional visit to set out control targets, establishing the appropriate treatment (folic acid, iodine, etc.), review the possible complications and give "green light" to the pregnancy.

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9.6. Complications of diabetes mellitus type 1 during pregnancy

Key question:

- How does pregnancy affect the development of the complications of diabetes mellitus type 1?

9.6.1. Evolution of retinopathy during pregnancy

The CPG NICE on pregnancy 2008[9] provides evidence on this issue.

A prospective cohort study[456] assessed the progression of retinopathy during pregnancy in 180 women (270 pregnancies) compared to 500 non-pregnant women during 6.5 years of follow up. It was observed that pregnant women had a 1.63 times greater risk of worsening retinopathy in the intensive treatment group compared with non-pregnant women ($p < 0.05$). The OR peaked during the second trimester (OR 4.26, $P = 0.001$) and persisted until 12 months after pregnancy (OR 2.87, $p = 0.005$).

Cohort study
2+

An observational study[457] evaluated the incidence, prevalence, and risk factors for progression of diabetic retinopathy during pregnancy. A total of 65 pregnant women with DM1 were evaluated before pregnancy, each trimester, and 12 months after delivery. Progression of retinopathy occurred in 77.5% of patients who had retinopathy before conception and 22.5% occurred in proliferative diabetic retinopathy. Only 26% of women who had no retinopathy in early pregnancy had a progression of it. Duration of diabetes ($p = 0.007$) and HbA_{1c} levels were higher in the progression group than in the group without progression at all times when it was assessed, but only in the third trimester, was the difference statistically significant ($p = 0.04$).

Longitudinal-observational Study
2+

A cohort study analyzed the progression of retinopathy in 154 women with DM1 during pregnancy and after 6 and 12 weeks after delivery[458] and found that 51 women (33.11%) had progression of retinopathy during pregnancy and regression was observed in 13 postpartum women (8.44%). Progression of retinopathy was significantly associated with changes in glycaemic control in early pregnancy, chronic hypertension and pregnancy-induced hypertension.

Cohort study
2+

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

9.6.2. Evolution of nephropathy during pregnancy

No studies have been found to analyze this issue.

Summary of evidence

Cohort study 2 +	Retinopathy diagnosed before pregnancy tends to worsen during pregnancy[456, 282], especially during the second trimester[456].
Cohort study 2 +	The progression of retinopathy is associated with changes in glycaemic control in early pregnancy, chronic hypertension and pregnancy-induced hypertension[458].

Recommendations

B	It is advisable to plan the pregnancy in women with diabetes mellitus type 1 to achieve adequate glycaemic control and conduct the evaluation of the possible retinopathy and nephropathy before and during pregnancy.
√	It is recommended to inform the couple on the mutual repercussions between diabetes mellitus type 1 and pregnancy, making explicit reference to the possible complications that can arise and the methods to prevent them

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9.7. Metabolic control during pregnancy

Key question:

- How does pregnancy affect the development of the complications of diabetes mellitus type 1?

Although there is agreement on the need to inform women with DM1 on the need for adequate glycaemic control before and during pregnancy, there is no agreement on what is meant by adequate glycaemic control during this time and what the goals to be set out are for these women in order to get better results for themselves and lower perinatal morbidity.

The CPG NICE 2008[9] included 23 cohort studies[459, 460, 461, 462, 463, 464, 465, 466, 467; 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478; 479, 480] and established an association between preconceptional control and the incidence of abortions and congenital malformations.

- **Risk of congenital malformations:**

A cohort study[459] on 488 women with DM1 linked the HbA_{1C} levels in the first trimester to the appearance of malformations ($p = 0.02$), demonstrating that the risk increases gradually to higher levels of HbA_{1c} in the first trimester of pregnancy — Cohort study 2+

Likewise, another cohort study[474] found that the rate of major malformations was significantly higher in women whose HbA_{1c} level in the first trimester exceeded values of 12.7%. — Cohort study 2+

A study[460] that included 435 pregnant women (289 with DM1 and 146 with DM2) compared women with HbA_{1C} levels above 8% in the first trimester with women with HbA_{1C} levels lower than this value, noting higher rates of congenital malformations in the first group [(8.3% *vs*. 2.5%, OR 3.5 (95% CI: 1.3 to 8.9), P <0.01]. — Cohort study 2+

Another cohort study that examined 142 pregnancies in women with DM1[476] detected congenital malformations in 17 neonates (six minor and eleven major). Baseline HbA_{1c} was significantly higher in the group with minor malformations [mean (SD): 9.3% (1.9), P <0.05)] and in the group with major malformations [mean (SD): 9, 6% (1.8), p <0.001)] than in the group without malformations [mean (SD): 8.0% (1.4)]. — Cohort study 2+

Congenital malformations were detected in 48% (3/63) of women with HbA_{1C} less than 8%, 12.9% (8/62) in those with HbA_{1C} from 8 to 8.9% and 35.3% (6/17) had average levels, which were equal, or greater than 10%.

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A study by Miller *et al*. in 116 women with DM1[470] showed that there were no malformations (0/19) in the offspring of women with HbA_{1C} levels of 6.9% or less. In women with HbA_{1C} levels in the range from 7.0 to 8.5%, the percentage who had malformations was 5.1% (2/39). Cohort study 2+

A cohort study that followed up 83 pregnant women[466], 63 with DM1 and 20 with DM2, examined the relationship between HbA_{1c} levels during the first trimester and congenital malformations. In 9 cases congenital malformations appeared, all with HbA_{1C} levels higher than 9.5% in the first trimester (7 with HbA1c above 11.5% and 6 with HbA1C higher than 13.5%). Cohort study 2+

Another cohort study[471] carried out in a sample of 229 pregnant women with DM1 found that the threshold for increased risk of abortion or malformations is glycaemia in the first trimester between 120 and 130 mg/dL or HbA_{1c} levels of between 12 and 13%. Below these glycaemic levels, the risk is comparable to that of non-diabetic women. Cohort study 2+

- **Risk of spontaneous abortions:**

A cohort study with a sample of 105 women with DM1[477] reported spontaneous abortions in 18 women. The HbA_{1C} levels during the first trimester were between [mean (SD) 9.4% (2.3)] which were not significantly different from the mean HbA1C level of pregnancies that resulted in a baby with malformations [mean (SD) 10, 3 (1.9)] or no adverse outcome [mean (SD) 8.9% (2.3)]. Cohort study 2+

In a cohort study[466] carried out in 83 women (63 women with DM1 and 20 DM2), the rate of spontaneous abortions was 26.5% (22 pregnancies). There were no spontaneous abortions in women with HbA_{1C} less than 7.5% in the first trimester. An abortion occurred in a woman with HbA_{1C} between 7.5 and 9.4%, 21 in women with HbA1C > 11.5% and two of them with HbA1C > 13.5%. Cohort study 2+

A cohort study carried out in 303 women with DM1[474] found that rates of spontaneous abortions were significantly higher when the HbA_{1c} in the first trimester was higher than 11.0% compared to normal average in non-diabetic women [mean (SD) 5, 9% (0.57)]. Cohort study 2+

A cohort study that analyzed 84 pregnancies in women with DM1[469] found that women who had a spontaneous abortion, had a significantly higher HbA_{1c} [mean (SD) 12.0% (0.6)] than women whose pregnancy progressed beyond 20 weeks [mean (SD) 10.7% (0.3), P <0.05]. The results suggest that poor glycaemic control around conception is a more important factor than in the weeks immediately preceding a spontaneous abortion. Cohort study 2+

In another cohort study with 215 women with DM1[471], 52 women (24%) had spontaneous abortions. The threshold value for increased risk of abortion or malformations is a glycaemia in the first trimester between 120 to 130 mg/dL or HbA1c levels of between 12 and 13%. Cohort study 2+

A cohort study of 116 pregnancies in 75 women with DM1[468] found to be significantly more likely for spontaneous abortions to occur when HbA_{1C} was higher than 12% (p <0.05).

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- **Other neonatal outcomes:**

A cohort study examined the effect of glycaemic control at different times during pregnancy, in trimesters of adverse outcomes (perinatal death and/or congenital malformations in 990 pregnancies)[465]. The mean HbA1C in the 0 to 3 months prior to conception was 8.0% (interquartile range 7.3 to 9.1) in the adverse outcome group compared with 7.6% (interquartile range 6, 8 to 8.5) in the other group (p = 0.005). Women with adverse clinical outcomes received preconception counselling less frequently (42% vs. 59%, P = 0.002) and performed less measurements of glucose levels on a daily basis until conception (23% vs. 35%, p = 0.019).

Cohort study 2+

In an observational study[481] 211 pregnancies in 132 women were analyzed, with 61 adverse outcomes (29%) including spontaneous abortions, terminations of pregnancy for medical reasons, neonatal deaths and congenital malformations. Mothers with poor glycaemic control before conception and at the time of conception (HbA1c ≥ 7.5%) had an adverse outcome rate almost three times higher than mothers with good glycaemic control [OR 2.59 (95% CI: 1.11 to 6.03) and OR 2.71, 95% CI 1.39 to 5.28, respectively)].

Observational study 3

In an SR[482] RCTs that compared different targets of glycaemic control in pregnant women with DM1 and DM2 were included. Three trials in women with DM1 (223 women and children), and all with a high risk of bias were included. Two trials compared objectives of very strict glycaemic control (3.33 to 5.0 mmol/L fasting blood glucose) with strict-to-moderate glycaemic control targets (4.45 to 6.38 mmol/L).

SR of poor quality RCT 1+/-

With a limited body of evidence, few differences in the outcomes between strict glycaemic control measures and strict-to-moderate measures were found in pregnant women with pre-existing DM1. Adverse effects were noted (increased preeclampsia, caesarean deliveries and children with high birth weight percentile> 90) for fasting glucose levels above 7 mmol/L.

Summary of evidence

Cohort study 2 +	Several prospective studies have demonstrated an association between good metabolic control during the first trimester of pregnancy and lower incidence of congenital malformations[459, 460, 466, 469, 470, 471, 474, 476].
Cohort study 2 +	The level of HbA_{1C} that has proven to be related to the non-presence of malformations is 6.9% or less[470].

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Cohort study 2 +	Poor glycaemic control around gestation is more related to the presence of a spontaneous abortion than glycaemic control during the weeks before it[469].
Cohort study 2 +	The risk of spontaneous abortions is higher with HbA_{1c} levels over 12% ($p < 0.05$)[468, 471].

Recommendations

B	In pregnant women with diabetes mellitus type 1, individualized targets regarding the self-monitoring of blood glucose should be agreed on, taking into account the risk of hypoglycaemia. HbA_{1c} levels must be maintained below 6.2%, if these can be reached safely.
B	These women should be informed that any decrease in HbA_{1C} levels below 6.2% reduces the risk of congenital malformations and likewise, they should be recommended no to exceed levels higher than 6.9%.
B	Pregnancy should be discouraged to pregnant women with diabetes mellitus type 1 whose HbA_{1c} levels are above 8% on a temporary basis until an optimal metabolic control is achieved.
D	Situations that make pregnancy inadvisable: • HbA_{1c} levels over 8%. • Severe nephropathy (plasma creatinine > 2 mg/dl or proteinuria> 3 g/24 hours and/or difficult to control HTA). • Ischemic cardiopathology. • Severe proliferative retinopathy, with poor visual prognosis. • Severe autonomic neuropathy.
√	Information is to be provided to the future pregnant woman and her partner on the need, first, to assess the situation of maternal diabetes to detect possible contraindications of gestation and, secondly, to express the desirability of an active participation of both to achieving the pre-conception objectives.
B	Monthly or bimonthly measurements of HbA_{1c} should be offered to women who are planning pregnancy.
B	Women who are planning pregnancy and require intensification of insulin therapy should be informed of the need to increase the frequency of self-analysis of blood glucose control including fasting and pre and postprandial controls. If necessary, the continuous insulin infusion pump therapy will be offered.

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√	Test strips for self-assessment of ketonuria or ketonemia if hyperglycaemia appears or the person is feeling bad are to be provided.
√	Care to the patient with diabetes mellitus type 1 during pregnancy planning, monitoring and delivery should be in a hospital that has staff dedicated specifically to these aspects (nurse educator, endocrinologist, obstetrician, and neonatologist).
√	During pregnancy, the frequency of visits should be at least on a monthly basis, with both endocrinology and obstetrics specialists.
√	Since it is recommended to assess HbA_{1C} levels monthly, it would be advisable to do it through a capillary sample and not a venous one.
√	An increase in the use of test strips for blood glucose, ketonuria and/or ketonemia measurements should be taken into consideration.
√	Glycaemic control optimization protocols should be available.
√	A childbirth care protocol with general guidelines on the needs of carbohydrate intake and insulin, which must be known by the staff involved, as well as a newborn care protocol should be set out.

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9.8. Contraception and diabetes mellitus type 1

Key question:

- What are the most recommended contraceptives in women with diabetes mellitus type 1?

In previous questions the importance of pregnancy planning in women with DM1 has been determined in order to intensify the treatment of DM1 until an adequate glycaemic control is achieved and collateral diseases are controlled (such as, retinopathy, nephropathy, etc.) prior to conception.

It is therefore important to identify the most effective and safest contraceptive methods for women with DM1.

The CPG NICE 2008[9] provides no evidence on this issue.

An SR conducted in women with diabetes (75% with DM1)[483] included three RCTs to compare the effectiveness and safety of hormonal versus non-hormonal contraceptive methods. The authors concluded that there was insufficient evidence to decide whether to prescribe the convenience of hormonal or non-hormonal contraceptives for women with DM1. By consensus of the authors, the copper intrauterine device (IUD) was recommended as safest choice for patients with DM until the safety of hormonal contraceptives is proven. However, it was also considered probable that the IUD that releases levonorgestrel (LNG) would also be safe, as its use has not been associated with effects on the glucose metabolism.

SR of RCT 1++

A WHO report[484] on medical eligibility criteria for different contraceptive methods evaluated both the medical condition of diabetes and all the complications and circumstances that can occur, establishing different recommendations based on the individual characteristics of each patient. These recommendations are summarised in Appendix 7.

Expert consensus 4

Summary of evidence

SR of RCT 1 + + Expert consensus 4	There is insufficient evidence on the effectiveness and safety of all contraceptive methods in women with DM1. The consensus recommendations come from prestigious institutions and organizations.

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Recommendations

D	Women with type 1 diabetes are recommended to use the copper IUD as safest contraception method. The use of the IUD that releases levonorgestrel (LNG) cannot be ruled out, as it has not been observed to affect the metabolism of glucose.

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9.9. Clinical management of diabetes mellitus type 1 in patients with special needs

Key question:

- How can the clinical management of diabetes mellitus type 1 for patients with special needs be adapted?

9.9.1. Immigrant Population

In recent years, Spain has become one of the European Union countries that receives the highest number of immigrants, being in 2009 the immigrant population 12% of the total number. It should be noted that 44.81% of all the immigrants registered in Spain are distributed among three provinces (Madrid, Barcelona and Alicante).

The clinical management of DM1 in immigrants can be difficult due to the existence of linguistic, cultural and religious barriers.

Clinical management of diabetes mellitus type 1 in Muslims patients during Ramadan

Ramadan is the holy month of Islam that takes place in the ninth month of the lunar calendar. During this period the Muslim believers practice fasting, both of solid and liquid foods including water, and medicine from sunrise to sunset. Generally, there are two intakes a day, one before dawn (suhoor) and one after sunset (iftar).

People under 12, the elderly, pregnant women and those with certain diseases are exempt from compliance. However, it is common for Muslim patients to insist on fasting during Ramadan, which significantly increases the risk of acute complications in people with DM1. The risks associated with fasting in people with diabetes are hypoglycaemia, hyperglycaemia, diabetic ketoacidosis, dehydration and thrombosis[485].

Al Arouj *et al*.[486] have been categorized by consensus patients with DM according to risk of complications during fasting:

Very high risk if there is:

- Severe hypoglycaemia three months beforehand.
- History of recurrent hypoglycaemia.
- Poor diabetic control.
- Ketoacidosis three months beforehand.
- Diabetes Type 1.

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- Intercurrent disease.
- Hyperosmolar coma three months before.
- Intense physical work.
- Pregnancy.
- Haemodialysis.

High risk if there is:

- Moderate control of diabetes (glycaemia 150-300 mg/dl, HbA_{1c} 7.5 to 9.0%).
- Renal insufficiency.
- Advanced macrovascular complications.
- Patients who live alone.
- Additional risk factors.
- Advanced age, health alterations.
- Drugs affecting the level of consciousness.

The categories identified by the author as "moderate risk" and "low risk" are only applicable to patients with DM2.

The CPG NICE 2004[7] includes this issue, but does not provide specific evidence on the subject and its recommendations were based on consensus.

The American Diabetes Association[486] recommends the administration of two doses of a mixture of NPH insulin and fast acting insulin type 30/70 before the two main intakes. It also recommended inverting the doses, administering the usual morning dose before the evening meal (iftar), and halving the evening dose, to be administered prior to a meal before dawn (suhoor) thus reducing the risk of hypoglycaemia during the day.

Expert opinion
4

In an RCT with crossover design at the University of Minnesota[487] carried out in 15 patients with DM1 and HbA_{1c} levels less than 7.5%, a dose of insulin glargine was administered at 10 pm and a dose of fast acting insulin before meals, comparing glucose levels every two hours during a day in which they received breakfast, lunch and dinner compared to another day in which they only received dinner (18 hour fast). No statistically significant differences were found between the two groups, except for glucose at 9 am. Only two episodes of mild hypoglycaemia were described during fasting.

RCT
1+

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In a randomized, crossover study in 64 patients with DM1 that was carried out in a health centre in Morocco, an insulin treatment based on two doses of mixed NPH and fast acting insulin versus two doses of mixed NPH insulin and ultra-fast insulin (lispro) analogue was compared. There was an improvement in postprandial glycaemia in the group treated with lispro (decrease of 45 *vs*. 61.2 mg/dl, p = 0.026). The number of hypoglycaemia was significantly lower in the group treated with lispro insulin compared to the group treated with fast insulin (15 *vs*. 21, p = 0.004)[488].

RCT
1+

In a study conducted in a medical centre in Lebanon that included 17 patients with DM1[489], who were administered 85% of the usual dose of insulin into two equal parts between suhoor (pre-dawn) and iftar (after dark), 70% as ultraslow insulin and 30% as fast acting insulin. With this pattern, no changes were recorded in HbA_{1C} levels nor an increased risk of hypoglycaemia.

Before Ramadan, intermediate acting insulin was changed to ultra slow insulin in all patients. The total dose of insulin administered to the fasting patients at the end of Ramadan [mean (SD) 45.7 U/day (14.4)] was less than the total dose of insulin administered before fasting [mean (SD) 52.8 U/day (13.1), p <0.05]. No episodes of severe hypoglycaemia were observed during the day.

Observational study
2+

In a descriptive study[490] conducted in Lebanon in 9 patients with DM1 who fasted during Ramadan a regimen based on a daily injection of insulin glargine and three doses of insulin lispro or aspart before each meal was applied during the week before fasting. At the beginning of fasting, the dose prior to Ramadan was reduced to 20% and a dose of insulin glargine and two doses of lispro or aspart were administered before suhoor and iftar. No significant differences were found in HbA_{1c} before and after fasting, although two patients discontinued fasting due to episodes of hypoglycaemia.

Descriptive study 3

Summary of evidence

1+	The basal bolus therapy eliminating the bolus of meals, which do not take place, allows adequate metabolic control in people with diabetes mellitus type 1 who practice fasting during Ramadan[486, 487, 488, 489].

Recommendations

Immigrant population. General recommendations

√	If the patient with diabetes mellitus type 1 presents difficulties to understand the language, the use of automatic translation systems (via telephone or audiovisual methods of open and closed questions) or by direct translation during the visit is recommended.
√	Likewise, the use of simple graphics that facilitate understanding of the disease and the guidelines to be followed, is recommendable.

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Recommendations for Muslim patients during Ramadan

Before Ramadan

√	Inform the health care team about the concept of Ramadan and the risks posed by fasting.
√	Plan the process in time for the celebration of Ramadan.
√	Identify Muslim patients with diabetes mellitus type 1.
√	Carry out a clinical interview with these patients to know their desire to fulfil the precept of Ramadan.
√	Inform patients about the possibility of not celebrating Ramadan due to having a chronic disease and the risks involved.
√	Evaluate the existence of major criteria to strongly discourage compliance of Ramadan: • Diabetes with poor metabolic control. • Chronic complications of advanced diabetes: renal failure, ischemic heart disease with unstable angor, advanced peripheral macroangiopathy. • Frequent hypoglycaemia, severe or without adrenergic clinic. • Diabetic ketoacidosis in the months prior to Ramadan. • Gestation. • Physical activity during the day. • Aged with dependence on others.
√	In the event that these criteria are not met and the patient wishes to fulfil the precepts, making the corresponding therapeutic changes before and during Ramadan regarding diet and exercise is deemed appropriate: • Optimize glycaemic and metabolic control 1-2 months before. • Specific diabetes education (symptoms of hyper-and hypoglycaemia, meal and physical activity planning, drug administration and attitude in case complications arise).

During Ramadan

√	Individualized care plan.
√	Frequent blood glucose determinations.
√	Avoid foods, which are rich in carbohydrates with rapid absorption and fats.
√	Eat more food s composed of complex carbohydrates.
√	Fruits, vegetables and yogurt can be included in the diet.
√	Practicing suhoor immediately before sunrise and not in the early morning.

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√	Drink unsweetened fluids to quench thirst.
√	Reduce fried foods.
√	Carry out regular physical activity, avoiding excessive exercise.
√	Break fasting if blood glucose is less than 60 or higher than 300 mg/dl.
√	Ensure adequate fluid intake.
A	Adapt drug treatment with insulin: as a general rule, a basal bolus therapy, which eliminates the bolus of meals not taken, is recommended.

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9.9.2. Patients with visual impairment

No studies have been found in this regard.

Recommendations

√	Provide educational materials in audio, Braille, large print or edited format.
√	Facilitate attendance to educational sessions performing them in locations accessible by public transport.
√	Advertise informative talks with brief advertisements in audio format.
√	If slides are used to transmit key information at educational chats, these should also contain a simple verbal description of the contents of each slide.
√	Provide information on self-control tools and techniques for people with visual impairment, including: • "Talking blood glucose monitoring kits" that guide the patient through a voice message on the steps for testing and communicate the results orally. • Glucometers with a large screen and easily recognizable numbers. • Glucometers with backlit display. • Techniques for tactile inspection of the feet.
√	Insulin injectors: • Provide patients with injectors, which contain different touch buttons for fast or slow insulin. • Insulin injectors emit some sort of sound when going from dose to dose in order to facilitate the patient's autonomy, and thus the dose can be calculated without seeing the wheel.

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10. Acute complications

10.1. Hypoglycaemia

Hypoglycaemia is the most common acute complication of diabetes. A Canadian CPG[491] defined hypoglycaemia by *Whipple's triad*:

1. Appearance of autonomic or neuroglycopenic symptoms;
2. A low level of glucose (<4.0 mmol/L or 72 mg/dl) for patients treated with insulin or products that cause insulin secretion;
3. Symptomatic improvement to the administration of carbohydrates.

However, there is no unanimity in defining the level of glucose to diagnose hypoglycaemia. The *American Diabetes Association*[492] established the level of blood sugar to define hypoglycaemia in adults at 70 mg/dl (3.9 mmol/l) and the Spanish Society of Diabetes[493], at 60 mg/dl (3.3 mmol/l).

Hypoglycaemia can occur in different circumstances:

- Excessive insulin doses.
- Not enough carbohydrates in meals.
- Meals delayed in time.
- Extra exercise for the dose of insulin administered.
- Administration of intramuscular insulin instead of subcutaneous tissue.
- Errors in the administration of insulin (fast acting insulin instead of delayed insulin or mistake in the dose).
- Shower or bath with very hot water shortly after having injected insulin.

The effects and short-term risks of hypoglycaemia can range from mild discomfort and unpleasant situations due to associated symptoms to risk situations, which may occur mainly in cases of severe hypoglycaemia, such as during driving or while operating machinery.

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10.1.1. Symptoms of suspicion

It is essential to recognize the symptoms of suspicion to initiate the treatment and prevent progression to severe hypoglycaemia

Recommendations

<table>
<tr><td rowspan="4">D</td><td colspan="4">Hypoglycaemia will be suspected if one or more of the following symptoms appear:

Symptoms of hypoglycaemia</td></tr>
<tr><td colspan="2">Autonomic/adrenergic/neurogeni</td><td colspan="2">Neurological/neuroglycopenic</td></tr>
<tr><td>• Sweating
• Pallor
• Tremor
• Tachycardia</td><td>• Anxiety
• Hunger
• Nausea
• Weakness
• Tingle</td><td>Psychiatric symptoms:
• Confusion
• Behavioural alteration
• Aggressiveness
• Slurred speech
• Lapses of consciousness</td><td>Neurological symptoms:
• Dizziness and weakness
• Headache
• Altered, double or blurred vision
• Aphasia
• Dysarthria
• Motor deficit, unsteady gait, lack of coordination
• Paresthesias
• Seizures</td></tr>
<tr><td colspan="4">Adapted from For the Reversal Treatment of Mild, Moderate and Severe hypoglycaemia. Holders of Interdisciplinary Clinical Manual CC15-25.</td></tr>
<tr><td>√</td><td colspan="4">It is recommended that people with type 1 diabetes, especially children and adolescents, carry some type of identification (e.g. bracelet) to facilitate the identification of acute complications such as hypoglycaemia and acting at an early stage.</td></tr>
</table>

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10.1.2. Criteria for evaluating the severity

Table 4. Classification of hypoglycaemia

Mild: autonomic symptoms are present. The person is able to self-treat.
Moderate: Neuroglycopenic symptoms are present. The person is able to self-treat.
Grave/Severe: requires the assistance of another person. A loss of consciousness may take place. The blood glucose level is usually less than 2.8 mmol/l (50.4 mg/dl).

Source: Canadian Diabetes Association [491].

Table 5. Classification of hypoglycaemia

Severe hypoglycaemia: Event that requires the assistance of another person to administer carbohydrates, glucagon or resuscitative measures. Glucose measurements may not be available during this event; but if there is recovery of the neurological functions after recovery of normal blood sugar, it will be considered that the incident was caused by a low concentration of glucose. **Documented symptomatic hypoglycaemia:** Event during which typical symptoms of hypoglycaemia are accompanied by a measure of blood glucose concentration ≤ 70 mg/dl (3.9 mmol/l). **Asymptomatic hypoglycaemia:** Event that is not accompanied by the typical symptoms of hypoglycaemia, but in which there is a measure of blood glucose concentration ≤ 70 mg/dl (3.9 mmol/l). **Likely symptomatic hypoglycaemia:** Event that has the typical symptoms of hypoglycaemia, but in which no measurement of blood glucose has been taken (but presumably was caused by a glycaemia ≤ 70 mg/dl (3.9 mmol/l). **Relative Hypoglycaemia:** Event in which the person states to have had any of the typical symptoms of hypoglycaemia and is interpreted as indicative of hypoglycaemia, and that in the measurement of glucose the value amounts to > 70 mg/dl (3.9 mmol/l) but is close to that figure.

Source: American Diabetes Association Workgroup on Hypoglycaemia 492.

Recommendations

√	Small children with diabetes mellitus type 1 always require adult assistance to solve hypoglycaemia. The severity of hypoglycaemia is established exclusively based on the symptomatology.

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10.1.3. Performance measures in case of hypoglycaemia

The goal of the treatment for hypoglycaemia is to provide a rapid rise to a safe blood sugar level, eliminating the risk of accidents or damage to the patient, and relieving symptoms quickly. It is also important to avoid overtreatment, which can lead to rebound hyperglycaemia and weight gain.

10.1.3.1. Mild or moderate hypoglycaemia

The RCT by Wiethop *et al*.[494] (n = 6) compared the administration of 10 g and 20 g of oral glucose, 1 mg of subcutaneous glucagon and placebo. Compared to placebo, the rest of the treatments significantly increased plasma glucose levels, albeit transiently. Glucagon achieved significantly higher glucose levels compared with other groups. RCT 1+

Another RCT[495], with 41 adults, compared seven methods of administering oral glucose (glucose solution, glucose tablets, glucose gel, sucrose solution, sucrose pellets, hydrolyzed polysaccharide solution and orange juice). The seven compounds were able to raise blood glucose levels after 20 minutes, although the glucose gel and orange juice did not increase, glucose levels as much as the others did. RCT 1+

A Canadian guide[491] proposes the administration of 15 g of oral glucose to produce an increase of approximately 37.8 mg/dl (2.1 mmol/l) in approximately 20 minutes, which would achieve the improvement or disappearance of the symptoms in most patients. If the oral glucose dose is 20 g, an increase of around 64.8 mg/dl (3.6 mmol/l) occurs in 45 minutes. Other options, such as milk or orange juice, are slower in recovering glucose levels and improving the symptoms. The use of glucose gel also produces a slow recovery (<1.0 mmol/l or 18 mg/dl increase in 20 minutes). Expert opinion 4

Subcutaneous or intramuscular administration of 1 mg of glucagon causes a significant increase in blood glucose ranging from 54 mg/dl to 216 mg/dl (3.0 mmol/l to 12.0 mmol/l) in 60 minutes. This effect is prevented in people who have consumed more than two standard measures of alcohol in the hours before, or people with advanced liver disease. The guide states that there are no studies in patients with gastropathy.

No RCTs, which had been specifically carried out with children, adolescents and pregnant women, were found.

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10.1.3.2. Serious or severe hypoglycaemia

Intramuscular glucagon vs. intravenous glucose

An RCT[414] compared the administration of 1 mg of IM glucagon with 50 ml of IV glucose at 50% in 29 adult patients who had been treated with insulin and had entered hypoglycaemic coma. There was a level of consciousness recovery significantly slower in the group treated with glucagon. Two of the patients who had been treated with glucagon required an additional administration of IV glucose, as there were no signs of clinical improvement within 15 minutes of the treatment. RCT 1+

Another RCT[496] compared the administration of 1 mg of IM glucagon to 50 ml of glucose at 50% in 14 adults with severe hypoglycaemia. The recovery time ranged from 8 to 21 minutes in the group treated with glucagon and from 1 to 3 minutes in the group treated with IV glucose. RCT 1+

Intravenous glucagon vs. intravenous glucose

An RCT[415] compared the IV administration of 1 mg of glucagon *vs*. 50 ml of IV glucose at 50% in 49 adults treated with insulin and hypoglycaemic coma. There was a recovery of the normal level of consciousness significantly slower in the group treated with glucagon. RCT 1+

The authors of the NICE CPG 2004[7] consider that 10% is the maximum amount of IV glucose, which should be administered to children and youth. CPG 4

Intravenous glucagon (IV) vs. intramuscular glucagon (IM)

An RCT[497] compared the effectiveness of glucagon depending on the route of administration (1 mg IM *vs*. 1 mg IV) in 99 patients (20 of them under 20 years old) following a treatment with insulin, with hypoglycaemia, treated in hospital emergency units. No significant differences were found between the two groups in the number of patients who awoke or were able to take oral glucose after 15 minutes of treatment. RCT 1+

A second RCT[498] also compared 1 mg of IM glucagon *vs*. 1 mg of IV glucagon in 15 adults to whom hypoglycaemia was provoked. After 20 minutes and 40 minutes of treatment, the treated group with IM glucagon showed glucose levels in plasma significantly higher than the group treated with IV glucagon. RCT 1+

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Intramuscular glucagon vs. subcutaneous glucagon

An RCT[499] compared the IV and SC administration of 20 μg/kg of glucagon, in 30 children and young people who had been provoked hypoglycaemia. No differences were found between groups in the levels of glycaemia or glucagon in the blood.

RCT 1+

Intranasal glucagon vs. subcutaneous glucagon

An RCT[500] compared the intranasal administration of glucagon *vs*. the SC administration, in 12 young people who had been provoked hypoglycaemia. No significant differences were found in blood glucose levels after 15 minutes. However, after 45 minutes, the increase in glucose levels was significantly higher in the group receiving the SC route. However, 90% of children and young people who received SC treatment had nausea, compared with the 10% in the group receiving intranasal insulin in which 4 children in this group had nasal irritation.

RCT 1+

Another RCT[501], carried out with six adults who had been provoked hypoglycaemia, showed no differences between the intranasal administration and the SC one, in the groups regarding an increase in plasma glucose levels.

RCT 1+

Intranasal glucagon vs. intramuscular glucagon

An RCT[502] compared the administration of intranasal glucagon *vs*. the IM administration in 30 adults with hypoglycaemia. The average increase in the levels of blood glucose was higher in the group given IM glucagon.

RCT 1+

Combination therapy of intravenous glucose + intramuscular glucagon vs. intravenous glucose

An RCT[503] comparing the combination therapy of IV glucose and IM glucagon *vs*. IV glucose in 18 adults with hypoglycaemia treated in emergency services found no significant differences in plasma glucose levels between the groups.

RCT 1+

Intramuscular epinephrine vs. intramuscular glucagon

An RCT[504] comparing the administration of IM epinephrine *vs*. IM glucagon in children and young people who had been provoked hypoglycaemia showed that epinephrine was significantly less effective than glucagon to raise plasma glucose levels. Nine of the 10 children and young people complained of severe nausea after the administration of glucagon.

RCT 1+

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Intravenous dextrose at 10% vs. intravenous dextrose at 50%

An RCT[505] compared two dextrose solutions at different concentrations (10% *vs*. 50%), with increments of 5 g of dextrose to a maximum dose of 25 g in 51 adults, treated for hypoglycaemia by ambulance emergency paramedics. No differences were found between the two treatments in relation to mean recovery time (8 minutes), the mean score on the Glasgow Scale of Consciousness or recurrent episodes of hypoglycaemia in the next 24 hours. Those treated with dextrose at 10% received less total dose of dextrose and their glucose levels after the treatment were lower.

RCT
1+

Educational programs to improve the identification of hypoglycaemia

Training to improve the identification of hypoglycaemia aims to instruct patients on the interpretation of physical symptoms, diet, exercise, the dosage and insulin action, and the measurements of blood glucose to suspect.

An RCT compared an educational program to improve the identification of hypoglycaemia and its impact on the number of hypoglycaemia *vs*. no education after starting more intensive management of diabetes[506]. No differences in the recognition of symptoms of hypoglycaemia between the groups were found, however, the educational program led to better detection of low glucose levels in patients who initiated intensive management of diabetes.

RCT
1+

An RCT in 111 adults with DM1[507] analyzed an educational program *vs*. a control intervention and found a better recognition for both low and high glucose levels and a significant reduction in the frequency of severe hypoglycaemia in the trained group.

RCT
1+

Another RCT[508] examined the effect of a structured psycho-educational training program in anticipation, awareness and treatment of hypoglycaemia in 60 people with a history of recurrent severe hypoglycaemia evaluated for 18 months. This study found that the program significantly decreased the number of mild, moderate and severe episodes of hypoglycaemia.

RCT
1+

An RCT[47] examined the effect of an educational program (HyPOS) in 164 patients suffering from hypoglycaemia, and found that this intervention was more effective than the traditional program of clinical care with regard to increased recognition of hypoglycaemia awareness, significantly increasing the threshold level of detection of hypoglycaemia and its treatment and significantly reducing the number of weekly episodes of hypoglycaemia undetected and the rate of mild hypoglycaemia. The rate of severe hypoglycaemia showed no statistically significant differences.

RCT
1+

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10.1.3.3. Pregnancy and breastfeeding

Regarding pregnancy, the NICE CPG 2004[7] makes the following recommendations: CPG 4

- Inform and advise pregnant women with diabetes on the risks of hypoglycaemia and lack of recognition of hypoglycaemia during pregnancy, particularly in the first trimester.
- Give women a glucose concentrated solution and glucagon and educate both themselves and their partners and acquaintances on their use.

Regarding the postpartum period, the NICE CPG 2008[9] made the following recommendations: CPG 4

- Advise women to reduce the insulin dose immediately after delivery and to monitor their blood glucose levels carefully to establish the appropriate dose.
- Inform women of the increased risk of hypoglycaemia in the postnatal period, especially during breastfeeding, and advise them to have a meal or snack available before or during breastfeeding.

Summary of evidence

Mild to moderate hypoglycaemia

RCT 1+	The administration of oral glucose causes a faster increase of glycaemia than orange juice and glucose gels[491, 493].
RCT 1+	The administration of subcutaneous glucagon causes higher blood glucose levels than the oral administration of glucose[494].
RCT 1+	The subcutaneous or intramuscular administration of 1 mg of glucagon causes a significant increase of glucose from 54 to 216 mg/dl (3.0 mmol/l to 12.0 mmol/l) in 60 minutes[491].

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Severe Hypoglycaemia

RCT 1+	In the case of severe hypoglycaemia, the recovery of consciousness is slower with the intravenous administration of 1 mg of glucagon than with the intravenous administration of 50 ml of glucose at 50%[415].
RCT 1+	The comparison of the effect produced by the intravenous administrations *vs*. the intramuscular administration of glucagon after 15 minutes has not shown definitive results: An RCT has shown no significant differences[497] while other RCT[498] showed blood glucose levels significantly higher with intramuscular administration.
RCT 1+	No differences were found in blood glucose levels or glucagon in blood by intramuscular or subcutaneous administration of 20 μ g/kg of glucagon[499].
RCT 1+	The comparison between the intranasal or subcutaneous administration of glucagon has not shown significant differences in blood glucose levels measured 15 minutes after administration[500, 501].
RCT 1+	One study has shown a higher average increase in blood glucose levels through the treatment with intramuscular glucagon than with intranasal glucagon[502].
RCT 1+	No significant differences were demonstrated in the plasma glucose levels between the combined therapy with intravenous glucose and intramuscular glucagon *vs*. intravenous glucose[503].
RCT 1+	Epinephrine is less effective than glucagon to increase plasma glucose levels[504].
RCT 1+	No differences were found between the treatment with intravenous dextrose at 10% *vs*. intravenous dextrose at 50% in relation to the mean recovery time (8 minutes) of hypoglycaemia, the mean score on the Glasgow Scale of Consciousness or recurrent episodes of hypoglycaemia in the following 24 hours[505].
RCT 1+	To prevent hypoglycaemia, once the episode has been overcome, the person should eat regular food that corresponds to that time of day. If the next meal is to take place more than an hour later, it is advisable to eat a snack that contains 15 g of carbohydrates and a source of protein.

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Recommendations

Mild or moderate hypoglycaemia (Appendix 8.1)

A	• Mild or moderate hypoglycaemia needs to be treated by oral ingestion of 10-20g of carbohydrates, preferably in the form of glucose tablets or solutions, sugar or sucrose. These are preferred to fruit juices or glucose gels. Examples of options containing 15 g of carbohydrates: • 15 g of glucose in tablets. • 15 g of sugar dissolved in water (3 teaspoons with sugar or 3 lumps of sugar). • 175 ml (3/4 cup) of juice or sugary drink. • 15 g (1 tablespoon) of honey.
√	Following the administration of oral carbohydrates, the patients or family caregivers must wait 10-20 minutes, measure the blood glucose levels again and repeat the intake of carbohydrates if the glucose level is less than 72 mg/dl (4.0 mmol/l).

Severe hypoglycaemia (Annex 8.2)

√	Severe hypoglycaemia in a conscious person must be treated by oral ingestion of 10-20 g of carbohydrates, preferably in the form of glucose tablets or equivalent. One must wait 15 minutes, measure the blood glucose levels again and repeat the intake of another 15 g of carbohydrates if the glucose level is less than 4.0 mmol/l (72 mg/dl).
√	Severe hypoglycaemia in an unconscious person over 5 years old, if diagnosed at home, should be treated with 1 mg of subcutaneously or intramuscularly injected glucagon. If it is a child under 5 years old, 1/2 mg of subcutaneously injected glucagon should be administered When it is possible to inject intravenously, it should be administered from 10 g to 25 g of glucose (20 cc to 50 cc of dextrose at 50%) for 1 to 3 minutes.
√	Caregivers or support people for patients at risk of severe hypoglycaemia should be trained in the administration of injected glucagon.
√	To prevent hypoglycaemia, once the episode has been overcome, the person should eat regular food that corresponds to that time of day. If the next meal is to take place more than an hour later, it is advisable to eat a snack that contains 15 g of carbohydrates and a source of protein.

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11. Chronic complications

11.1. Cardiovascular risk in patients with diabetes mellitus type 1

Diabetes is associated with an increased risk of cardiovascular disease. There are different approaches to calculate the level of cardiovascular risk in patients with diabetes. One school of thought suggests that the cardiovascular risk for diabetes is considered like a cardiovascular disease. This assumption should be based on prognostic studies, which compare the risk of cardiovascular events in patients with DM to patients who have suffered an acute myocardial infarction (AMI). Another option is to use *cardiovascular or coronary risk equations or tables* to select patients who can benefit most from interventions in cardiovascular primary prevention. In order to make decisions on therapy or intensify therapy (glycaemic control, antiplatelet, lipid lowering, etc.) it is important to know which groups of patients are at increased cardiovascular (CV) risk and who would benefit most of those treatments.

The CPG on DM2, published in our health context[509], discussed this in its chapter on "Screening and treatment of macrovascular complications." It has been upgraded for patients with DM1 from the evidence provided by this CPG, as no studies have been found on this matter.

Cohort studies 2+

To compare cardiovascular morbidity and mortality in patients with diabetes and AMI 15 cohort studies were analyzed[510, 511, 512, 513, 514] that assessed the risk of coronary events in diabetic patients compared to patients with a history of ischemic heart disease and compared to the general population. All studies show an increased coronary risk in diabetic patients compared to the general population. However, the comparative results of coronary mortality among diabetic people and people with a history of ischemic heart disease are contradictory. The differences in results could be explained by multiple factors: differences in the inclusion criteria, lack of uniformity in the definition of diabetes and ischemic heart disease, the way to collect data, inclusion of incident or prevalent cases, patient characteristics (age groups, gender, years of evolution of diabetes), or methodological aspects (difference in the confounding factors considered, population-based cohort or not, different outcomes, follow-up losses, etc.).

Studies analyzing the results by gender agree in pointing that DM in women involves a higher relative risk for coronary heart disease than in men with diabetes[510, 511, 512, 514] and in some cases this risk is the same[510, 512] or even higher[510, 513] to that of women with a history of ischemic heart disease.

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Some studies have assessed the duration of DM and conclude that it is an independent risk factor[515] and that, after 15 years of evolution of the disease, coronary risk is equated with a history of ischemic heart disease,[514, 515, 516].

Based on this evidence it cannot be said that cardiovascular risk is the same in patients with diabetes and in patients with a history of CV disease, therefore other criteria are needed to identify patients at increased CV risk, being possibly the evolution for more than 15 years of diabetes one of them.

Another widely used tool to classify diabetic patients according to CV risk has been the implementation of cardiovascular or coronary risk tables. They estimate the probability of coronary or cardiovascular events in a given time depending on the presence or absence of other risk factors. The risks are constructed based on a special type of cohort study: the "clinical prediction rules" (CPR). The validity and applicability of a CPR to a given population first requires its creation based on a cohort using a multivariate analysis and then a validation process, first in the source population and then in different populations in which the rules want to be applied[517].

There is a risk function exclusively for diabetic patients based on the results of the UKPDS study. It has the advantage of using the years of duration of diabetes and HbA_{1c} levels as independent risk factors and providing, as well as the coronary risk, the risk of stroke.

The Verifica study[518], performed on 5732 patients, of whom 941 (16.4%) had diabetes, found no significant differences between the expected event rate by the calibrated Framingham equation with those really observed in the follow-up cohort in the different risk categories. The study population was relatively young (mean 56.3 years) so it is assumable that the evolution of the disease was relatively short.

Currently, the REGICOR equation (also called calibrated Framingham), is the CPR that has a better validation among our population[518, 519, 520].

The development group of this CPG (GEG) has considered that in case of using a clinical prediction rule, the most appropriate would be REGICOR. However, the population included in the Verifica study, who validated this prediction rule in Spain, includes general population over 35 years old with a very small proportion of patients with DM1. Therefore, none of the clinical prediction rules developed so far can be recommended, because they probably underestimate cardiovascular risk in patients with DM1.

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Summary of evidence

Cohort studies 2 +	Cardiovascular risk cannot be stated as being similar in patients with diabetes and in patients with a history of CV disease, so other criteria are needed to identify patients with higher CV risk, being maybe the evolution of diabetes for more than 15 years one of them[509, 510, 511, 512, 513, 514, 515, 516].
Cohort studies 2 +	Another widely used tool to classify patients with diabetes depending on CV risk, has been the application of arterial risk clinical prediction tables. They estimate the probability of coronary or cardiovascular events in a given time depending on the presence or absence of other risk factors. Currently the REGICOR equation (also called calibrated Framingham), is the CPR that has a better validation among our population[518, 519, 520]. However, the population included in the Verifica study, who validated this prediction rule in Spain, includes general population over 35 years old with a small proportion of patients with DM1 and therefore may underestimate the cardiovascular risk in adults with type 1 diabetes.

Recommendations

B	The use of arterial risk clinical prediction rules is not recommended in adult patients with diabetes mellitus type 1, as these may underestimate their cardiovascular risk.
√	An individualized evaluation of the cardiovascular risk of patients with diabetes mellitus type 1 based on the presence or absence of risk factors such as age, genre, duration of the disease, glycated haemoglobin levels, blood pressure, smoking or LDL levels is recommended.
√	The evaluation of arterial risk factors should be made at least annually and include: • age, • evolution of the disease, • Family history of vascular disease, • smoking habits, • albumin excretion ratio, • blood glucose control, • blood pressure, • complete lipid profile (including HDL-C, LDL-c and triglycerides) • abdominal adiposity.

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√	Adults with a high rate of albumin excretion (microalbumin) or two or more features of the metabolic syndrome should be managed as high-risk category.
√	Adults with diabetes mellitus type 1 who are not in the category of higher risk but have some arterial risk factor (over 35 years old, family history of premature coronary disease, high-risk ethnicity or severe lipidemia alterations or blood pressure) should be managed as a moderately high risk group.

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11.2. Diabetic retinopathy

Key question:

- Is there any medical treatment (not surgical, not laser) to prevent diabetic retinopathy?
- When should the screening of diabetic retinopathy start?
- How often should diabetic retinopathy screening take place?
- What should be the techniques for the screening of diabetic retinopathy?

Diabetic retinopathy (DR) is a major complication of diabetes. The following information is known about its incidence:

- In developed countries, DR is the leading cause of blindness in people under 60.
- This disease is usually detected when more than 15 years have elapsed from the diagnose of diabetes.
- Most of the anomalies caused by DR are silent and do not cause any symptoms.
- Current treatments of DR are mainly based on laser photocoagulation and surgery. The laser photocoagulation treatment is an aggressive therapy, and requires an early diagnosis of the retinopathy to achieve good results.

Most patients who develop DR are asymptomatic until advanced stages (macular oedema and/or proliferative DR), and once they reach these phases treatment may be less effective. As progression can be fast and available therapies can be beneficial to the improvement of symptoms and to slow the progression of the disease, it is important to perform regular screening for diabetic retinopathy.

11.2.1. Preventive medical treatment of diabetic retinopathy

Key question:

- Is there and medical treatment (not surgical, not laser) to prevent diabetic retinopathy?

The CPG NICE 2004[7] provides no evidence on this issue.

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The main source of evidence comes from a systematic review of good quality clinical trials[521] that analyzes the effectiveness of interventions for primary and secondary prevention of diabetic retinopathy and presents the following results:

Primary prevention of retinopathy

Intensive diabetes treatment

The study Diabetes Control and Complications Trial (DCCT)[522], carried out in 1441 DM1 patients randomly assigned to intensive treatment [(HbA_{1c} <7.2% (48 mmol/mol)] *vs*. conventional treatment, found a 76% decrease in the incidence of DR (95% CI: 62% to 85%). RCT 1+

Drugs that inhibit the renin-angiotensin-aldosterone

The DIRECT-Prevent 1 study[523] included 1421 patients with DM1 without retinopathy, normotensice and with albuminuria, randomly assigned to a treatment with candesartan (16 mg/24 h during the first month and 32 mg in the second month) *vs*. placebo, with a 4.7-year follow-up. According to this study, the treatment with candesartan did not reduce significantly the incidence of DR, defined as two or more changes in the Early Treatment Diabetic Retinopathy Study scale levels [RR 0.82 (95% CI: 0.67 to 1)]. RCT 1+

Instead, applying more restrictive criteria to define the incidence (at least 3 levels in Early Treatment Diabetic Retinopathy Study scale), the protective effect was statistically significant [RR 0.65 (95% CI 0.48 to 0, 87)] and persisted when adjusting for baseline characteristics such as duration of diabetes, HbA_{1c} and SBP [RR 0.71 (95% CI 0.53 to 0.95)].

Vasodilator drugs

A Cochrane review[524], which examined the effectiveness of pentoxifylline, concluded that while this drug can be effective in preventing retinal neovascularisation and its recovery, no studies have analyzed the methodological quality enough, thus, no conclusive results have been found. SR pf RCT 1++

Angioprotector drugs

An RCT[525] analyzed the effect of calcium dobesilate versus placebo in the permeability of the blood-retinal barrier in patients with type 2 diabetes and early diabetic retinopathy. This trial randomly assigned 194 patients to a treatment with 2 g of calcium dobesilate *vs*. placebo on a daily basis. A total of 137 patients completed the study, which lasted 24 months. RCT 1+

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The primary outcome analyzed was the reason for further penetration into the vitreous (RPPV). The mean changes in the base levels after 24 months were significantly lower in the treatment group [mean (SD) -3.87 (2.03), P = 0002] than in the placebo group [mean (SD) 2.03 (2.86)]. The difference remained regardless of the diabetes control levels. A subgroup analysis in patients without antihypertensive and/or lipid-lowering drugs also showed a significant difference [mean (SD) -3.38 (13.44) *vs*. 3.50 (13.70), P = 0.002) after 24 months.

The findings of the trial show a significant activity of calcium dobesilate versus placebo in the prevention of the blood-retinal barrier breakdown regardless of diabetes control, being drugs well tolerated by patients.

Secondary prevention

Intensive treatment of diabetes

In a meta-analysis of 17 RCTs with a total of 529 patients[526,527], the conventional treatment was compared with the intensive treatment for 5 years. After 6 and 12 months of follow-up, the risk of retinopathy progression showed no statistically significant differences between both groups but became significantly lower in the intensive therapy group [OR 0.49 (95% CI 0.28 to 0.85), P = 0.011) after more than two years of follow up.

SR of RCT
1+

The *Diabetes Control and Complications Trial Study* (DCCT) trial, which included 1055 adults and 156 adolescents, carried out eye examinations, assessment of visual acuity and eye fundus photographs. The study showed a reduction of 54% in the progression of DR (95% CI: 39% to 66%) in patients undergoing intensive treatment. The evaluation of the results after 10 years of follow up[528] determined that the HbA_{1c} was similar between the original group of intensive therapy and the group receiving conventional treatment. The adults from the intensive therapy group showed a slower progression of diabetic retinopathy than the conventional therapy group

RCT
1+

Another trial[529], involving 70 patients with DM1 with low C-peptide levels and nonproliferative mild to moderate DR, compared the intensive treatment (insulin pump) versus the conventional treatment. During the first 2 years of follow-up, a greater progression of diabetic retinopathy was observed in the intensive treatment group. After 2 years, the trend equated, and even less deterioration was observed in the intensive treatment group.

RCT
1+

In the *Stockholm Diabetes Intervention Study trial*[530], the intensive treatment was compared to the conventional treatment in 96 patients with nonproliferative DR. Retinopathy increased in both groups, but after 5 years the outcome was worse for the conventional therapy group (OR 0.4, p = 0.04).

RCT
1+

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The Oslo study[275, 276, 277] compared 45 patients with DM1 who received intensive treatment with insulin pump *vs*. insulin treatment with multiple injections (5-6/per day) and *vs*. conventional treatment (2 injections per day). It was found that HbA_{1c} levels greater than 10% were associated with increased risk of retinopathy progression (p = 0.014) and lower values of 7-8% with a lower risk of progression.

RCT
1+

A more recent study[531] included 65 patients randomized to a treatment group with infusion pump (n = 36) *vs*. a standard treatment group (n = 29). No significant differences were found between the two groups in terms of baseline retinopathy, metabolic control or proteinuria, or of the progression of diabetic retinopathy.

RCT
1+

Renin-angiotensin-aldosterone inhibitor drug

The DIRECT-Protect 1 study[523] showed no significant decrease in the risk of proliferation of DR in the treatment group with candesartan (16 mg/24 h during the first month and 32 mg in the second month) *vs*. placebo [RR 1.02 (95% CI 0.80 to 1.31), P = 0.85].

RCT
1+

The EUCLID (*EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus*) study[532] was carried out with 360 normotensive patients with DM1 and normal albumin, who were randomly assigned to a group treated with lisinopril (10 mg/day, increased to 20 mg/day after 3 months once having reached the DBP <75 mm Hg target) *vs*. placebo. After a 2-year follow-up, there was a 50% decrease in the progression of DR (95% CI: 28% to 89%) and the progression to proliferative DR was of 80%.

RCT
1+

In the *Renin Angiotensin System Study* (RASS)[533], a multicentre controlled trial with 285 normotensive patients with DM1 and normal albumin, the patients were randomized to a treatment with losartan (100 mg/per day), enalapril (20 mg/per day) or placebo. During the 5-year follow-up the progression of diabetic retinopathy was assessed, this being defined as a progression of two or more steps in the retinopathy severity scale. The results showed a reduction in the incidence of retinopathy progression in the groups treated with inhibitors of the renin-angiotensin-aldosterone system, which was reduced by 65% in the group treated with enalapril [OR 0.35, (95% CI 0.14 to 0.85)] and 70% in the group treated with losartan [OR = 0.30 (95% CI 0.12 to 0.73)], regardless of the changes in blood pressure.

RCT
1+

Drugs with platelet antiaggregatory effect

An SR[534] that evaluated the effectiveness of acetylsalicylic acid (ASA) alone or in combination with dipyridamole for the treatment of DR (ASA 650 mg/per day to 990 mg/per day, dipyridamole 225 mg/per day) in studies lasting from 8 weeks to 5 years, found a significant increase of microaneurysms in the placebo group *vs*. the group that followed the treatment with ASA.

SR of RCT
1++

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The BTRS Belgian trial[535] that evaluated the effectiveness and safety of a treatment with ticlopidine 250 mg/per day *vs*. placebo found no significant differences between both groups. RCT 1+

The TIMAD study[536] evaluated the effectiveness and safety of ticlopidine (500 mg) for the treatment of diabetic retinopathy in patients with DM1 and DM2. Ticlopidine was effective in preventing the occurrence of microaneurysms (p = 0.03) versus placebo. However, the group receiving ticlopidine (n = 215) had higher rates of adverse effects and dropouts that the placebo group (n = 220). RCT 1+

A study that evaluated the effects of the treatment with dipyridamole[537] in 31 insulin-dependent patients, showed a lower retinopathy deterioration in patients treated with dipyridamole versus placebo after 30 months (p <0.05) and at the end of the study (36 months) (p <0.0025). RCT 1+

A clinical trial carried out in the Spanish healthcare context[538], in 17 patients with insulin-dependent diabetes and retinopathy, found a significantly better evolution (less leakage in the fluorescein examination and fewer microaneurysms) in the group treated with 300 g of triflusal 3 times per day for 2 years. However, no significant differences were found in terms of visual acuity and visual campimetry. RCT 1+

Summary of evidence

Primary prevention	
RCT 1+	The intensive treatment of diabetes with HbA_{1c} levels below 7.2% reduces the risk of retinopathy[522].
RCT 1+	The treatment with candesartan (dose of 16 mg/24 hours to 32 mg/24 hours) may be protective to the occurrence of diabetic retinopathy (*increase of at least 3 levels in the Early Treatment Diabetic Retinopathy Study scale*)[523].
RCT 1+	The evidence available does not show conclusive results on the effectiveness of pentoxifylline in preventing retinal neovascularization[524].
RCT 1+	Calcium dobesilate (2 g/day) may be effective in preventing the blood-retinal barrier[525] in patients with diabetes.
Secondary prevention	
SR of RCT 1++ RCT 1+	Intensive treatment of diabetes with HbA_{1c} levels below 7.2% could slow the progression of diabetic retinopathy after 2 years of evolution of the disease[526, 527, 529] after 5 years and 10 years[530 528], although no study has yet shown any significant differences with the conventional treatment 531.
RCT 1 +	HbA_{1c} levels below 7% are associated with a better progression of diabetic retinopathy[275, 276, 277].
RCT 1 +	Treatment with lisinopril (10 mg/per day, increased to 20 mg/per day after 3 months having reached the DBP <75 mm Hg target) may improve the progression of diabetic retinopathy compared to placebo (p <0.0025) 532.

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Recommendations

A	It is important to inform people with diabetes mellitus type 1 and their families that the control of long-term blood glucose with HbA_{1c} levels lower or equal to 7% decreases the incidence and progression of diabetic retinopathy.

11.2.2. Diabetic retinopathy screening techniques

The CPG NICE 2004[7] provides evidence that has been included in each of the subsections.

Direct ophthalmoscopy

According to the SR by Cummins *et al*.[539], direct ophthalmoscopy does not comply with the necessary standards to constitute a screening tool because its sensitivity is low, regardless of the training received by the health professionals who use it: DS II

- *Direct ophthalmoscopy with mydriasis carried out by primary care physicians:*
  Sensitivity in detecting vision-threatening retinopathy 33-66%; detection of preproliferative retinopathy and proliferative retinopathy: 32-50%[540].
- *Direct ophthalmoscopy with mydriasis carried out by ophthalmologists:*
  Sensitivity in detecting threatening retinopathy: 65% sensitivity for the detection of proliferative retinopathy: 70%[540].

  The CPG NICE 2004[7] places the sensitivity at 91% (76-97%), when performed by an ophthalmologist using a slit lamp in mydriatic eye.
- *Direct ophthalmoscopy with mydriasis carried out by other professionals:*
  Sensitivity: 27% to 81% when performed by other professionals (endocrinologists, hospital doctors, technicians, etc.).

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Indirect biomicroscopy with slit lamp

A study of diagnostic tests included in the systematic review Cummins *et al*.[539] indicates that this technique, carried out by experienced staff, can achieve sensitivities similar to retinal photography. DS II

A study[541] carried out in 189 patients (32 patients with DM1) analyzed the diagnostic capability of slit lamp biomicroscopy for the detection of early vascular changes identified by fluorescein angiography, obtaining a sensitivity and specificity of 91.2% and 97.9%, respectively. The concordance obtained between both tests was 87%. DS Ia

The CPG SIGN DM 2001[11] states that: DS II

The slit lamp biomicroscopy, used by properly trained staff, can achieve similar[542] or higher[543] sensitivities to those achieved by retinal photography, and with a less technical failure rate. However, the slit lamp biomicroscopy is of limited value as a screening tool [544].

Retinal Cameras

The CPG of DM SIGN 2001[540] indicated that retinal photography often achieves a sensitivity of 80% and is more effective than direct ophthalmoscopy, reaching a sensitivity of 80% in rare cases, even when performed by trained specialists[542]. DS II

A prospective study[545] performed 108 ophthalmic scans on 55 people with DM to evaluate the diagnostic performance of the retinography at 45° non-mydriatic with a central image or three images compared to the technique used in the *Early Treatment Diabetic Retinopathy Study* (7 35 mm stereoscopic mydriatic colour photographs) as gold standard. The sensitivity and specificity of the non-mydriatic retinography system at 45 degrees with 3 images for DR were 82% and 92%, respectively, and for the system with a central image, the values were 71% and 96% respectively. This study concluded that the fundus images from 45º to 3-colour field without mydriasis could be an effective screening tool to identify critical degrees of DR and diabetic macular oedema that need to be referred to a specialist. A central image at 45º is enough to determine the absence or presence of DR and diabetic macular oedema, but not enough to graduate its clinical significance. DS II

A study involving[586] patients (103 with DM1)[546] compared the use of the indirect ophthalmoscopy performed by an ophthalmologist (gold standard), conventional photography and digital photography, and found similar results to those reported in previous studies: lower sensitivities from the ophthalmoscopy than from the photography and similar sensitivities between the conventional and the digital photography (both above 90%) with 89% and 87% specificities, respectively. The rate of non-evaluable images or that required repetition was 50% lower in the digital photography. DS II

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According to the SR by Cummins *et al*.[539], the results are not consistent in connection with the use of mydriasis in retinal photography cameras and there are few differences in accuracy and failure rate of retinal cameras used with or without mydriasis. SR of DS II

The review carried out by Facey *et al*.[547] indicated that there is no strong evidence to suggest that mydriasis reduces failure rates, although the studies available point in this direction. Moreover, up to 6% of patients considered mydriasis unacceptable. Failure rates of retinal cameras are estimated around 4.4% for the dual field with mydriasis and 3.5% for a single field with mydriasis. SR of DS II

Summary of evidence

DS II	Retinography using a non-mydriatic 45-degree 3 field camera is an effective tool for screening diabetic retinopathy critical degrees that need to be referred to a specialist[539, 542, 545, 546, 547].
DS II	A central image at 45 degrees is enough to determine the absence or presence of diabetic retinopathy and diabetic macular oedema, but not enough to graduate clinical significance[545].

Recommendations

B	The retinal digital photography obtained by non-mydriatic camera should be implemented in retinopathy screening programs for adults and children with diabetes mellitus type 1.
B	Should a camera not be available, screening will be carried out through an ophthalmoscopy (with or without mydriasis), which will be evaluated by an ophthalmologist.
√	The use of retinal digital photography obtained electronically by a non-mydriatic camera facilitates the screening performance for both the patient and the health staff.
√	Although retinal digital photography may detect many clinically significant alterations, digital photographs of the retina should not replace the full initial examination and with mydriasis of the retina.

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11.2.3. Start time and frequency of screening for diabetic retinopathy

The CPG NICE 2004[7] includes the following evidence:

Age of onset for screening

A cohort study[548] carried out in 937 patients aged 6 to 20 years old showed that 9% of children under 11 had retinopathy (n = 110, mean age 9.5 years), while in children over 11 years (n = 827, mean age 14 years) the percentage increased to 29%. The risk of developing retinopathy increased according to the duration of DM [OR 1.22 (95% CI: 1.16 to 1.29)], age [OR 1.13 (95% CI: 1.06 to 1, 21)], and higher levels of HbA_{1c} [OR 1.26 (95% CI: 1.11 to 1.43)]. Based on these data, the authors of this study recommend initiating screening of DR from the age of 12.

Cohort study 2+

Frequency of screening

The work by Younis *et al*.[549] estimated optimum screening intervals by an actuarial survival analysis from the incidence rates found in the 'Liverpool Screening Programme' between 1991 and 1999.Thus, it determined a mean screening interval free of sight-threatening retinopathy of 5.7 years (95% CI: 3.5 to 7.6 years) for patients without retinopathy at baseline screening, 1.3 years (95% CI: 0.4 to 2.0 years) for incipient retinopathy, and 0.4 years (95% CI: 0 to 0.8 years) for mild preproliferative retinopathy.

Cohort study 2+

In the study by Olafdottir *et al*.[550] 296 diabetic patients were analyzed (96 with DM1) whose evolution of DR was assessed every two years for a period of 10 years. The study of these patients showed the following results:

Cohort study 2+

- Of the total number of patients evaluated, 172 (46 with DM1) did not develop retinopathy within 10 years of follow-up [HbA_{1c}: Mean (SD) 7.8 (1.6), duration of diabetes: mean (SD) 18 years (7)].
- Of the total number of patients evaluated, 96 (38 with DM1) developed mild nonproliferative DR [HbA_{1c}: Mean (SD) 8.1% (1.3), duration of diabetes mean (SD) 18 years (6)].
- Of the total number of patients evaluated, 6 (2 with DM1) developed clinically relevant macular oedema [HbA_{1c}: mean (SD) 9.6% (1.4); duration of diabetes (SD) 20 years (4)].
- Of the total number of patients evaluated, 23 (11 with DM1) developed preproliferative DR [HbA_{1c}: mean (SD) 8.4% (1.7), duration of the diabetes mean (SD) 19 years (5)].

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- Of the patients evaluated, 4 (2 with DM1) developed proliferative DR [HbA_{1c}: mean (SD) 9.5% (1.7), duration of diabetes 18, 15, 18 and 12 years].

A retrospective observational study conducted in the Basque country[551] that estimated the most adequate frequency of screening for diabetic retinopathy in 490 patients (70.8% with DM1), found that 86% of the patients free of retinopathy at the baseline examination remained free of retinopathy after 2 years. When considering the impact in relation to the development of high-risk retinopathy, it was found that among patients with DM1, over 95% of patients remained free of high-risk retinopathy at the end of the fourth year, regardless of the time of evolution and the metabolic control of their diabetes. 94% of patients with non-proliferative mild retinopathy at baseline remained free of high-risk retinopathy at the end of the two years. The results of this study indicate that the frequency recommended to screen high-risk retinopathy in patients without retinopathy is 4 years and 2 years in people with diabetes mellitus type 1 with nonproliferative mild diabetic retinopathy, although the data suggest that for people with good metabolic control of diabetes this interval could be even 3 years.

Observational study 2+

Summary of evidence

Cohort study 2 +	The risk of developing retinopathy increases according to the duration of diabetes, age and higher HbA_{1c} levels[548, 550].
Observational study 2 +	86% of patients free of retinopathy at the baseline examination remain free of retinopathy after 2 years of evolution[549, 551].
Observational study 2 +	94% of patients with nonproliferative mild retinopathy at the baseline study remained free of high-risk retinopathy at the end of the 2-year follow-up[549, 551].

Recommendations

B	In people with diabetes mellitus type 1, it is recommended to start screening for retinopathy after puberty, or after 5 years since the diagnosis of diabetes.
B	If retinopathy is detected, it is considered advisable to perform a screening for retinopathy once a year.
B	Should retinopathy not be detected in the baseline examination of the retina, it is recommended to perform a retinopathy screening every 2 or 3 years.

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11.3. Diabetic nephropathy

Key question:

- Which are the criteria for referral to nephrology specialists of patients with diabetic nephropathy?
- Which is the pharmacological treatment of patients with diabetes mellitus type 1 and microalbuminuria?
- Which is the frequency of screening for diabetic nephropathy?
- At what age or years of evolution is screening for diabetic nephropathy due?
- What methods should be used to screen diabetic nephropathy?

Diabetic nephropathy (DN) is one of the most serious complications of diabetes and the single most important cause of the development of end renal stage disease (ESRD), leading to an increase of premature morbidity and mortality in these patients. Its prevention and treatment are possible with early diagnosis, hence the importance of screening for its detection.

11.3.1. Criteria for referral of patients with diabetic nephropathy to specialized care nephrology units

Chronic renal failure (CRF) is defined as the decrease in renal function, expressed as decreased glomerular filtration rate (GFR) below 60 ml/min/1.73 m 2 of body surface or the presence of renal damage persistent for at least 3 months. The diagnosis of CRF is directly confirmed by the presence of histological alterations, or indirectly, by parameters such as microalbuminuria or proteinuria, or alterations in the urinary sediment.

The classification of renal damage according to the GF is as follows:

Table 6. Kidney damage depending on the glomerular filtration

Stage	GF(ml/min/1.73m^2)(glomerular filtration)	Description
1	> 90	Kidney damage with normal GF
2	60-89	Kidney damage, slight decrease in GF
3	30-59	Moderate decrease in GF
4	15-29	Severe decrease in GF
5	<15 or dialysis	Pre-dialysis/dialysis

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From stage 3, it is considered that there is renal failure, although these alterations must be confirmed for at least 3 months to confirm the chronicity of the disorder.

In clinical practice, the assessment of the renal function must be performed by the following methods:

- Calculation of the GF through the MDRD or Cochcroft-Gault formulae. The determination of serum creatinine cannot be used as single parameter for the assessment of the renal function.
- Microalbuminuria. Collecting a single morning urine sample by the determination of the albumin/creatinine ratio (normal <30 mg/g or mcg/mg) is advisable. This ratio represents a good estimation of proteinuria and prevents urine collection for 24 hours.

It is a known fact that late referral of CKD patients to specialized care units in nephrology is associated with negative consequences: initiation of renal replacement therapy in a worse clinical situation, in an unplanned way and with the need in many cases of urgent haemodialysis with vascular access through temporal catheters; preventable hospitalization; accelerated loss of renal function, etc. In addition, late referral of patients with CKD to specialized care units in nephrology has emerged as an independent factor of increased mortality risk after starting dialysis[552, 553; 554, 555; 556; 557]. Moreover, patients with diabetes start renal replacement therapy with a significantly higher comorbidity than patients without diabetes[558].

It is estimated that in Europe 35% of patients are referred late to a nephrologist[559, 560]. In Spain, the percentage is 23%, being the average creatinine clearance in these patients 30 ml/min[552, 555]. A study carried out in Canada that describes the characteristics of patients arriving for the first time to the nephrology clinic[561], indicated that the mean creatinine clearance (SD) in these patients was 64 ml/min 39, but two-thirds of the cases had a creatinine clearance less than 60 ml/min, and 20 patients (13%) had CKD at stage 4. Another study[562], which retrospectively analyzed all patients seen for the first time in the nephrology unit of the Hospital General Universitario Gregorio Marañón in Madrid between January and December 2003 (n = 612, 28.4% with diabetes) observed renal insufficiency in 64% of cases, a high prevalence of arterial hypertension (HTN) (71%), and use of inhibitors of the renin-angiotensin system in only 42% of hypertensive patients. These studies show a delay in referral of patients to nephrology, which worsens the prognosis of the patient and the costs for the healthcare system. The ability to act promptly in the early stages of kidney damage and slow the evolution to progressive renal disease requires careful planning of renal damage detection and intensive treatment against two etiological factors of renal failure: hypertension and diabetes.

Therefore, it is important to determine the optimal time in the clinical course of the disease in relation to the degree of renal function in which a patient should be referred to the specialized care units in nephrology.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and it rapidly was not been reviewed

The CPG NICE 2004[7] does not include studies that examine directly the criteria for referral to a nephrologist of patients with DM1 and diabetic nephropathy.

The *American Diabetes Association*[563] suggests considering referral when the GFR is less than 60 ml/min/1.73 m^2 of body surface or has problems with the managing of blood pressure or hyperkalemia. Expert consensus 4

The *Royal College of Physicians*[564] provides the same criteria for referral of patients without diabetes: Expert consensus 4

I) *Glomerular filtration*

- <15 ml/min/1.73 m^2 of body surface: immediate referral.
- 15-29 ml/min/1.73 m^2 of body surface: urgent referral (routinely referral if it is known to be stable).
- 30-59 ml/min/1.73 m^2 of body surface: routinely referral in the following cases:
  - Progressive fall in GFR/increase in serum creatinine.
  - Microscopic hematuria.
  - P/CR> 45 mg/mmol or 396.12 mcg/mg.
  - Unexplained anaemia (Hb <11 g/dl), abnormal potassium, calcium or phosphate.
  - Suspected systemic disease.
  - Uncontrolled blood pressure (> 150/90 mm Hg on three measurements).
- 60-89 ml/min/1.73 m^2 of body surface: referral is not necessary, unless there are other problems.

II) Kidney problems independent of glomerular filtration

- Immediate referral:
  - Malignant hypertension.
  - Hyperkalemia (potassium> 7 mmol/l).
- Urgent referral:
  - Proteinuria with oedema and low serum albumin (nephrotic syndrome).
- Routinely referral:
  - Proteinuria and P/CR> 100 mg/mmol in urine.
  - Microscopic proteinuria and haematuria.
  - Macroscopic haematuria but negative urological tests.
  - Increased proteinuria without diabetic retinopathy.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

Coordination is needed between primary and specialized care in all stages of chronic kidney disease.

In the consensus document SEN-SEMFyC[565] it is proposed that the referral to nephrology services should be agreed in each health area between the primary care physicians and the nephrology reference service, with written action plans and regular reviews. Expert consensus 4

The referral should be made taking into account the stage of the renal disease, the patient's age, the speed of the renal failure progression, the degree of proteinuria and the occurrence or absence of warning signals.

Summary of evidence

Expert consensus 4	No specific evidence was found to answer this question. The information available comes from the consensus of experts from prestigious entities[7; 563; 564, 565].

Recommendations

D	It is recommended to refer to specialized care units in nephrology those patients with diabetes mellitus type 1 who have at least one of the following criteria: 1.With glomerular filtration > 45 ml/min/1.73 m^2 of body surface area: • Increasing albuminuria or albuminuria/creatinine ratio > 300 mg/g. • Uncorrected anaemia (Hb <11g/dl) despite iron treatment. • Refractory hypertension (3 drugs). 2.With glomerular filtration 30-45 ml/min/1.73 m^2 of body surface area: • Individual assessment, taking into account the age and rate of progression or of kidney failure, provided that it meets the criteria above regarding proteinuria, anaemia and refractory hypertension. 3.With glomerular filtration <30 ml/min/1. 73 m^2 of body surface area: • In all cases. **Preferred referral criteria** • Fast increase of serum creatinine:> 1 mg/dl in a month. • Hematuria associated to proteinuria once urological diseases are discarded through renal ultrasound scan. • Severe hyperkalaemia (> 7 mEq/l).

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11.3.2. Treatment of patients with diabetes mellitus type 1 and microalbuminuria

Diabetic nephropathy is defined as the progression from renal functional impairment to ESRD, going through intermediate stages marked by the appearance of microalbuminuria and proteinuria.

It is known that microalbuminuria is a powerful predictor of renal and vascular risk, although as test it is not entirely specific. It is of interest to know the pharmacological interventions that could prevent the progression of nephropathy.

The CPG NICE 2004[7] provides the following evidence:

An SR with meta-analysis[566] demonstrated a beneficial effect on the rate of urinary albumin excretion in patients treated with angiotensin converting enzyme (ACE) inhibitors (54% lower) (269 patients treated with 50 mg/day of captopril; 146 at 10 mg/day of lisinopril; 186 patients with 1.25/5 mg/day of ramipril and 16 patients with 20 mg/day of enalapril and 25 to 10 mg/day of enalapril, and 34 with 2 mg/day of perindopril) *vs*. placebo.	SR of RCT 1++
Three RCTs[567, 568, 569] compared the effects of an ACE inhibitor versus of calcium channels antagonists in people with DM1 during follow-up periods between 1 and 4 years. One study showed greater reductions in blood pressure with perimdopril compared with nifedipine, but showed no effect in the albumin excretion rate or the glomerular filtration rate with any interventions[567]. Two other studies, comparing nisoldipine (20-40 mg/day) *vs*. lisinopril (10-20 mg)[568], and perindopril (4 or 8 mg) *vs*. nitrendipine (20 or 40 mg)[569] showed a decrease in macroalbuminuria significantly higher in patients treated with ACE inhibitors.	RCT 1+
A study of 352 patients with type 1 diabetes and microalbuminuria, with a 7-year follow up[570] showed that 13.9% of patients progressed to macroalbuminuria; 35.5% remained with microalbuminuria, and 50.6% returned to normoalbuminuria. The percentage of patients with antihypertensive treatment was smaller in the group that progressed to macroalbuminuria (57%) compared with those who did not progress (47%) or returned to normoalbuminuria (24%).	Cohort study 2+
Another observational study[571], with a 10-year follow-up to 373 patients with DM1, confirmed an increase in the prescription of ACE inhibitors in the 10 years of follow up (17 to 67%) in patients with microalbuminuria. The progression from microalbuminuria to proteinuria was common in patients treated with ACE inhibitors (6.3/100 person-years), thus the authors felt that this treatment was not effective.	Cohort study 2+

More than 5 years have passed since the publication of this clinical practice guideline and its validity has not been reviewed

Summary of evidence

SR of RCT 1 + +	The following angiotensin converting enzyme (ACE) inhibitor drugs have shown to provide a beneficial effect on the rate of albumin excretion: captopril (50 mg/day), lisinopril (10 mg/day), ramipril (1.25 to 5 mg/day), enalapril (10-20 mg/day) and perindopril (2 mg/day).

Recommendations

A	The pharmacological treatment of choice in hypertensive and normotensive patients with microalbuminuria is an angiotensin converting enzyme inhibitor (captopril, lisinopril, ramipril, enalapril and perindopril) with a progressive increase in the therapeutic dose to achieve the desired response.
A	During pregnancy and in the case of existing renal artery bilateral stenosis, the treatment with angiotensin converting enzyme inhibitor drugs is contraindicated.
√	During the treatment with an inhibitor of angiotensin converting enzyme, the levels of creatinine and potassium should be monitored.
√	If there is a contraindication or intolerance to the angiotensin converting enzyme inhibitors, a treatment with angiotensin II receptor antagonists is recommended.
√	The goals of treatment are to control blood pressure and reduce the urinary albumin excretion. In normotensive patients, the dose administered will be the maximum tolerated.

1.1.3.3.Screening methods of diabetic nephropathy

The CPG NICE 2004[7] provides no evidence on this issue.

In a study of diagnostic tests[572] with 99 patients with DM1, both the albumin concentration and the albumin/creatinine ratio, measured in the first morning urine sample showed high sensitivity and specificity against the cumulative excretion rate of albumin for 4 hours, using as cut-offs for the concentration urinary albumin 20 mg/ml and for the albumin/creatinine ratio 2.5 mg/mmol (22 mcg/mg). The authors of this study conclude that the high sensitivity, specificity and simplicity of these tests make them suitable for the screening of microalbuminuria in patients with DM1. DS Ib

In another study[573] the concentration of albumin *vs*. the albumin/creatinine ratio in urine as benchmarks for the diagnose of microalbuminuria obtaining sensitivity levels of 77% and 92%, respectively, and specificity levels of 77% and 82%, respectively, using cut-off points to define the presence of microalbuminuria 31 ug/ml for the concentration of albumin and 32.5 mcg/mg for the albumin/creatinine ratio, were compared. DS Ib

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11.3.4. Start time of screening for diabetic nephropathy

The CPG NICE 2004[7] included a descriptive study that analyzed 3250 patients with DM[574] and observed an albumin excretion greater than or equal to 20 g/min in 30.6% (95% CI: 29% to 32.2%) of patients and in 19.3% (95% CI: 15.6% to 23%) of the patients with a disease progression between 1 and 5 years.

Descriptive Study 3

11.3.5. Frequency of screening for diabetic nephropathy

No evidence has been found concerning this issue, so the recommendations are based on existing expert group consensus.

A CPG[575] recommended carrying out an annual screening by determining microalbuminuria in urine.

Expert opinion 4

Another CPG published by the *American Diabetes Association*[51] recommended by consensus as follows:

Expert opinion 4

- Perform an annual evaluation of the urine albumin excretion in those patients with DM1 with a time of evolution of the disease equal to or longer than 5 years.
- Making a serum creatinine determination at least annually in adults with diabetes, with the aim of estimating the glomerular filtration rate (GFR) and study the degree of chronic renal disease.

Summary of evidence

DS Ib	The albumin/creatinine ratio in urine correlates well with albuminuria for 24 hours, and has high sensitivity (92%) and specificity (82%) to detect microalbuminuria and macroalbuminuria[572].
Descriptive study 3	Between 16% and 23% of people with an economic evolution of the disease between 1 to 5 years have a urinary albumin excretion higher than or equal to 20 g/min[574].
Expert consensus 4	An annual evaluation has been established as a criterion for screening diabetic nephropathy[51, 575].

Recommendations

B	The measurement of the albumin/creatinine ratio in a sample of first morning urine is recommended as a method for the detection and monitoring of diabetic nephropathy.
D	5 after the diagnosis of diabetes mellitus type 1, an annual screening of the nephropathy is recommended.

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11.4. Diabetic foot

Key question:

- Should a diabetic foot screening take place?
- Which is the frequency of screening for diabetic foot?
- At what age or years of evolution should a diabetic foot screening take place?
- What method should be used to perform a diabetic foot screening?

Diabetic foot (DF) includes a group of syndromes in which the presence of neuropathy, ischemia and infection produces tissue damage or ulcers due to minor trauma, resulting in significant morbidity that can even lead to amputation.

Diabetic foot complications can be prevented with a proper strategy, which includes early diagnosis, risk classification and effective prevention and treatment measures.

11.4.1. Effectiveness of screening for diabetic foot

The CPG NICE 2004[7] does not provide evidence to answer this question.

An RCT[576] that included 192 high-risk patients, in which they were randomly assigned to a detection and prevention program for diabetic foot (weekly visits to the podiatrist and hygiene maintenance, protective footwear, every day care and footwear education) *vs*. usual care. In the intervention group a significant reduction of amputations was observed compared to the group receiving traditional care ($p < 0.01$), but showed no significant differences in the incidence of ulcers (2.4% in the experimental group *vs*. 3.5% in the control group)[576].

RCT
1+

Prospective studies[576, 577, 578] have shown significant reductions in the incidence of amputations by careful inspection of the foot, artery evaluation, exploration by assessment of the skin colour, temperature, presence of pulses, determining the ankle-arm index and evaluation of sensory neuropathy using monofilament.

Observational studies
2+

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11.4.2. Frequency of screening

No evidence has been found to provide data on the appropriateness of screening frequency for diabetic foot. The information available is from the consensus of experts from different institutions.

Different CPGs agree on the recommendation to perform an annual systematic exploration of the foot and identify the risk factors for the occurrence of ulcers and necrosis in diabetic patients[7, 491, 579].

Expert consensus 4

Table 7. Risk classification of diabetic foot. Recommended inspection frequency [7; 509]

Risk (Classification)	Features	Frequency inspection
Low risk	Preserved sensitivity, palpable pulses	Annual
Increased risk	Neuropathy, absence of pulses and other risk factors	Every 3-6 months (control visits)
High risk	Neuropathy or absent pulses together with deformity or skin changes or previous ulcer	Every 1-3 months
Ulcerated foot		Individualized treatment, possible referral

11.4.3. Starting time of screening

No studies have been found to provide robust evidence on the optimal time to start screening.

11.4.4. Screening methods

An SR[580] analyzed the diagnostic performance of several methods:

- **Monofilament (Appendix 9)**

The neurological examination of the patient based on the sensitivity to light pressure is performed using the 5.07 (10 g) Semmes-Weinstein monofilament.

SR of diagnostic test studies

In three prospective studies, the monofilament identified patients at high risk of ulceration, with sensitivity of 66-91% and specificity 34-86%, positive predictive value of 18-39% and negative predictive value of 94-95%[580].

DS II

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- **Turning fork** DS II

It is a simple and inexpensive method for measuring vibration sensation[580], but has problems regarding reliability. According to a diagnostic tests study[581] it is more inaccurate in predicting ulcers than the monofilament, although it may be an alternative should there be no monofilament available.

Oyer *et al*.[582] analyzed diabetic peripheral neuropathy in 81 patients (11 with ulcers), through the 128 Hz turning fork, to assess its accuracy and reproducibility and compare it with the 10 g monofilament. The RR of ulcer was 15.3 for patients whose perception of vibration of the tuning fork was equal to or less than 4 seconds. The authors of this study concluded that the turning fork method is effective and reproducible, provides a quantitative estimation of the degree of neuropathy in patients with diabetes and can demonstrate the presence of neuropathy in cases that are considered normal in the 10g monofilament test.

- **Biotensiometer** DS II

According to the study results by Mayfield *et al*.[581], the biotensiometer exceeds the reliability limitations of the turning fork as it can regulate the different vibratory thresholds. A vibration threshold over 25V has 83% of sensitivity, 63% of specificity, a positive probability quotient of 2.2 (95% CI 1.8 to 2.5), and a negative probability quotient of 0.27 (95% CI 0.24 to 0.48) to predict foot ulcer after 4 years.

Nather *et al*.[583] studied the incidence of sensory peripheral neuropathy in patients with diabetes without previous diabetic foot problems at different times of the progression of the disease using 3 different tests (prick test, 5.07 Semmes-Weinstein 10 g monofilament and the biotensiometer) to detect the threshold of perception. DS II

No significant differences were found in the ability to detect sensory neuropathy between the prick test and the neurometer, and the results of both tests were significantly better than those performed with the 5.07 Semmes-Weinstein 10g monofilament.

Summary of evidence

RCT 1 +	Diabetic foot screening decreases the incidence of amputation in patients with diabetes mellitus[576, 577, 578].
Expert consensus 4	Different clinical practice guidelines agree to carry out annual systematic explorations of the foot and identify the risk factors for the occurrence of ulcers and necrosis in patients with diabetes[7, 491, 579].
SR of diagnostic test studies 2	Diabetic foot screening should include medical history, identification of foot deformities and an assessment of the loss of sensitivity through monofilament[580].

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Recommendations

<table>
<tr><td>A</td><td>It is recommended that patients with diabetes mellitus type 1 are involved in structured screening, risk stratification, and prevention and treatment of the foot at risk programs.</td></tr>
<tr><td>√</td><td>Diabetic foot screening in people with diabetes mellitus type 1 should begin after 5 years of progression of the disease as from puberty.</td></tr>
<tr><td>D</td><td>A module on foot care education should be included in consonance with the risk assessment.</td></tr>
<tr><td>B</td><td>Diabetic foot screening should include a thorough annual examination of the feet to identify risk factors, prediction of ulcers and amputations; inspection of the foot and soft tissue; assessment of footwear, musculoskeletal examination, assessment of peripheral arterial disease symptoms using an evaluation of the foot pulses, supplemented by the determination of the ankle-arm index in some cases, and the loss of sensitivity tests assessed by monofilament or alternatively by the turning fork.</td></tr>
<tr><td rowspan="5">D</td><td colspan="3">Three levels of monitoring are recommended depending on the risk factor of patients:</td></tr>
<tr><td>Risk (Classification)</td><td>Features</td><td>Inspection Frequency</td></tr>
<tr><td>Low risk</td><td>Preserved sensitivity, palpable pulses</td><td>Annual</td></tr>
<tr><td>Increased risk</td><td>Neuropathy, absence of pulses and other risk factors</td><td>Every 3-6 months (with control visits)</td></tr>
<tr><td>High risk</td><td>Neuropathy or absent pulses together with deformity or skin changes or prior ulcers</td><td>Every 1-3 months</td></tr>
<tr><td></td><td>Ulcerated foot</td><td></td><td>Individualized treatment, possible referral</td></tr>
<tr><td>√</td><td>Since diabetes is the most frequent cause of non-traumatic amputation of lower limbs, it is desirable to standardize the process of education and prevention, diagnosis and treatment of diabetic foot, in a multidisciplinary way, with the aim of reducing the number of amputations and comorbidity involved.</td></tr>
</table>

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11.5. Erectile dysfunction in people with diabetes mellitus type 1

Erectile dysfunction (ED) is known as the difficulty to achieve and maintain an erection enough to be able to have a satisfying sexual relationship, microvascular or neuropathic complication that can occur in patients with diabetes 584.

The *Study of Male Erectile Dysfunction (EDM)*, carried out in Spain[585], determined that DE affects approximately 34-45% of men with diabetes, and 12% of men between 25 and 70 years of the general population. The risk factors include advanced age, longstanding diabetes, inadequate glycaemic control, smoking, hypertension, dyslipidemia, androgen deficiency states and cardiovascular disease.

11.5.1. Treatment of erectile dysfunction

- Phosphodiesterase inhibitors

Phosphodiesterase (PDE_5) is an enzyme that hydrolyses the cyclic guanosine monophosphate enzyme (GMP_c) in the penile cavernous tissue, making it guanosine monophosphate. The inhibition of PDE_5 increases the GMP_c level, which induces relaxation of the cavernous and vascular musculature with vasodilatation and consequent penile erection[586].

Sildenafil, vardenafil and tadalafil are potent, reversible and competitive PDE_5 inhibitors. Their mechanism of action is to maintain the levels of nitric oxide, "universal vasodilator» previously induced by the excitation.

The CPG NICE 2004[7] does not provide evidence to answer this question.

An RS[587] identified 8 RCTs (5 about sildenafil) on the efficacy of inhibitors of PDE_5 *vs*. placebo in patients with diabetes, of which 20% had DM1.

SR of RCT
1++

The meta-analysis on the effectiveness of PDE_5 inhibitors indicated in a consistent and significant way that all three drugs (sildenafil, vardenafil and tadalafil) were superior to placebo. Of the total, 976 men were assigned to receive a PDE_5 inhibitor and 741 to the control group. The results showed a WMD 6.6 (95% CI 5.2 to 7.9) for the *International Index of Erectile Function* (IIEF) scale at the end of the study in favour of the PDE_5 inhibitors arm.

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Regarding the safety of the PDE_5 inhibitors, the adverse event most frequently reported was headache with a total of 141 episodes in the 1,012 patients in the group of patients treated with PDE_5 inhibitors, compared with 28 of 755 in the control group [RR 3.66 (95% CI: 2.51 to 5.35)]. The second most frequent event was flushing, with 103 episodes in 970 patients in the group with PDE 5 inhibitors, [RR 13.21 (95% CI 6.01 to 29.03)]. Symptoms of the upper airway and flu-like syndromes, dyspepsia, myalgia, back pain, and abnormal vision, in descending order of frequency were also reported. The RR for developing any adverse reaction was 4.8 (95% CI 3.74 to 6.16) in the PDE_5 inhibitors arm, in comparison with the control group.

In the SR by Nehra *et al*.[588] numerous studies evaluating the efficacy and safety of PDE 5 in patients with DM1 and DM2 were included. Sildenafil improved the erectile function compared to placebo ($p = 0.0001$) in DM1 patients regardless of the HbA_{1c} levels and the degree of progression of the disease. Baseline HbA_{1c} levels did not appear to influence the response to tadalafil in men with DM1 and DM2. SR of RCT 1++

The response was similar to tadalafil in men with DM and without DM, regardless of the levels of HbA_{1c}, the diabetes therapy, or the previous use of other PDE 5 inhibitors (sildenafil). Success rates were 60% with 10 mg of tadalafil and 65% with 20 mg ($p < 0.001$) *vs*. placebo, according to the scores on the SEP2, and 49% with 10 mg of tadalafil and 53% with 20 mg ($p < 0.001$) *vs*. placebo, according to the SEP3 scores.

These studies have shown similar efficacy for the three agents (sildenafil, tadalafil, and vardenafil), with a significant improvement in the erectile function of patients with DM.

Another SR[589] included a total of 67 studies examining the PDE_5 inhibitors, intracavernous alprostadil and penile prostheses. SR of RCT 1++

The PDE_5 inhibitors were selected as a first-line treatment for erectile dysfunction, with an average efficiency of 50% and a favourable safety profile. The alprostadil was the most commonly used drug, but the combination of papaverine, phentolamine and alprostadil represented the most effective medical treatment for patients whose erectile dysfunction was unresponsive to monotherapy.

The intracavernous administration of vasoactive drugs was the second line of treatment when PDE_5 inhibitors failed. Papaverine (20-80 mg) and alprostadil were the main drugs used for the intracavernous treatment. Alprostadil represented the most effective and the only approved monotherapy treatment.

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Papaverine (7.5 to 45 mg) and phentolamine (0.25 to 1.5 mg), and combinations of papaverine (8-16 mg), phentolamine (0.2-0.4 mg), and alprostadil (10-20 mg), showed the highest efficacy rates (especially in the mixture of the three) in cases which were difficult to treat. Complications of intracavernous pharmacotherapy included penile pain (50% of patients, after 11% of injections), prolonged erections (5%), priapism (1%) and fibrosis (5-10%). However, no studies identified the current incidence of complications by fibrosis after intracavernous injections. The dropout rates were 41% to 68% on the desire for a permanent treatment modality, the lack of a suitable partner, due to the poor response (especially among older people), fear of needles, fear of complications and loss of spontaneity in sex.

Regarding penile prostheses, these showed excellent results at a functional and safety level in relation to the implantation of penile prostheses.

A placebo-controlled RCT in men with DM1 and DM2 (n = 425)[352] showed significant improvements in the erectile function scores of IIEF-EF and the *Sexual Encounter Profile 3* (SEP3), with satisfactory rates after 12 weeks with a 10 or 20 mg dose of vardenafil, compared with placebo (p <0.0001). No association was found between vardenafil and the level of glycaemic control (defined as HbA_{1c} level). The responses to SEP3 were significantly higher for those receiving 10 mg and 20 mg of vardenafil regardless of the glycaemic control.

RCT
1+

• Apomorphine

The sublingual apomorphine (Uprima ®) or apomorphine hydrochloride is a non-selective agonist of dopamine receptors that acts on the paraventricular nucleus of the hypothalamus. This drug is marketed in Spain since 2001 with a sublingual formulation of 2 and 3 mg.

The CPG NICE 2004[7] does not provide evidence to answer this question.

An SR[590] which included 4 RCTs studied sublingual apomorphine (2-6 mg) *vs*. placebo[591, 592, 593, 594], with a total of 1594 men, stated that 45% of men had normal erections with apomorphine, compared to 29% in the placebo group [RR 1.4 (95% CI 1.3 to 1.7), NNT: 6.6 (95% CI: 5.0 to 9.6)].

SR of RCT
1++

Another clinical trial carried out in 130 patients with diabetes[594], randomly assigned to a treatment with sublingual apomorphine (14.74% patients with DM1) or placebo (15.25% patients with DM1) analyzed the improved erections after 4 weeks of treatment. The sexual response rate was 22% for apomorphine, compared with 17% for placebo, the difference not being relevant (p = 0.48).

RCT
1+

The 2 RCTs included in this SR demonstrate that apomorphine is less effective than sildenafil: the percentage of successful attempts was 75% in the group with sildenafil *vs*. 35% in the group with apomorphine (p <0.001)[595] and 73.1% in the group with sildenafil *vs*. 62.7% with apomorphine (p <0.0004), with a 17.5% of the population with diabetes[596].

RCT
1+

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Another RCT of crossover design[597] evaluated the overall effectiveness of sublingual apomorphine versus sildenafil (23.14% DM). Apomorphine was less effective than sildenafil in the percentage of successful intercourses (40.3 *vs*. 83.3, p <0.001), in the sexual relationship satisfaction and overall satisfaction. Sildenafil was preferred over apomorphine.

RCT 1+

An open, randomized crossover trial in 131 patients (9.3% DM1)[598], previously untreated showed greater efficacy of sildenafil versus sublingual apomorphine (measured according to the IIEF questionnaire), in the percentage of successful attempts (62.7 % *vs*. 28.3%) and in patient preference (95% preferred sildenafil).

RCT 1++

A randomized crossover RCT[599] studied 131 patients (7.6% DM), randomly divided into two groups: 66 with sildenafil and 64 with sublingual apomorphine without masking. A statistically significant difference was found between the two interventions. The comparison between the before and after treatments showed differences in favour of sildenafil (p <0.001).

RCT 1++

A descriptive study[600], which conducted a survey to 11186 primary care physicians, concluded that the majority of patients treated with sublingual apomorphine (28.5% with DM) considered it ineffective, and also that it had many adverse effects. The most reported adverse events were headache and nausea.

Descriptive Study 3

• Penile Prosthesis

The CPG NICE 2004[7] does not provide evidence to answer this question.

A systematic review included in an evaluation report[601] with observational studies indicated that penile prostheses was highly effective, with rates of 80-90% of free persistent complication after 5 years, besides getting adequate erections for intercourse in 70-90% of patients. The surgical complications reported were: erosion or abrasion of the area, infection, mechanical failure of the prostheses or the cylinders or migration of any of its components. The heterogeneity in the variables included in the follow-up and assessment criteria made it difficult to compare the results between the studies.

SR of observational studies 2++

Another study[602] carried out a retrospective follow-up (1990-2004) of 200 patients with penile prostheses (40% with DM), analyzing three types of implants: AMS 700CX® (3- component inflatable), AMS Ambicor® (2-component inflatable) and 600-650 AMS® (semi-rigid prosthesis). Patient satisfaction and his partner was very high with the three types of prostheses, though it was less with the AMS 600-650®. Natural erections and higher stiffness than before the implantation in most cases were achieved. 20% of patients experienced serious complications after surgery: 9 (22.5%) had infections, 18 (45%) mechanical failure and 13 (32.5%) erosions.

SR of observational studies 2+

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

Another study[603] analyzed the survival rate of the AMS 600® prosthesis, which was significantly higher than that of the inflatable prosthesis AMS 700 CXM®. The overall failure rate of the AMS 600® prosthesis was 16.4%. The survival failure rate was 22.2% in the inflatable prosthesis and the most common cause was some mechanical failure of the cylinder. Neurogenic erectile dysfunction is associated with increased failure of the AMS 700 CXM ® prosthesis.

Observational study 3

- Psychotherapy

The CPG NICE 2004[7] does not provide evidence to answer this question.

In an SR[604], nine randomized and two *quasi-randomized* trials were analyzed, which included 398 men with ED (141 in the psychotherapy group, 109 in the medication group, 68 with psychotherapy along with medication, 20 with vacuum devices and 59 in the control group). The results of these studies indicated that group therapy focused on the symptoms showed greater efficacy in comparison with the control group.

SR of RCT 1+

In addition, group psychotherapy showed a greater reduction in the "persistence of erectile dysfunction" after the treatment than the control group (without treatment) [RR 0.40 (95% CI 0.17 to 0.98), n = 100, NNT 1.61 (95% CI: 0.97 to 4.76)].

Group psychotherapy with sildenafil citrate, *vs*. sildenafil alone, reduced more the "persistence of ED" [RR 0.46 (95% CI 0.24 to 0.88), NNT 3.57, (95% IC: 2 to 16.7), n = 71] and patients were less likely to drop out from the treatment [RR 0.29 (95% CI: 0.09, 0.93)].

- Vacuum devices

Vacuum devices (VD) essentially consist of a plastic cylinder connected to a pump, which can be operated by hand, or battery, and one or more tension rings. The penis is inserted into the cylinder and the activation of the pump removes the air from inside the cylinder causing the creation of a vacuum. This causes the blood to enter the penis, which immediately widens in a similar way to a natural erection. Once an adequate erection is produced, a tension band is fastened around the penis to maintain the erection impeding the outflow of blood. The vacuum inside the cylinder is then released and the cylinder removed from the penis. It is important that the tension ring be also removed within 30 minutes.

The CPG NICE 2004[7] does not provide evidence to answer this question.

Effectiveness

A retrospective study of cases among the Spanish population[605] described that 63.3% of patients achieved satisfactory erections in over half of attempts with VDs.

Descriptive Study 3

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

Later another study[606] compared the effectiveness of mono-therapy with VD *vs*. sildenafil *vs*. both treatments in patients with various aetiologies of ED. It was observed that the mono-therapy and the combination therapy showed significant differences in terms of erectile function compared to the pre-treatment. In all the other aspects analyzed (relationship satisfaction, orgasmic function, sexual desire and overall satisfaction) only the combined treatment was statistically significant compared with the pre-treatment.

Observational study 2+

Another study[607] included a sequence of interventions - sildenafil citrate; vacuum devices (VD); intracavernosal injection (ICI) of alprostadil, sildenafil citrate together with ICI of alprostadil; ICI of alprostadil together with VDs and penile prosthesis in patients with DM2 where the previous intervention had failed. The patients had a 2-year follow-up and the effectiveness was measured by the IIEF scale. The results showed that of 284 patients, 81 (28.5%) had a positive response to sildenafil, 7 (2.5%), to DVC, 113 (39.8%) to ICI with alprostadil, 24 (8.5 %) to the combination of sildenafil with ICI of alprostadil (0.7%), 2 to ICI together with VD, and 15 (5.3%) required a penile prosthesis implant. Fourteen patients (4.9%) had a negative response to all treatments. In conclusion, the progressive treatment program for ED seems very effective for patients with diabetes.

Observational study 2+

Adverse Effects

A study[605] analyzed the side effects in 33 patients of which 27 had pain, 7 had penile ecchymosis, 5 had block in ejaculation and 5 had complaints with the rings. The only variables that were associated with lower use after 12 months were the lack of effectiveness of the device and the rejection of it by the couple ($p < 0.05$). The presence of pain was associated with a higher rate of early discontinuation in the medium term ($p < 0.05$), but not to late dropout ($p > 0.05$).

Descriptive Study 3

A descriptive study[608] that included 36 patients with ED who used VD stated that of the 36 patients studied, 3 (10%) had pain, 2 (5.5%), haematoma, 1 (2.7%), numbness; and 1 (2.7%), maceration.

Descriptive Study 3

Preferences of patients

A study[608] assessed the preference of 36 patients with ED who had had successful results both with the vacuum devices and sildenafil. Of all the patients, 12 (33.3%) chose to continue using a VD and 24 (66.6%) preferred sildenafil. Those patients who preferred the vacuum device justified their choice by the adverse side effects of sildenafil. Those patients who chose sildenafil justified their preference for its greater efficiency, convenience and ease of use.

Descriptive Study 3

More than 5 years have passed since the publication of the Clinical Practice Guideline and its validity has not been reviewed

- Intracavernosal therapy: intracavernosal alprostadil

Alprostadil is the natural form of prostaglandin E1 (PGE1). It has a wide variety of pharmacological actions, including vasodilation and platelet aggregation inhibition. Erection occurs normally between 5 and 15 minutes after the intracavernous injection. Its duration depends on the dose administered.

The CPG NICE 2004[7] does not provide evidence to answer this question.

Alprostadil vs. placebo

An RCT[609] compared the alprostadil injection with placebo in 296 men between 21 and 74 years old. It compared injections of 2.5, 5, 10 and 20 mg of alprostadil vs. placebo. None of the men responded to placebo and all the doses of alprostadil increased the proportion of individuals with "full erection" under clinical evaluation ($p < 0.01$) and achieved at least a 70% erection for 10 minutes or more ($p < 0.001$). It was also found that a higher proportion of men responded to higher doses, thus suggesting a dose-response relationship. — RCT 1+

The study published by Colli *et al*.[610] compared alprostadil with placebo. Its results indicated a complete lack of response in the placebo group while the groups treated with different doses of alprostadil had a full erection in 38.6% at doses of 5 mg and 55.5% at doses of 10 mg. The latter considered the response good or excellent. — RCT 1+

Intracavernosal alprostadil vs. sildenafil

The study by Wang *et al*.[611] evaluated the results of the treatment in 54 randomized patients with ED to receive treatment with oral sildenafil or intracavernosal injection of PGE1 for 4-9 months (mean 6 months). The efficacy rates in the two groups were 80% for sildenafil and 83.3% for PGE1, a difference that was not statistically significant. Two of the six patients who did not respond to sildenafil had enough erections when receiving the intracavernosal injection of PGE1. None of the 4 patients who did not respond to the intracavernosal injection of PGE1 achieved an erection enough for intercourse when they received sildenafil. The authors concluded that both oral sildenafil and the intracavernosal injection of PGE1 are effective for patients with different aetiologies of ED. — RCT 1+

A descriptive study in 31 patients with DM2[612], found that 76.5% of the injections with alprostadil in trained patients were satisfactory to perform sexual intercourse, and 72.5% were satisfactory for the couples. Penile pain appeared in 61.3% of patients as adverse effect. — Descriptive Study 3

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

Heaton *et al*.[613] evaluated the intracavernosal alprostadil therapy in 277 patients with diabetes, 31 of them with DM1. The response rates of total erection were similar in DM1 (705/821, 86%) and DM2 (4869/5931, 82%). — Descriptive Study 3

Domínguez *et al*.[614] evaluated 500 patients treated with intracavernosal alprostadil injection, and obtained a complete response in 405 cases (81%); incomplete in 70 (14%) negative in 25 (5%). Adverse effects were detected in 50 patients (10%). — Descriptive Study 3

Summary of evidence

RCT 1 +	As for the treatment of erectile dysfunction in patients with diabetes, the intervention that has better results in terms of effectiveness, safety and patient preference the treatment with phosphodiesterase inhibitors, especially if associated with group psychotherapy, followed by intracavernosal alprostadil and mechanical devices such as prosthesis and vacuum devices[601, 602, 603, 604, 605, 607, 608, 609, 610, 611, 612, 613, 614].

Recommendations

A	The treatment with phosphodiesterase inhibitors is recommended as first choice for the treatment of erectile dysfunction in people with type 1 diabetes.
A	In case of contraindication or poor tolerance, intracavernosal alprostadil is proposed as an alternative.
B	As a third option treatment, mechanical methods can be considered, such as vacuum devices and inflatable prosthesis (in this order).
A	In case all previous methods fail, sublingual apomorphine treatment can be considered.

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11.6. Painful diabetic neuropathy

The International Association for the Study of Pain defines neuropathic pain as pain triggered or caused by a primary lesion or dysfunction of the nervous system (central or peripheral)[615]. Diabetic peripheral neuropathy is a symmetric sensorimotor neuropathy predominantly affecting the lower limbs (foot and ankle) and, less frequently, to the top. The patient complains of continuous pain, burning, which can be accompanied by paroxysmal crises of lancinating or electric pain; this pain may be spontaneous or secondary to small stimuli. In this case, everyday environmental stimuli such as the touch of clothing, a light breeze and temperature variations can cause pain.

Appendix 10 shows the dosage and the most common side effects of the medications typically used for neuropathic pain [616].

11.6.1. Treatment of painful diabetic neuropathy

The CPG NICE 2004[7] does not provide evidence to answer this question.

An SR[617] evaluated the efficacy of antidepressants, anticonvulsants, opioid antagonists of N-methyl-D-aspartic acid and capsaicin tramadol *vs*. placebo in pain relief. The main result was expressed as "moderate pain relief or relief by 50%". SR of RCT 1++

Tricyclic antidepressants (amitriptyline, desipramine, imipramine) or classical anticonvulsants (carbamazepine, lamotrigine, valproate sodium) showed greater efficacy against placebo than serotonine reuptake inhibitors antidepressants (SSRIs, citalopram or duloxetine) and that new anticonvulsants (oxcarbazepine, gabapentin, pregabalin). The duration of the studies was less than six months, so it was not possible to draw conclusions about the long-term effectiveness.

An SR on drugs for the treatment of diabetic neuropathic pain[618] published 5 trials published up to 2004, comparing tricyclic antidepressants *vs*. gabapentin, carbamazepine or SSRIs antidepressants. No differences were found regarding a reduction in the intensity of pain, nor in the percentage of patients who discontinued the treatment due to adverse effects, except for a study comparing paroxetine *vs*. imipramine, which found more discontinuation in the treatment with imipramine. These studies included a small number of patients and a duration of between 2 and 6 weeks, which limits the validity of their results. SR of RCT 1++

Several systematic reviews have evaluated the efficacy of gabapentin, carbamazepine and opioids for neuropathic pain[619, 620, 621, 622], in various indications, which included the treatment of diabetic neuropathy. In the SR on opioids[622], the intermediate term studies (from 8 days to 8 weeks) showed that oxycodone, morphine, methadone and levorphanol were effective in reducing neuropathic pain. SR of RCT 1++

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A trial carried out in India[623] compared amitriptyline *vs*. lamotrigine in a crossover study which lasted two weeks. No differences were found in efficacy. The adverse effects were more common with amitriptyline (drowsiness, anticholinergic effects) while lamotrigine resulted in increases in serum creatinine that led to the discontinuation of the treatment in 4 patients with diabetes. RCT 1+

An RCT[624] compared the intervention with duloxetine 60 mg *vs*. the usual treatment (mainly gabapentin, amitriptyline and venlafaxine) for neuropathic pain in DM1 (9.3%) and DM2 (90.7%), for 52 weeks, after a double-blind period of 13 weeks. No differences were found in efficacy or quality of life and a good tolerance to duloxetine was observed. RCT 1+

An RCT[625] compared the combination of morphine with gabapentin *vs*. the treatment with gabapentin or morphine alone. Pain relief was significant with the association of these drugs, although adverse effects (constipation, sedation and dry mouth) were more common with the drug combination. RCT 1+

An SR with meta-analysis[626] analyzed 18 studies and compared the efficacy of gabapentin *vs*. tricyclic antidepressants to treat diabetic neuropathy and postherpetic neuralgia. SR of RCT 1++

In the direct comparative studies no significant differences were observed regarding pain control between gabapentin and tricyclic antidepressants in patients with diabetic neuropathy [RR 0.98 (95% CI 0.69 to 1.38)]. Likewise, for both medical conditions, the abandonment of the therapy due to adverse events did not differ between patients treated with gabapentin and tricyclic antidepressants [RR 0.27 (95% CI: 0.03 to 2.34)]. In the studies with placebo (indirect comparisons), both gabapentin and tricyclic antidepressants were superior to placebo in pain control [RR 2.18 (95% CI 1.78 to 2.67) and [RR 5, 27 (95% CI 3.05 to 9.11)]. As regards adverse effects, gabapentin alone was significantly associated with an increased risk of discontinuation of the therapy due to the presence of adverse effects.

An SR with meta-analysis[627] carried out an indirect analysis to assess the effectiveness of duloxetine, pregabalin, gabapentin and amitriptyline, and their tolerance, using placebo as a common comparator. To this end, a total of 11 double-blind RCTs were selected with a placebo control group, with a parallel or crossover design, which lasted between 5 and 13 weeks, and pain reduction criterion of 50%. Of the 11 studies, 3 included duloxetine; 6 studies, pregabalin, and 2 studies, gabapentin. The results indicated that all three drugs were more effective than placebo for the treatment of pain. Duloxetine was more effective than placebo ($p < 0.001$), but caused a greater dropout due to the occurrence of side effects [NNT/NNH 11 (95% CI: 7-23), $P < 0.001$] for duloxetine]. Pregabalin was also more effective than placebo and also showed higher percentage of dropout by the presence of adverse effects [NNT/NNH 19 (95% CI 10-48), $P < 0.001$]. Gabapentin was also more effective than placebo ($p < 0.001$). SR of RCT 1++

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The authors concluded that duloxetine is a suitable option for the treatment of painful diabetic neuropathy, comparable to antiepileptic drugs such as gabapentin and pregabalin.

Another SR[628] investigated the efficacy of duloxetine for painful diabetic neuropathy and fibromyalgia compared with other antidepressants. The review included six studies (three of them in patients with painful diabetic neuropathy), with a total of 2,216 patients (over 1,000 with painful diabetic neuropathy), 706 treated with placebo and 1,510 with duloxetine at doses of 20, 60 and 120 mg/day. 41% of patients treated with duloxetine achieved a pain reduction of 50%, versus 24% in the placebo group [NNT 5.9 (95% CI: 4.8 to 7.7) to achieve a 50% reduction of pain]. No significant differences were shown between the treatment with doses of 60 mg or 120 mg, or between patients with DM or fibromyalgia. The dropout rates for treatment failure were 9% in placebo patients and 4% in patients with duloxetine. Dropout due to the occurrence of side effects was higher in the group treated with duloxetine than among the patients treated with placebo (15% and 8%, respectively). The most common side effects (data from 3 trials) were nausea, drowsiness, constipation and loss of appetite.

SR of RCT
1+

An SR[629] with meta-analysis assessed the efficacy of an adhesive dressing with lidocaine at 5% for pain management of diabetic neuropathy, compared with other treatments or placebo. This SR included an RCT that met the planned goals. The dressing showed significantly better results in terms of quality of life (measured by EQ5D) than pregabalin. There was no difference between the group treated with the dressing *vs*. other drugs (amitriptyline, capsaicin, gabapentin and pregabalin) in relieving pain or patient satisfaction with the treatment. All treatments were rated more effective regarding pain relief than placebo.

SR of RCT
1++

An RCT[630] analyzed the effect of sodium valproate (A) and glyceril trinitrate (GTN) in spray (B) alone or in combination (C) for the treatment of neuropathic pain. The results showed a significant pain reduction after 3 months ($p < 0.001$/$p < 0.05$) in the treatment groups A, B and C *vs*. placebo. Pain reduction was lower in the groups with a single drug than with the combination of both ($p < 0.05$).

RCT
1+

Another RCT[631] compared the efficacy, safety and tolerability of long-acting oxycodone (12 hours) in combination with gabapentin in comparison with placebo plus gabapentin in diabetic patients with moderate to severe neuropathic pain.

RCT
1+

The results of the study indicate that those patients treated with oxycodone in combination with gabapentin experienced a clinical reduction of pain of over 30% ($p = 0.007$) compared with the pretreatment (74% *vs*. 47%, $p = 0.003$). On the other hand, the treatment with oxycodone appears to reduce the need for additional analgesia ($p = 0.029$) and improves disrupted sleep ($p = 0.05$), although there are no differences in the quality of sleep ($P = 0.209$). With respect to the presence of side effects, there were differences between both groups (88% *vs*. 71%), being the most cited side effects constipation, fatigue, drowsiness, nausea, and dizziness. The reasons for leaving the clinical trial differed between the groups, being the main reason the presence of side effects (64%) for the experimental group versus the placebo group who did mostly for lack of therapeutic effect (54%, 3 times higher than in the experimental group).

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An RCT[632] evaluated the efficacy of venlafaxine in the symptomatic treatment of painful neuropathy in patients with type 2 diabetes (n = 60). Analyzing the evolution of basal pain until the end of the study (8 weeks), significant differences were observed from the second week through the questionnaire and the McGill Melzack numerical scale (p = 0.01). Given these results, the authors considered that the response to the treatment was good in 56% of cases (*vs*. 6.6% in the control group) and moderate in 36% (*vs*. 16.6% in the control group). 10% of patients in the treatment group and 76.6% in the control group did not respond to the treatment. The prospective evaluation showed that the decreasing intensity of pain was significantly lower in the group treated with venlafaxine HC1 during the weeks 4 and 8 (p = 0.01) than in control group.

RCT
1+

Summary of evidence

SR of RCT 1 + +	In the short term (treatments shorter than 6 months) classical antidepressants (amitriptyline, desipramine, imipramine) and classical anticonvulsants (carbamazepine, lamotrigine, valproate sodium) are more effective in the treatment of painful diabetic neuropathy than serotonin reuptake inhibitors antidepressants (citalopram, duloxetine) and new anticonvulsants (oxcarbazepine, gabapentin, pregabalin)[617].
SR of RCT 1 + +	Opiates drugs (such as oxycodone, morphine, methadone, levorphanol) are more effective than placebo in treating painful diabetic neuropathy[619, 620, 621, 622].
RCT 1 +	No significant differences were demonstrated in the treatment of painful diabetic neuropathy with lamotrigine vs. amitriptyline[623].
RCT 1 +	The treatment of diabetic neuropathy with duloxetine (60 mg) vs. gabapentin, amitriptyline or venlafaxine, showed no differences in pain relief[624].
RCT 1 +	The combined treatment with gabapentin morphine is more effective than the treatment with one of the two drugs separately, but has more adverse effects[625].
SR of RCT 1 + +	No direct comparative studies have shown significant differences in terms of pain control between gabapentin and tricyclic antidepressants in patients with diabetic neuropathy [RR 0.98 (95% CI 0.69 to 1.38)][626].

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SR of RCT 1 + +	Indirect comparisons versus placebo indicate that duloxetine (60 mg and 120 mg) is an option for the treatment of painful neuropathy comparable to gabapentin or pregabalin[627, 628].
RCT 1 +	Sodium valproate and nitro-glycerine sprays are effective in the management of pain, either alone or in combination versus placebo, the combination being more effective than both[630].
RCT 1 +	The oxycodone in combination with gabapentin is effective in reducing pain as much as 33% compared to gabapentin alone and reduces the need for additional analgesia[631].
RCT 1 +	Venlafaxine is effective in pain reduction up to 53%, significantly better than placebo[632].
	Regarding the occurrence of adverse effects: • Overall duloxetine is well tolerated (especially the dose of 60 mg) being the most common side effects: nausea, sleepiness, constipation, lack of appetite, headache and dizziness[627, 628]. • Gabapentin has a significant dropout rate due to its lack of efficacy[627]. • Duloxetine has fewer adverse effects than gabapentin[627].

Recommendations

√	As first line of treatment for mild cases, analgesics such as acetaminophen or ibuprofen or paracetamol or aspirin, as well as treatments of local use such as the arch, to isolate the foot are recommended.
A	When these measures fail, the use of tricyclic drugs (low to medium dose) is recommended, taken just before the time of day when the symptoms are more annoying. The diabetic patient must be informed about the type of trial, as it is not always successful.
A	When the response to treatment is insufficient, drugs may be associated with different mechanisms of action, such as antiepileptics (gabapentin or pregabalin), opioids (such as morphine, oxycodone, or tramadol) or duloxetine, monitoring the response and the adverse effects.

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12. Organizing the medical consultation

12.1. Transition of patients with diabetes mellitus type 1 from the paediatric services to the adult services

The transition of adolescents with DM1 from paediatric to adult care is a critical process that can generate a decline in self-care and affect glycaemic control.

No study has been found that examines the effectiveness of a structured intervention during the transition from paediatric services to adult services compared to the usual practice in people with DM1.

The NICE Guide 2004[7] summarized the information provided by studies that analyzed through surveys and which reflected the perceptions of patients, their satisfaction with the care received, their opinion on the best age for the transition or the optimum time between the last paediatric visit and the first on to adult care[633, 634, 635, 636, 637, 638, 639].

Patient satisfaction

The study by Kipps *et al*.[635] measured the satisfaction of some patients from Oxford (UK) that had recently been transferred was measured. 53% of patients considered important to know the endocrinologist before the transition, compared to 46% who did not consider it relevant. — Descriptive study 3

Age of transition

In the study by Salmi *et al*.[639], the transition was performed at a mean age (SD) of 17.5 (0.5) years (range 16.5 to 18.8 years). The decision on the age at which the transition was to be made was taken by the doctor according to the level of maturity of each patient. — Descriptive study 3

In the study by Pacaud *et al*.[636] the mean age of transition was 18.5 years, being the age proposed by patients less than this. — Descriptive study 3

In another study, in which a telephone survey was carried out in 101 patients[641], the optimal age for transfer was 18 years according to 58.4% of the participants. — Descriptive study 3

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Effects on glycaemic control

Another study[642] involving 191 young people, analyzed the effect of an intervention based on a system of recall appointments (a coordinator contacted the young patients through telephone calls, messages to mobile phones or email reminders) with telephone support outside the usual hours of consultation, during the transition of adolescents to adult hospital care. Comparing the data with previous data obtained from other adolescents with diabetes, admissions due to diabetic ketoacidosis decreased 33% (p = 0.05), as well as the length of hospital stay for this cause in 3.6 days for 3.5 years (p = 0.02).

Observational study 2+

In the study by Busse *et al*.[641] made by a telephone questionnaire to 101 patients [58 women, mean age (SD) 22.1 years (2.4)] after the transition, showed that after this phase, the attendance to medical consultation decreased [mean (SD) 8.5 years (2.3) *vs*. 6.7 years (3.2)]. However, the mean HbA_{1c} level did not change significantly before and after the transition [mean (SD) 8.5% (1.5) *vs*. 8.4% (1.7), P = 0.441].

Descriptive study 3

A retrospective study in 62 young patients with DM1[640] which compared the transition with structured and unstructured programs identified higher levels of HbA_{1c}, in the group that followed a structured transition program at the first visit in the adults service care (p < 0.01) and after a one-year follow-up (p <0.05).

Descriptive study 3

Summary of evidence

Descriptive study 3	For people with diabetes mellitus type 1 it is important to know the adult endocrinologist before the transition from paediatric endocrinology care[640, 638], as well as the presence of the paediatrician at the first visit with the endocrinologist[640].
Descriptive study 3	The transition is usually performed at around the age of 18[639, 636, 641].
Descriptive study 3	Although during the transition, there can be lifestyle changes regarding attendance to checkups[642], this does not appear to significantly impact on glycaemic control[641].

Recommendations

C	To set up at least one consultation visit involving both the paediatrician who has been responsible for the treatment during childhood and the endocrinology specialist who will attend the patient with diabetes mellitus type 1 in the future is recommended, so that they agree and fix the treatment together with the adolescent.

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12.2. Initial study of the newly diagnosed patients with diabetes mellitus type 1

After the diagnosis of DM1, a full assessment of the patient is to be carried out to detect the existence of possible complications and to set out the management plan, which will include aspects such as diabetes education, dietary advice and exercise and pharmacological treatment patterns. It is important to determine the elements that could enhance the effectiveness of this initial study.

No trials comparing the efficacy and safety between the different options of initial study for people newly diagnosed with DM1 have been found.

Thus the recommendations have been developed by consensus of the GEC, from previous guidelines proposed in July,[7; 51].

Recommendations

In the newly diagnosed DM1 patients, the following assessments are recommended:

√	**Medical history**	• Domestic, social, cultural-recreational aspects, level of education. • Emotional situation. • Assessment of family and social support.
√		• Prior diabetic history.
√		• Vascular risk factors. • Smoking.
√		• Family history of diabetes and artery or autoimmune disease.
√	**General exploration**	Height, weight, BMI, TA.
A	**Further tests**	HbA_{1c}.
B		Full examination of the retina with mydriasis.
B		Albumin excretion (timed microalbuminuria or albumin/creatinine ratio).
√		Lipid profile once the glycaemic profile is stabilized.
B		Anti TPO, FT4 and TSH antibodies.
B		Transglutaminase and IgA antibodies to assess celiac disease.

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D		Regular measuring of the C peptide or specific autoantibodies or to confirm the diagnosis of DM1 is not advised, but its use should be considered to determine the aetiology of DM in doubtful cases.
B		Discarding autoimmune thyroid disease and celiac disease in the early onset of diabetes mellitus type 1 in children and adolescents is discarded.
D	**Genetic study**	In cases in which mild sustained hyperglycaemia is identified in a young person, without obesity and/or mild diabetes history in two generations, in the absence of anti-pancreatic autoimmunity and HLA not compatible with DM1, MODY 2 diabetes should be ruled out.
D		If hyperglycaemia is more severe and progressive, MODY 3 diabetes should be ruled out.
D		If genetic testing is negative for MODY 2 and MODY 3 diabetes, then the rest of MODY varieties should be ruled out too.
B (Adults)/ A (Children)	**Educational and support materials**	Updated information should be provided to the adults, children and adolescents with diabetes mellitus type 1 together with their families at the time of diagnosis, and periodically thereafter, on the existence of diabetic support groups, both locally and nationally and how to contact them. (Appendix 11.2)

12.3. Follow-up and control consultations: tests and frequency

There is evidence that good control of diabetes is key to reduce and delay the complications associated with DM1. Therefore, it is necessary to perform periodic reviews to determine whether the glycaemic control objectives for each patient are being achieved or not, to set out the relevant modifications. Likewise, an integrated diabetes management goes through a regular assessment of possible changes in various risk factors and the earliest possible detection of complications associated with the disease.

Summary of evidence

No studies have been found to analyze the features that must be included in the follow-up study of patients with DM1. So the recommendations are based on the proposals of previous guidelines and the consensus of the GEG.

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The *American Diabetes Association*[51] raised the need for an integrated assessment of the person with diabetes and their evolution, including the assessment of his/her psychological and social situation.

The European Guide to the International Diabetes Federation[643] recommends the integration of these activities into one annual visit, which should include the assessment of metabolic control (HbA_{1c}), examination of the injection sites, assessment of educational aspects and the patient's skills, assessment of the cardiovascular risk factors and their adjustment to the objectives and the evaluation of possible complications.

Recommendations

√	It is recommended to design an individualized care plan, which should be reviewed annually to adjust to the desires, personal circumstances and medical findings of each patient. The specific details of this individual plan must be registered in writing and include aspects related to: • Diabetes education, including dietary advice. • Insulin. • Self-assessment and management of blood glucose (insulin dose modification, mild and severe hypoglycaemia and awareness of it and hyperglycaemia ketosis). • Assessment and management of late complications, including foot exam. • Assessment and management of arterial risk factors. • Psychosocial problems and dental disease. • Frequency of communication with the professional team. • Further consultation planned, including the next annual review.

Strength of recommendation	Periodic reviews	Children and young people	Adults
D	**HbA_{1c}**	From 3 to 4 times a year or more regularly if there is a concern about poor glycaemic control.	
C	**Inspection of injection sites**	In each visit.	
√	**Measurement of height, weight and calculation of BMI**	In each visit in a private room.	The same with the exception of size in adults.

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Assessment of arterial risk factors

Strength of recommendation		Children, adolescents and young people	Adults
√	**Blood pressure**	Annually.	In each visit.
√	**Complete lipid profile**	Annually after the age 12.	Annually
√	**Abdominal circumference**	–	Annually
√	**Smoking**	Annually from adolescence.	Annually
√	**Family history of arterial disease**	–	Annually
D	**Eye exam**	As the general population.	Visual acuity every 2-3 years.
D	**Dental exam**	As the general population.	
√	**Nephropathy**	Annual measuring of the albumin/creatinine ratio in a sample first thing in the morning 5 years after the evolution of the disease is recommended.	
B	**Arterial risk**	Arterial risk tables, equations or calculation programs are not recommended because arterial risk calculation programs may underestimate the risk in adults with diabetes mellitus type 1. Individual assessment is recommended depending on the presence or absence of risk factors.	
B	**Retinopathy**	If there is no retinopathy or it is mild, it is recommended to carry out screening every 2-3 years after puberty or after 5 years of evolution. If there is retinopathy, it is recommended to assess the evolution once a year.	
√	**Rating autoimmune thyroid disease and celiac disease**	Every two years for the first 10 years of the disease progression and then every five years.	

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13. Dissemination and Implementation

13.1. Dissemination and implementation strategy

Clinical practice guidelines are useful to improve the quality of care and outcomes for the patient. The big challenge now is to get the professional to adhere to the recommendations of these guidelines. This calls for an implementation strategy aimed at overcoming the existing barriers in the environment in which it will be applied.

The plan to implement the DM1 guide includes the following interventions:

1. Presentation of the guide by the health authorities to the media.
2. Presentation of the guide to the Directorate and Sub-directorate of the Primary Health Care and Specialized Care Units of the different Health Services.
3. Institutional presentation of the guide in collaboration with the Quality Agency of the Ministry of Health, Social Policy and Equality, to the different scientific and professional societies involved.
4. All presentations will highlight the educational material made for the patient in order to facilitate its distribution among all the health professionals as well as among the patients with this health problem.
5. Effective and addressed distribution to the professional groups involved (physicians specialized in Endocrinology and Nutrition, paediatric endocrinologists, diabetes nurse educators, nutritionists) to facilitate its distribution.
7. Dissemination of the guide in electronic format in the websites of the Ministry of Health, Social Policy and Equality, GuíaSalud, Osteba and the companies involved in the project.
8. Publishing of the guide in scientific magazines.
9. Setting up of criteria for good attention in contract programs and clinical management contracts, following the provisions of the guide.
10. Evaluation of the effectiveness of implantation, establishing systems to support the clinical decision, integrating the guide and the selected indicators in the computer program used in Specialized Care.

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13.2. Implications for clinical practice

Target figures of glycosylated haemoglobin

A strict metabolic control objective requires people with diabetes to involve highly and have a high level of knowledge about their disease and for the health staff to make an extra effort in diabetes education and patient support. Therefore, the consultation time devoted to education, both initially and during the progression of the treatment should be programmed.

Proteins in patients with nephropathy

Formulating diets for people with type 1 diabetes and renal failure on dialysis poses difficulties, since these patients should limit their intake of carbohydrates and proteins, together with the volume of fluid and ions (potassium). Therefore, this task requires the support of nutrition experts.

Continuous Glucose Monitoring Systems

Although the technology for continuous glucose monitoring is evolving towards greater simplification of the systems and to a reduction of costs, there are difficulties for its use in the clinical practice because of possible limitations in its availability, the difficulties that new technologies can pose to patients, and the increase in the costs involved.

Hospital management vs. outpatient management, at the time of diagnosis of diabetes mellitus type 1

The outpatient management of newly diagnosed patients with diabetes mellitus type 1 can be influenced by the organization of healthcare services and the distance between the patient's home and place of consultation, sometimes making hospitalization more appropriate.

Insulin preparations

The use of insulin analogues is widespread due to the preferences of patients and also partly due to the action policies of the pharmaceutical industry, which have been limiting the presentations available on human insulin.

Rotation of injection sites

The rotation of injection sites depends primarily on the patient's preferences. However, the training team teacher should stress the desirability of rotation to avoid lipodystrophy.

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Islet transplantation vs. pancreas transplantation

Pancreas transplantation should be performed, when indicated, in centres with a surgical team expert in transplants in general and pancreas in particular.

It is desirable that the monitoring of metabolic control is performed by a person specifically trained and knowledgeable in the management of immunosuppressive therapy, taking into account its influence on metabolic control.

The performance of islet transplantation poses difficulties in relation to the limitations on the number of donors, the technological limitations and the need for more than a pancreas for obtaining a suitable or sufficient number of islets.

Start time and frequency of screening for diabetic retinopathy

The completion of the retinopathy screening with intervals of 2 or 3 years in the absence of retinopathy at the baseline examination is a benefit for the patient (reducing the number of trips to consultation, medical visits and loss of hours or work) without an increased risk of non-detection of retinopathy and also a benefit for the health services, as it reduces the burden of care and the consequent release of medical and administrative time that can be spent on other tasks.

Criteria for referring the patient with diabetic nephropathy to a nephrologist

In some areas of the country, assistance to specialized care nephrology units will require patients to travel to health centres outside their treatment area.

Screening for diabetic foot

In Spain, the applicability of the recommended interventions for diabetic foot screening may be limited. While the activities of screening and risk stratification are considered feasible, there are no uniform and structured benefits to derive and treat the foot at risk, with variations between the different autonomous communities.

Although the recommended measures are feasible and easy to implement, they require training and especially consultation time, making them difficult to implement, given the lack of time to attend patients in an outpatient consultation.

Transition of patients from paediatric services to adult services

It is possible that the paediatrician and the adult endocrinology specialist do not see patients in the same centre, which would hamper the implementation of the minimum recommendations laid out in this CPG for the transfer of patients from paediatric services to adult health services.

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13.3. Proposed indicators

Treatment and monitoring

Degree of good control with glycosylated haemoglobin
Formula:
ID = a × 100/b, where: a. Number of people with DM1 with a glycated haemoglobin rate below 7%. b. Total number of people diagnosed with DM1.
Definition/clarifications:
• All patients who, at the time of performing the cross-section for the extraction of data, have in their last analytical determination a glycosylated haemoglobin rate <7 %, will be considered in the numerator. The remaining patients, above that amount or fail to show such determination in the last year, will be considered as not complying with the criteria. • This indicator is the result of two factors to consider. One, the degree of coverage determination for people with DM1, and another, the degree of good control achieved among the population who have undergone the test. With this data at least the minimum number of people with DM1 who are known to have good control among the entire population with this diagnosis can be stated.
Disaggregation:
By autonomous community, age and sex.
Source of information:
Primary Care and/or Specialty Care information system.
Frequency:
Triennial.
Comment:
To obtain this indicator the prior agreement of standardized information collection and sharing systems at NHS level is required.

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Degree of poor control with glycosylated haemoglobin
Formula:
ID = a × 100/b, where: a. Number of people with DM1 with a glycosylated haemoglobin rate above 9%. b. Total number of people diagnosed with DM1 who have undergone determination.
Definition/clarifications:
All patients who, at the time of performing the cross-section for the extraction of data, have in their last analytical determination a glycosylated haemoglobin rate > 9%, will be considered in the numerator.
Disaggregation:
By autonomous community, age and sex.
Source of information:
Primary Care and/or Specialty Care information system.
Frequency:
Triennial.
Comment:
To obtain this indicator the prior agreement of standardized information collection and sharing systems at NHS level is required.

Addressing complications and special situations

Incidence of amputations in people with type 1 diabetes
Formula:
ID = a × 100/b, where: a. Number of admissions of people with DM1 who have undergone a non-traumatic amputation of the lower limbs not due to causes other than diabetes within one year. b. Estimated population with DM1.
Definition/clarifications:
Numerator: codes from 84.10 to 84.17 and 250 as principal diagnosis.
Disaggregation:
By autonomous community, age and sex.
Source of information:
• For the numerator the source will be the MBDS at discharge. • For the denominator the prevalence estimation of DM1 from data of the National Health Survey will be used.

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Percentages of complications in pregnancy, childbirth and puerperium
Formula:
ID = a × 100/b, where: a. Number of admissions due to complications related with DM1 which occurred during pregnancy, childbirth or puerperium. b. Number total admissions of women with DM1 after any attention related to pregnancy, childbirth or puerperium.
Definition/clarifications:
• Numerator: must include the code 648.0 of the ICD-9-CM, whether listed as main or as secondary diagnose. • Denominator: includes the codes 630-677 of the ICD-9-CM, and must include, also the code 250.01 for type 1 diabetes or 648.0 as main and secondary diagnose.
Disaggregation:
By autonomous community and by age group.
Source of information:
MBDS at discharge.
Term:
Annual.

Renal Transplantation
Formula:
ID = a × 100 000/b, where: a. Number of kidney transplants performed in people with DM1 in a given year. b. Estimated population with DM1.
Disaggregation:
It will be found for the whole NHS, by sex and age.
Source of information:
• Numerator: National Transplant Organisation. • Denominator: estimation of DM1 prevalence from data provided obtained from the National Health Survey.
Frequency:
Biennial.
Comment:
The denominator may be replaced or supplemented by sources of information coming from the health system (Primary and/or Specialist Care) on records of people diagnosed with DM1.

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Pancreas transplant
Formula:
ID = a × 1,000,000/b, where: a. Number of people who have undergone a pancreas transplant. b. Population in that year.
Disaggregation:
To be used for the whole NHS, by age and sex.
Source of information:
• Part A: National Transplant Organisation. • Part B: Population forecast by the National Statistics Institute.
Frequency:
Biennial.

Premature death from diabetes type 1
Formula:
ID = a × 100 000/b, where: a. Deaths due to DM1 before the age of 65 and before the age of 75 in one year. b. Population from 0 to 64 years old and from 0 to 74, respectively, in that year.
Definition/clarifications:
They will be calculated as gross and as adjusted rates.
Disaggregation:
By autonomous community and sex.
Sources of information:
• Part A: Death records provided by the National Statistics Institute. • Part B: Population forecast by the National Statistics Institute.
Frequency:
Annual.

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Training, research, innovation

Training in diabetes education
The evaluation will be carried out through a descriptive memoir of the training activities in diabetes education conducted in each Autonomous Community. Every two years, it will include as follows: • Types of intervention performed. • Routes and methods used. • Target populations at which they are aimed. • If any evaluation has been performed and the results achieved.

Research project
Formula:
Number of publicly funded research projects, either through the Instituto de Salud Carlos III, the Ministry of Health, Social Policy and Equality, or through direct autonomic funding, related to DM1.
Disaggregation:
For fields of research within the subject area of diabetes or in related research areas.
Sources of information:
Instituto de Salud Carlos III and the Autonomous Communities.
Frequency:
Annual.

Finally, it is important to point out, that other indicators, while important, are not prioritized and thus have not been included, sometimes due to validity or interpretability problems, others for not being its fundamental utility at the level of operational management, and other for feasibility problems to be obtained at the current time.

Among them, the extent to which the progress in data operating systems permits, the advisability of providing systems that enable progress in certain aspects should be considered.

As an example and as a future line, the knowledge of the degree of control of each of the other cardiovascular risk factors that can coexist in the diabetic person, or the actual number of diabetics suffering from various chronic complications, or other aspects that deepen their knowledge of the situation and the clinical course of these patients, can be mentioned.

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14. Future research

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Usefulness of the diagnostic determination of autoantibodies

It would be desirable to conduct studies to evaluate the diagnostic technique of autoantibodies and use the one with better sensitivity and specificity.

Further clinical trials are needed to analyze the inmunointervention in newly diagnosed patients with diabetes mellitus type 1.

For the participation of people with diabetes mellitus type 1 in inmunointervention clinical trials, their characterization based on C-peptide, specific autoantibodies and HLA is essential.

Autoimmune diseases associated with diabetes mellitus type 1

New prospective studies are needed to determine the optimal screening interval for autoimmune diseases in patients with diabetes mellitus type 1.

Formal education for people with diabetes mellitus type 1 and/or their family

Investigating our health context about the possibility of education for patients with diabetes mellitus type 1 in a more favourable environment than the health centres is proposed. In other countries, it is possible to do it at home, both at the moment of diagnosis and during the follow-up. There is a professional called the "visiting nurse" who belongs to the patient's referred endocrinology service, who identifies the problems at home and carries out a detailed analysis of the patient's situation.

Studies are needed to analyze the effectiveness of educational programs, considering the potential confounders factors (time dedicated, changes in the treatment, frequency of visits, etc.).

Community support arrangements in diabetes mellitus type 1

Studies are needed regarding interventions conducted in the workplace and school to support people with diabetes mellitus type 1.

Fibre in the diet

Studies are needed to analyze the potential benefits of a diet high in fibre for people with diabetes mellitus type 1.

Continuous Glucose Monitoring Systems

More studies are needed on the various systems of continuous glucose monitoring, with more patients and a longer follow-up and in specific patient groups such as pregnant women, children, etc.

Insulin preparations

There need to be long-term clinical trials carried out to verify the long-term safety and effectiveness of insulin analogues.

Continuous subcutaneous insulin infusion pump

Comparative studies should be carried out analysing pump infusion and multiple daily injections of insulin to properly assess the long-term effects on metabolic control and complications.

It would be desirable to perform prospective randomized studies that explore the use of continuous subcutaneous insulin infusion pumps versus conventional treatment (especially multiple insulin injections) during pregnancy.

Rotation of injection sites

It would be interesting to conduct studies to rate the frequency of lipodystrophy, its relationship with the practice or not of rotating injection sites and their involvement in metabolic control.

Metformin added to insulin in adolescents with diabetes mellitus type 1

Studies are needed in adolescents with diabetes mellitus type 1 to analyze a larger sample and follow-up periods to evaluate the efficacy and safety of long-term metformin.

Islet vs. pancreas transplantation

It would be advisable to carry out studies oriented at obtaining technical analysis of as many islets as possible, as well as to extend their viability.

Prevalence of mood disorders in people with diabetes mellitus type 1

It would be advisable to conduct studies that analyzed the prevalence of depression, anxiety or eating disorders in people with diabetes mellitus type 1 in our context.

Studies are needed to assess the effectiveness of possible strategies for early identification of patients with eating disorders.

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Start time and frequency of screening for diabetic retinopathy

Considering the widespread non-mydriatic and digital retinal cameras at national level, carrying out a longitudinal study in patients with diabetes mellitus type 1 which allows setting out evolution periods in the degree of involvement of retinopathy as a function of the different risk factors is proposed.

Criteria for referring the patient with diabetic nephropathy to a nephrologist

Further studies are necessary to determine the best time for referral of people with diabetes mellitus type 1 to care units specializing in nephrology.

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Appendixes

Appendix1. Reference centres which can carry out genetic studies to rule out MODY diabetes

Laboratorio de Genética Humana Facultad de Medicina de Albacete (UCLM)

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M. Pilar López Garrido (Group Leader: Dr. Julio Escribano)
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Facultad de Medicina de Albacete (UCLM)
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Genes studied:

- GCK (MODY2): 10 modifying exons (1a, 2-10) and the promoting region (-1 to -870).
- HNF 1A (MODY3): 10 coding exons and the promoting region (-1 to -291) of the gene.

Technique used: automated DNA sequencing

Hospital Clínic de Barcelona

Contact:
Dra. Roser Casamitjana/Dr. Josep Oriola
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Genes studied:

- HNF-4A (MODY1) of exons 1a and 2 to 10.
- GCK (MODY2): exons 2 to 10.
- HNF-1A (MODY3): exons 1 to 10.
- HNF-1B (MODY5): exons 1 to 9.

Technique used: direct sequencing.

Hospital Universitario de Cruces. Bizkaia

Contact:
Dr. Luis Castaño
Unidad de Investigación Hospital de Cruces
Plaza de Cruces s/n
E48903 Barakaldo-Bizkaia
Tel: 946006099/946006473

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Genes studied and techniques used:

- HNF-4A (MODY1): sequencing and MLPA
- GCK (MODY2): dHPLC, sequencing and MLPA
- HNF-1A, TCF1 (MODY3): sequencing and MLPA
- IPF1 (MODY4): sequencing and MLPA
- HNF-1B, TCF2 (MODY5): QMPSF, sequencing and MLPA

Hospital Universitario La Paz, Madrid

Contact:

Dr. Angel Campos Barros,
Servicio de Genética Médica,
Edif. Laboratorios, 2ª planta Hospital Universitario La Paz
Pº de la Castellana 261, 28046 Madrid
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Fax:(34) 91 207 1040
e-mail: acamposbarros@yahoo.es

Genes studied:

- HNF-4A (MODY1)
- GCK (MODY2)
- HNF-1A (TCF1) (MODY3)
- PF1 (MODY4)
- HNF-1B (TCF2) (MODY5)
- NeuroD1 (MODY6)
- PAX4
- KCNJ11 (neonatal diabetes)
- INS (neonatal diabetes)

Techniques used:

- *Screening of punctual mutations and microdeletions* (<25 bp) *in coding sequences, intron/exon transitions and regulatory sequences* by DHPLC (WAVE 3500 HT System) and/or *HiRes Melting* ("High Resolution Melting Analysis"; LightScanner Systems by Idaho Technologies and LightCycler 480, Roche) and direct sequencing of the variants identified.
- Direct DNA sequencing.
- Genotyped functional polymorphisms and known mutations using functional Hi-Res Melting and DHPLC.
- Hemizygosity analysis by total or partial deletions of genes affected by MLPA.

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Universidad Complutense de Madrid

Contact:
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Tel: 91 3941445 Fax: 91 3941691
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Genes studied and techniques used:

- HNF-4A (MODY1) SSCP
- GCK (MODY2) SSCP
- HNF-1A (TCF1) (MODY3) Direct sequencing (DS)
- IPF1 (MODY4) DS
- HNF-1B (TCF2) (MODY5) DS
- NeuroD1 (MODY6) SSCP
- Kir 6.2 DS

Hospital Carlos Haya de Málaga

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Appendix 2. Sweeteners

Non caloric		**Caloric**	
Do not alter glucose		Modify glycaemia	
Saccharin	E 954 *	Sucrose:	ordinary sugar
Aspartame	E 951 *	Fructose:	fruit sugar and honey
Acesulfame	K E 950 *	Maltose:	beer sugar
Cyclamate	E 952 *	Lactose:	milk sugar
Sucralose (can be used in cooking and baking)	E 955 *	Provide 4 calories per gram	
Neohesperidine	E 959 *	Sugar alcohols or polyols: Sorbitol E 420, E 967 Xylitol, Maltitol E 965, Mannitol E 421, E 966 Lactitol inter alia	
		(Check the label so as to not exceed recommended intakes and avoid the laxative effect that may occur)	
*Industrial terms for labelling		Provide about half the amount of calories of the first	

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Appendix 3. Caloric needs calculation

Caloric needs are calculated from the maximum acceptable weight according to sex, physical activity and reductions are applied according to the age and excess weight, using the following formula:

(Maximum acceptable weight × physical activity) - age - overweight

Maximum acceptable weight:	Man	27 × height^2 (meters)
	Woman	25 × height^2 (meters)

Energy requirements according to physical activity:		**Kcal/kg/day**
Basal metabolism		24
Bed rest or minimal activity		30
Light activity	Man	42
	Woman	36
Medium activity	Man	46
	Woman	40
Strenuous activity	Man	54
	Woman	47
Exceptionally intense activity	Man	62
	Woman	55

Reduction by Age		**Excess weight Reduction**
19-49 years.....	5% reduction	10-20% if overweight (25 ≤ BMI <30)
50-59 years.....	10% reduction	30 – 40% if obese (BMI ≥ 30)
60-69 years.....	20% reduction	
≥ 70 years.....	30% reduction	BMI = weight (kg)/height 2 (meters)

Sample calculation of a diet

64-year-old woman, 1.56 m tall and 70 kg housewife.

BMI calculation:	70/(1.56)^2 =28.8 (overweight)
Calculation of acceptable weight:	25 × (1.56)^2 = 60.7 kg
Type of activity: (WHO table)	60.7 × 36 (housewife) = 2185 kcal/day
Age: (WHO tables)	185 - 20% (64 years) = 1748 kcal/day

Weight reduction according to current weight:

- If there is overweight, 10-20% will be subtracted from the calculated kcal
- If there is obesity 30-40% is to be subtracted

In this example, 1,748 - 20% = 1,400 kcal/day

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Appendix 4. Menu-based method

Eating patterns of 1,800 calories

Breakfast	• A glass of skim milk or two low-fat natural yogurts • 40 g of cheese, ham or tuna • 40 g of bread or 30 g of toast or 30 g of cereals
Midmorning	• A medium piece of fruit • 20 g of bread
Food	• A dish of any vegetable or salad (escarole, endive, chard, spinach, mushrooms, asparagus, cucumbers, tomatoes, peppers, cabbage, aubergine, cauliflower, courgette, green beans, carrots, artichokes, onions, beets, Brussels sprouts...) • To choose o 200 g of potatoes o 80 g of bread o 80 g of pulses (lentils and chickpeas) o 240 g of peas or beans o 60 g of rice o 50 g of pasta (soup, macaroni, noodles, spaghetti, cannelloni...) • To choose: o 100 g of meat (beef, veal, rabbit, chicken) o 150 g of any fish • A medium piece of fruit
Midafternoon	• Half a glass of skim milk or a low fat yogurt • 20 g of bread, 15 g of toast or 15 g of cereals
Dinner	• A plate of any vegetable or salad • To choose o 200 g of potatoes o 80 g of bread o 80 g of pulses (lentils, chickpeas) o 240 g of peas or beans o 60 g of rice o 50 g of pasta (soup, macaroni, noodles, spaghetti, cannelloni) • To choose o 150 g of any fish o 40 g of cheese or fresh + egg omelette • A medium piece of fruit
Supper	• Half a glass of milk

Notes: Three tablespoons of oil for the day.

If not stated otherwise, weights are in raw and clean.

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1800-calorie eating patterns

Examples of 1800-calorie menus

Breakfast	• A glass of skim milk • 40 g of bread • 40 g of tuna	• Two low-fat yogurts • 30 g of toast • 40 g of ham	• A glass of skim milk • 15 g of cereal without sugar • 15 g of toast, 40 g of cheese
Midmorning	• A medium sized apple • 15 g of toast	• 2 or 3 tangerines • 20 g of bread	• A small banana (100 g) • 15 g of toast
Food	• A bowl of mixed salad • A dish of macaroni or spaghetti (60 g raw, 12 tablespoons cooked) • A steak of 100 g of beef or veal (or: 100 g of minced meat for the pasta) • A peach	• A dish of spinach • 100 g of chicken with baked potatoes • 40 g of bread • 300 g of strawberries	• A dish of asparagus, aubergine, peppers or mushrooms • A dish of lentils or chickpeas (60 g raw, 6 tbs cooked) • 20 g of bread • 150 g of fish (e.g. sardines grilled) • A pear
Mid-afternoon	• A low-fat yogurt • 20 g of bread	• Half a glass of skim milk • 15 g of cereals without sugar	• A low-fat yogurt • 15 g of toast
Dinner	• A dish of green beans • 100 g of potatoes • 40 g of fresh cheese + 40 g of sweet ham • 40 g of bread • An orange	• A tomato salad • Soup pasta (30 g raw, 6 tbs cooked) • 40 g of bread • 150 g white fish (monkfish, hake) grilled or boiled • A slice of watermelon	• A plate with a slice of melon and 40 g of Serrano ham • An one egg omelette (of asparagus, mushrooms or aubergine) • 80 g of bread
Supper	• Half a glass of milk	• A yogurt	• Half a glass of milk

Notes: Three tablespoons of oil for the day
If not stated otherwise, weights are in raw and clean

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Appendix 5. Servings based method and measuring cup

Feedings meal plan

Poor in cholesterol

1.500 Calories

CARBOHYDRATES	**52 %**
PROTEINS	**18%**
FATS	**30%**

Without salt: Yes / No

NUMBER OF SERVINGS

	MILK	PROTEIC FOOD	VEGETABLES	FLOURS	FRUITS	FATS
BREAKFAST ..... **h**	1			2		1
MID-MORNING ..... **h**					2	
LUNCH ..... **h**		2	1	4	2	1
MID-AFTERNOON ..... **h**	0,5					
DINNER ..... **h**		2	1	4	2	1
BEFORE SLEEPING ..... **h**	0,5					

AMOUNT OF FOOD PER SERVING

The weight of the food is raw and clean. Flours can be measured already cooked.

MILK
(10-6-6-120) 200 ml of milk = 1 cup = 2 yogurts



FATS
(0-0-10-90)



1 spoonful of oil, mayonnaise*
10 g butter*, margarine *
40 g of olives
30 g of cream*, milk cream *
15 g of dried fruits

FLOURS
(10-1,5-0-46)



60 g peas, broad beans,
50 g potatoes, sweet potatoes
20 g pulses (lentils, chickpeas...)
20 g bread, chestnuts
15 g toasts, milk cereals
15 g rice, semolina, flour 15 g pasta (soup, macaroni, noodles, spaghetti, cannelloni…)

1 measuring cup = 2 servings boiled in water

FOOD PROTEIC FOOD
(0-10-5-85)



50 g of beef, ox, chicken, rabbit, lamb*, pork*
75 g of white/blue fish, seafood*
40 g of cold meats*
40 g of cheese: fresh, creamy *mature*
1 egg*

FRUIT
(10-0-0-40)



150 g of melon, watermelon, strawberries, grapefruit.
100 g of apricot, orange, pear, tangerine, lemon, plum, pineapple, kiwi, apple.
50 g of banana, grapes, cherries, figs, custard apple, medlars.

VEGETABLES
(10-0-0-40)



300 g of escarole, lettuce, endives, chards, spinaches, mushroom, asparagus, cucumber, tomatoes, peppers, cabbage, aubergine, cauliflower, courgette, green beans.
150 g of carrots, artichokes. onion, beetroot, Brussels sprouts

Poor in cholesterol
Restrict food marked with*
Restrict battered food and sauces with cream, butter, and milk cream.
Take milk and skimmed yogurts
Use olive oil to cook

If diet is without salt, the patient should:
Avoid salty food and those marked with.
Avoid sparkling water, canned and smoked food.
Do not add salt to the food
Herbs can be added to the food.

(In parenthesis are the grams of carbohydrates, proteins, fats and calories per serving)

THE FOOD FROM EACH GROUP IS INTERCHANGEABLE,THUS IT IS THE SAME TO HAVE 150 g OF MELON OR 100 g OF APPLE.

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MEASURING CUP



How to use this cup?

The measuring cup of cooked food *(adapted for 2 servings), is an instrument that measures and exchanges the food from the FLOURS group: potatoes, pasta, peas, broad beans, pulses, rice, and bread.*

1 full measuring cup filled to the indicated sign for each food, once cooked, is equivalent to 40 grams of bread.

Nº OF SERVINGS	WEIGHT RAW	APPROX WEIGHT COKED	AMOUNT COOKED
2 SERVING	• 120g peas, broad beans	120-130 g	 1 measuring cup filled until the indicated sign for each food
	• 100 g potatoes	100 g	
	• 40 g pulses (lentils, beans, chickpeas)	80-100 g	
	• 30 g rice	90-120 g	
	• 30 g pasta (soup, spaghetti, noodles, macaroni...)	60-90 g	

The main advantage of measuring and exchanging these foods, once cooked is that they can be easily exchanged for 40 grams of bread.

Changing the menus

Adapting the feeding plan recommended to the family working menu.

**This measuring cup has been developed and validated by the team Endocrinology and Nutrition Service. It received the award of the Asociación Catalana de Educadores en Diabetes in 1991.*

Depending on the number of servings from the FLOURS group which have been recommended in your feeding plan, the following exchanges can be done.

2 servings from the flours group means that you can choose between:

1 cup		Without bread
without cup	40 g	

4 serving from the flours group means that you can choose between:

2 cups		Without bread
1 cup		+ 40 g 
without cup		+ 80 g 

2 servings from the flours group means that you can choose between:

3		Without bread
2 cups		+ 40 g 
1 cup		+ 80 g 
without cup		+ 120 g 

**Consult your healthcare professional (dietician, doctor, nurse) controlling your feeding plan on the number of servings recommended.*

More than 5 years have passed since the publication of the Clinical Practice Guideline, and its validity has not been reviewed

Reference: Margarida Jansà-Mercè Vidal. Enfermeras educadoras en diabetes Servei d'Endocrinologia i Diabetes. Unitat d' Educació Terapéutica. Institut Clínic de Malalties Digestives i Metaboliques. Available at: http://www.aedn. es/resources/articulord22.PDF

Appendix 6. Exchange and equivalence system

Equivalence table of commonly used measures

Glass of water or cup of milk	200 ml
1 yogurt	125 ml
1 tablespoon of oil	10 ml
1 heaped tablespoon of sugar	20 g
1 tablespoon of rice (uncooked)	20-25 g
1 tablespoon of flour	20-25 g
1 tablespoon of oil	5 ml
1 tablespoon of sugar	10 g
1 packet of sugar	10 g
1 sugar cube	5 g
1 tablespoon of jam	20-25 g
1 individual portion of jam	15 g
1 single serving of butter	15 g
1 handful (closed hand) of rice or small pasta	20-25 g
1 cup of rice or small pasta	80-100 g
2 tablespoons of raw lentils	20 g
3 tablespoons of raw chickpeas	40 g
20 pieces of macaroni	15 g
1 bowl of vegetables	200-300 g
1 piece of normal sized fruit	150 g
1 wineglass	100 g
1 potato slightly greater than an egg	100 g

Available at: www.fisterra.com/material/dietary

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Food exchange list

1. Dairy	
Quantity of food per exchange unit	**Food**
200 ml	Milk.
250 g	Yoghurt, curd, custard, Actimel (drinking yoghurt).
100 g	Queso de Burgos (fresh cheese)*.
60 g	Petit Suisse.
* To be avoided in the diet without salt, or to be substituted for the unsalted equivalent. Avoid salty, canned, cooked, smoked foods.	

2. Protein foods	
Quantity of food per exchange unit	**Food**
Meat with 2-6 grams of fat	
60 g	Cooked ham *, veal kidneys, leg of lamb.
50 g	Ostrich, ox, horse, tripe, goat, rabbit, venison, pheasant, liver (pork, lamb, chicken, beef), pig, chicken, turkey, partridge, hare, lean beef, venison.
Meat with 6-12 grams of fat	
50 g	Quail, lean pork, pigeon, half-fat beef
30 g	Lean Serrano ham*, pork loin*.
Meat with 13-25 grams of fat ❤	
75 g	Chopped* mortadella*, sausage*, black pudding*.
50 g	Bacon*, pork, lamb chop and rack, spicy sausage *, pork shoulder (ham)*, white pudding *, pate*, fat beef, sausage (salami) *, sobrasada *.
25 g	Serrano ham *, pork chop.
Fish with 2-6 grams of fat	
75 g	Pollock, clam, cod, whiting, catfish, bream, clams, lobster, bream, squid, crab, crab, whitebait, mussels, crayfish, shrimp, prawn, lobster, sole, sea bass, hake, halibut, mussels, canned mussels *, trash fish, crab, oysters, halibut, flounder, whiting, barnacle, swordfish, skate, monkfish, turbot, mullet, bream, cuttlefish, trout, scallops.
50 g	Fresh anchovies, shrimp, conger eel, carp, bream, scallop.
Fish with 6-12 grams of fat	
50 g	Eel, baby eel, herring, fresh tuna, Iberian nase, white tuna, fresh anchovy, mackerel, dogfish, smooth hound, horse mackerel, grouper, mullet, cornetfish, salmon, smoked salmon *, canned sardines*.
35 g	Canned anchovies*, canned tuna*.
Eggs	
90 g	Egg.
75 g	Chicken egg.

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2. Protein foods	
Quantity of food per exchange unit	**Food**
Nuts	
40 g	Almond, lupine, hazelnut, peanut, coconut, pine nuts, pistachios, sunflower seed, pumpkin pipe, nut.
Cheese	
50 g	Roquefort*❤, mozzarella*❤, brie*❤, sliced cheese for sandwich*❤, soft cheese *.
30 g	Cabrales cheese*❤, gruyere*❤, Dutch cheese*❤.
Vegetable Protein	
65 g	Tofu.
40 g	Loath.
30 g	Soya.
* To be avoided in the diet without salt, or to be substituted by the unsalted equivalent. Avoid salty, canned, cooked and smoked foods. ❤ Limit on a diet low in saturated fat.	

3. Food hydrocarbon	
Quantity of food per exchange unit	**Food**
Tubers	
50 g	Potato, sweet potato, yam.
12 g	Tapioca.
Pulses and nuts	
20 g	Chickpeas, peas, dry broad beans, dry beans, lentils, chestnuts.
Cereals and their by-products	
20 g	Bread (white, brown, loaf), breakfast cereals *.
15 g	Rice, wild rice, bulgur, couscous, biscuits, flour, semolina, pasta (noodles, cannelloni, spaghetti, macaroni, lasagne, tapioca), toasted rusks, toasted sweetened corn cereal, muesli.
Sugars and their by-products	
30 g	Jam.
15 g	Chocolates©, honey.
10 g	Sugar, sweets.
Bakery	
15 g	Croissant ❤, cake ❤, bun ❤, muffins ❤.
* To be avoided in the diet without salt, or to be substituted by the unsalted equivalent. Avoid salty, canned, cooked and smoked foods. ❤ Limit on a diet low in saturated fat.	

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4. Fruits	
Quantity of food per exchange unit	**Food**
150 g	Acerola, blueberry, raspberry, currant, lemon, melon, blackberry, grapefruit, watermelon.
100 g	Apricot, blueberry, plum, strawberry, large strawberry, pomegranate, kiwi, apple, tangerine, passion fruit, quince, peach, orange, nectarine, papaya, flat peach, pear, pineapple, orange juice.
50 g	Early fig, kaki, cherry, cherimoya, fig, lychee, mango, medlar, banana, grape, pineapple in syrup, peaches in syrup.
15 g	Raisins, dates, dried date, dried fig.

5. Vegetables	
Quantity of food per exchange unit	**Food**
300 g	Celery, acerola, chicory, chard, aubergine, watercress, broccoli, zucchini, corn salad, thistle, cabbage, cauliflower, mushrooms, kohlrabi, endive, escarole, asparagus, spinach, lettuce, purple cabbage, hearts of palm, cucumber, pepper, radish, mushrooms, tomato.
200 g	Turnip tops, green beans, turnip, turnip greens, leek.
100 g	Artichoke, pumpkin, onion, Brussels sprouts, sweet bean, sweet corn, beetroot, carrot.

6. Fats and oils	
Quantity of food per exchange unit	**Food**
70 g	Avocado.
40 g	Olives *
30 g	Cream, egg yolk.
20 g	Low calorie mayonnaise.
10 g	Oil (olive, sunflower, corn), mayonnaise butter ❤, margarine ❤.

* To be avoided in the diet without salt, or to be substituted by the unsalted equivalent. Avoid salty, canned, cooked and smoked foods.
❤ Limit on a diet low in saturated fat.

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Appendix 7. Eligibility criteria for contraceptives in women with diabetes*

Score	
1	Use the method in any circumstance.
2	Generally use the method.
3	Use of the method is not usually recommended unless other more appropriate methods are not available or not accepted.
4	Do not use the method.

CC	Combined contraceptives.
COC	Combined oral contraceptives.
CIC	Combined injectable contraceptives.
CCP	Combined Contraceptive Patch.
VCR	Combined Vaginal Ring.
PC	Progestin -only contraception.
POC	Progestin-only oral contraceptives.
D/EN	Depot medroxyprogesterone acetate (DMPA)/norethisterone enanthate (NET-EN).
LNG/ETG	Levonorgestrel implants (Norplant and Jadelle) and etonogestrel implant.
IUDs	Intrauterine Device.
IUS	Levonorgestrel-releasing IUD (20 mg every 24 hours).

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* *Source*: Adapted from A WHO Family Planning Cornerstone. Medical Eligibility Criteria for Contraceptive Use. World Health Organization 2009; Fourth edition.

	AC a				APS b			IUD
HORMONAL CONTRACEPTIVE METHODS	**Low dose AOC ≤ 35 mg of ethenyl estradiol**	CIC	CCP	VCR	POCs	D/ EN	LNG/ ETG	IUD-LNG
a)History of gestational disease.	1	1	1	1	1	1	1	1
b) Non-vascular disease:								
– Non-insulin dependent.	2	2	2	2	2	2	2	2
– Insulin dependent.	2	2	2	2	2	2	2	2
c) Nephropathy/ Retinopathy/Neuropathy.	3/4	3/4	3/4	3/4	2	3	2	2
d) Other vascular disease or diabetes for <20 years.	3/4	3/4	3/4	3/4	2	3	2	2

[a] Although the carbohydrate tolerance may change with the use of combination hormonal contraceptives, the main concern is the vascular disease caused by diabetes and the additional risk of arterial thrombosis by combined hormonal contraceptive use.

[b] Non-vascular disease: the PCs may slightly influence the carbohydrate metabolism.

Nephropathy, retinopathy, neuropathy or other vascular disease or diabetes for more than 20 years' duration: concern exists about hypo-estrogenic effects and reduced HDL, particularly among the users of DMPA and NET-EN, as these may persist for some time after stopping their use. Some PCs may increase the risk of thrombosis, although this increase is substantially less than the COC.

	MB			IUD
NON-HORMONAL CONTRACEPTIVE METHODS	**C**	E	D	DIU-CU
a) History of gestational disease.	1	1	1	1
b) Non-vascular disease:				
– Non-insulin dependent.	1	1	1	1
– Insulin dependent.	1	1	1	1
c) Nephropathy/Retinopathy/Neuropathy.	1	1	1	1
d) Another vascular disease or diabetes lasting <20 years..	1	1	1	1

MB: Barrier methods

C = Male latex condoms, Male polyurethane condoms, Female condoms
E = spermicide (film, gel, tablets, foam).
D = diaphragm (with spermicide), cervical cap.

Intrauterine device IUD IUD-CU: Copper IUD.

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SURGICAL STERILIZATION PROCEDURES FOR WOMEN	CATEGORY	CLARIFICATIONS/EVIDENCE
a) History of gestational disease.	A	Note: If glycaemia is not controlled, referral to a higher level centre is recommended.
b) Non-vascular disease: – Non-insulin dependent – Insulin dependent.	C C	Note: there is a decrease in healing and an increased risk of wound infection. Preventiv e antibiotics are recommended. Evidence: Women with diabetes were more likely to have complications when undergoing sterilization.
c) Nephropathy/Retinopathy/ Neuropathy.	E	1
d) Another vascular disease or diabetes lasting <20 years.	E	1
SURGICAL STERILIZATION PROCEDURES FOR MEN	**CATEGORY**	**CLARIFICATIONS/EVIDENCE**
Diabetes.	C	Clarification: the people with diabetes are more prone to postoperative infections of wounds. If there are any signs of infection, antibiotics should be given.

A-Accept: There is no medical reason to deny sterilization to a person in this condition.

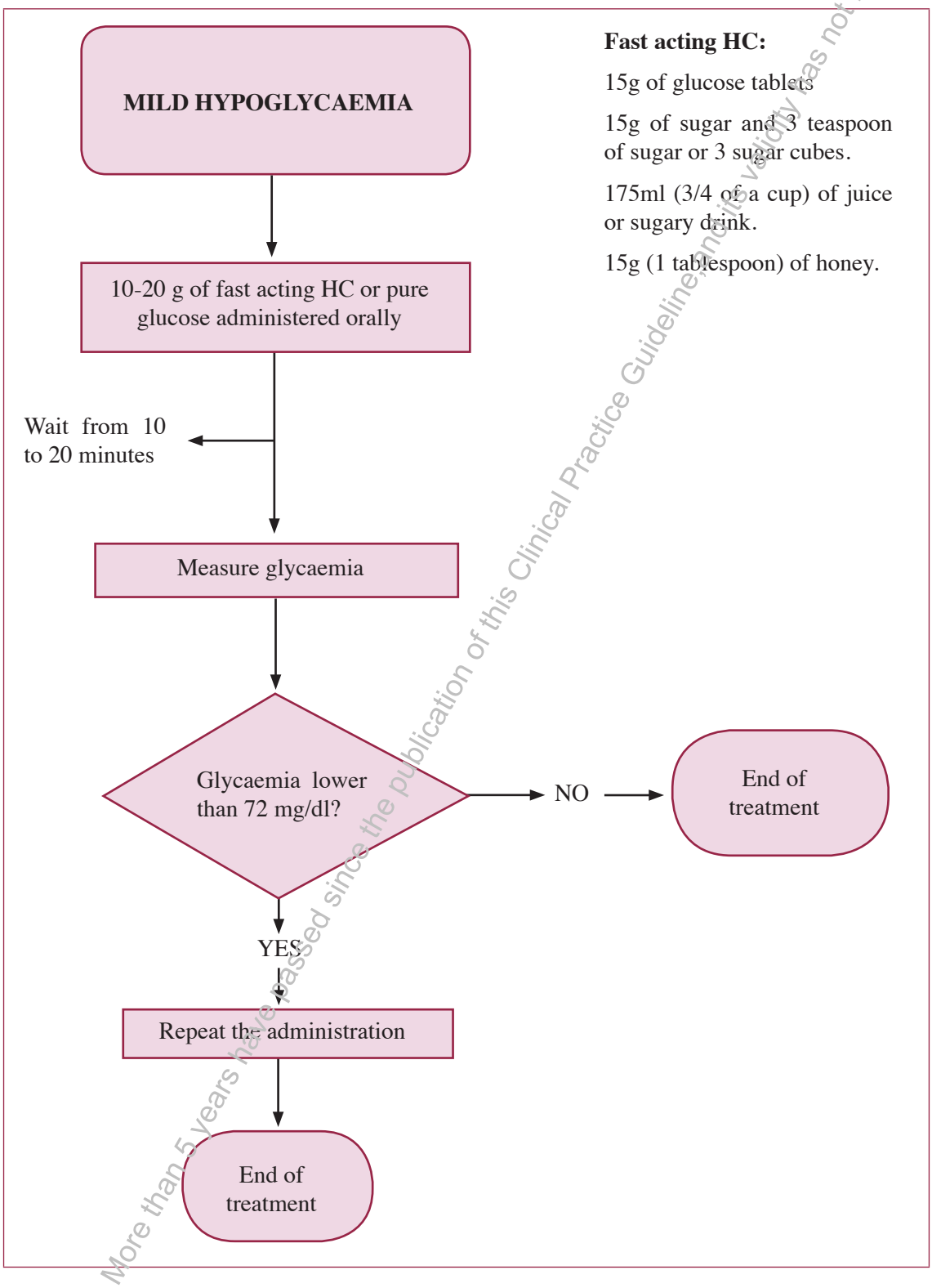
C-Care: The procedure is usually done routinely, but with preparation and additional concerns.

E-Special: The procedure must be carried out in locations with surgeons and experienced personnel, and the equipment needed to provide general anaesthesia and other medical support backup. These conditions also require the ability to decide on the most appropriate procedure and anaesthesia regimen. Alternative temporary methods of contraception should be offered; if necessary refer the patient or if there is any further delay.

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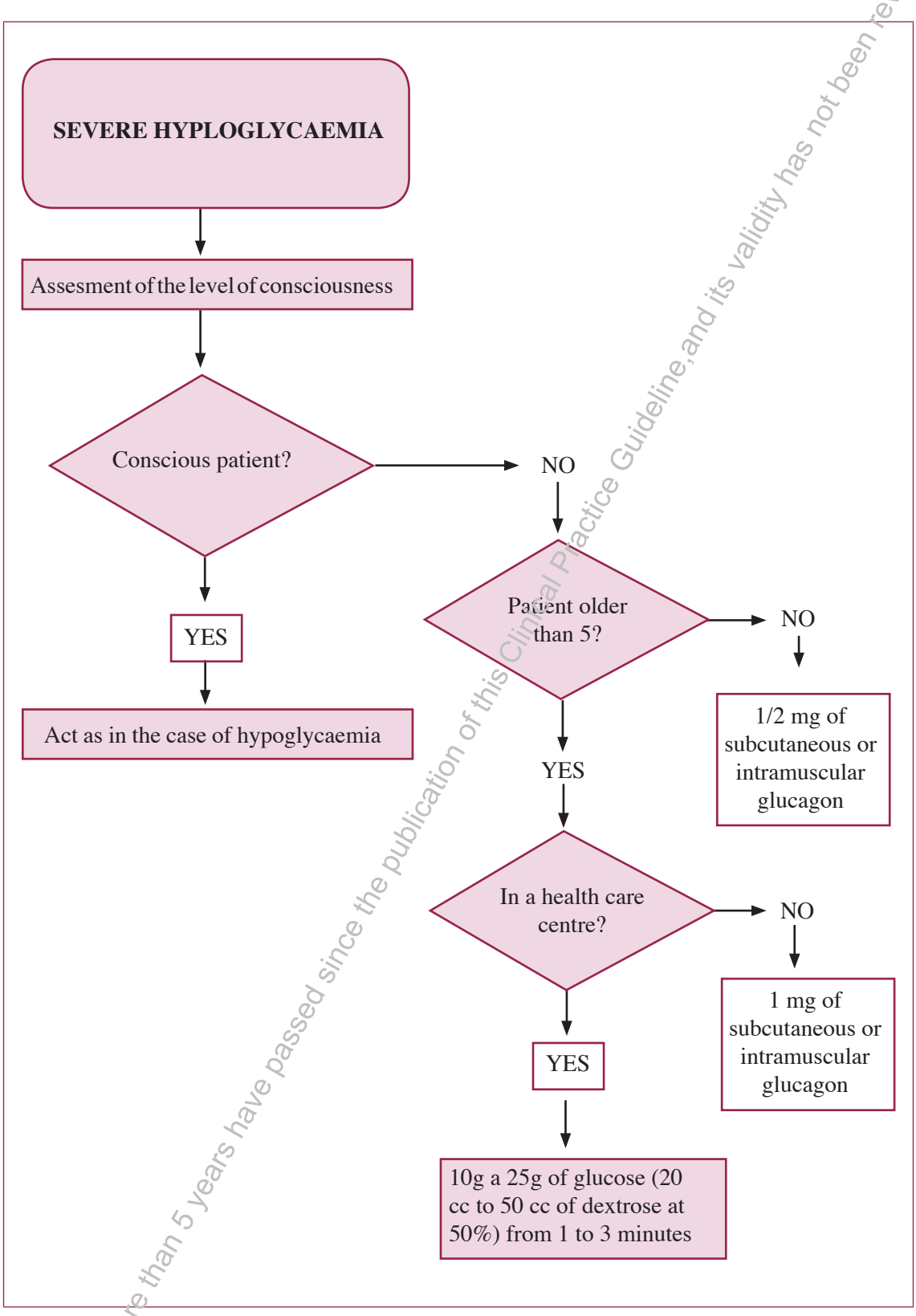
Appendix 8. Treatment of hypoglycaemia

8.1. Mild hypoglycaemia



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8.2. Severe Hypoglycaemia



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Appendix 9. Use of the monofilament (509)

It evaluates the pressure and touch sensitivity, which has been termed "protective sensation".

It is composed of a nylon filament attached to a handle, which when bent, applies a constant pressure of 10 g, regardless of the force applied.

Rules for using the monofilament (MF)

The monofilament is applied perpendicularly to the patient's skin and the pressure will increase until the MF bends. It is at this point when it is analyzed.

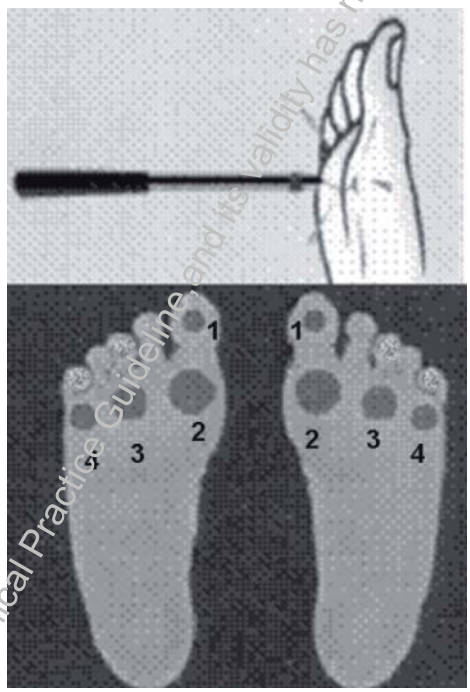
It should be kept leaning over 1-2 seconds.

The exploration will take place at four plantar points on each foot: first toe (distal phalanx), base of the first, third and fifth metatarsal.

(Note: When there is hyperkeratosis, the monofilament is applied in the area around it, or the scan will be repeated once the callus has been removed).

Each of these locations will be scored 1 or 0, depending on whether the patient is sensitive or not. The sum of the values will state the MF sensitivity index (0 to 8).

It is considered a sensitive patient only when the score is 8/8.



Precautions in the use of monofilament

It must be ensured that patients have previous experience: apply the MF in a different area and which is easy to see (upper extremities, face...), so that they can get an idea of the type of feeling.

During scanning: the patient will close his eyes and will be told: "Now I will put this device on different parts of both feet: let me know when you feel them and try to tell me where you feel them: in which foot, finger, on the sole... " At the time when the MF is being applied, the question "Do you feel it now?" must be avoided. At some point, ask this question without applying the monofilament.

In patients with any insensitive point, the scan will be repeated in those points at the end of the first scan (repeated two times). If that point appears to be sensitive the second time, it will be considered sensitive.

In patients with all sensitive points (MF index = 8) a single scan will be enough.

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Appendix 10. Drugs for neuropathic pain

Dose and most common side effects of the drugs most frequently used in neuropathic pain (406)

Drug	Dose	Adverse Effects	Observations
ANTIDEPRESSANTS			
TRICYCLIC Amitriptyline	ID: 10-25 mg/day in single dose at bedtime. Increase 10-25 mg each week. HD: 50-150 mg/day. MD: 150 mg/day.	Anticholinergic: dry mouth, constipation, urinary retention, and tachycardia. Other: orthostatic hypotension, sedation, confusion, weight gain or cardiac effects such as conduction block.	Treatment should be withdrawn gradually.
Duloxetine	ID: 60 mg/day in a single dose with or without food. HD: 60 mg/day. MD: 120 mg/day in divided doses.	Nausea, drowsiness, headache and dizziness.	The response should be evaluated after two months. It is unlikely to obtain an additional response after this period. Treatment should be withdrawn gradually.
ANTIEPILEPTICS			
Gab apentin	ID: 300mg/8 h. Increase by 300 mg every week. HD: 1200-1400mg/day. MD: 3600 mg/day.	Sleepiness, mood disturbances, diarrhoea, ataxia, fatigue, nausea and dizziness.	Reduce dose in cases with renal impairment and in the elderly.
Pregabalin	ID: 50-150 mg/day in 2-3 doses. Increase by 50-150 mg each week. HD: 300-600 mg/day. MD: 600 mg/day.	Dizziness, constipation, fatigue, nausea, sedation, weight gain, blurred vision.	Caution if used with glitazones, for the greater likelihood of peripheral oedema and increased weight gain. Reduce dose in cases with renal impairment and in the elderly.
Carbamazepine	ID: 100-200 mg/day in 3-4 doses. Increase by 100-200 mg every week. HD: 600-1200 mg/day. MD: 1600 mg/day.	Ataxia, dizziness, diplopia, and nausea. There have been rare reports of agranulocytosis or aplastic anaemia.	
OPIOIDS			
Tramadol	ID: 50 mg/day in 2 doses. Increase by 50 mg every week. HD: 50-100 mg/6-8 h MD: 800 mg/day.	Nausea, vomiting, sweating, feeling dizzy dry mouth, sedation, increased risk of seizures, serotonin syndrome.	The adverse effects increase with the speed of the titration. Dose adjustment is required in renal or hepatic impairment.
Morphine	ID: 5-15 mg of quick release every 4 hours. After 7-15 days move on to delayed release. HD: 120 mg/day. MD: 180 mg/day.	Nausea, vomiting, constipation, drowsiness, and dizziness.	It is usually necessary to treat the constipation it provokes.

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Appendix 11. Information for Patients

11.1. International Charter of rights and responsibilities of people with diabetes

Vision

The vision of the Charter is to:

- Optimise the health and quality of life of people with diabetes
- Enable people with diabetes to have as normal a life as possible
- Reduce or eliminate the barriers to people with diabetes realising their full potential as members of society.

The Charter

- Sets out the rights as well as the responsibilities of people with diabetes
- Acknowledges the wide global variety in the quality of healthcare as well as customs and practice that impact in different ways on people with diabetes
- Represents the 'gold standard' in care, treatment, prevention and education to which all countries and people can aspire.

1. The Right to care

People with diabetes have the right to:

- Early diagnosis and affordable and equitable access to care and treatment, regardless of race, ethnicity, gender and age, including access to psychosocial care and support.
- Receive regular, reliable advice, education and treatment in accordance with evidence-based practice that centres on their needs, irrespective of the setting in which they receive that care.
- Benefit from proactive health sector community outreach, education and prevention campaigns in every healthcare setting.
- Access to high-quality services and care during and after pregnancy and childbirth.
- Access to high-quality services and care during childhood and adolescence, recognising the special needs of those not necessarily in a position to represent themselves.

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- Appropriate transitional care, addressing the progression of the disease and the changes that occur with age.
- Continuity of appropriate care in disaster and emergency situations.
- Be treated with dignity and respect - including respect for individual, religious or cultural beliefs and parental insights - by healthcare providers, and feel free to make complaints about any aspects of diabetes services without detriment to their care and treatment.
- Information relating to their diabetes being kept confidential and not disclosed to third parties without their consent and the choice whether or not to take part in research programmes, without detriment to care and treatment.
- Advocate, individually and collectively, to health providers and decision makers for improvements in diabetes care and services.

2. Right to Information and Education

People with diabetes and the parents or carers of people with diabetes have the right to:

- Information and education about diabetes, including how it can be prevented, how early detection in high-risk individuals is an advantage, how the disease can be managed effectively and how to access education and clinical resources.
- High quality diabetes self-management education at diagnosis and whenever needed that integrates the clinical, behavioural and psychosocial aspects of diabetes in a group or individually.
- Be involved in assessing, planning and implementing as well as monitoring their own care and health goals.
- Reliable information about the names and dosage of any therapies and medication, their actions and potential side effects and interactions with other medical conditions and therapies, specific to the individual.
- Individual access to their medical records and other relevant information if requested and the right for that information to be shared.

3. Right to Social Justice

People with diabetes are entitled to:

- Be a fully engaged member of society, treated with respect and dignity by all, without feeling the need to conceal the fact they have diabetes.
- Affordable medicines and monitoring technologies.

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- Be treated fairly in employment and career progression while acknowledging that there are certain occupations where identifiable risks may limit the employment of people with diabetes.
- Be treated with respect and dignity by all sections of society.
- Not to be discriminated against in the provision of all forms of insurance cover and in applying for a driving licence.
- Be fully supported in pre-school activities, schools, during extra-curricular activities and social clubs as well as in workplaces and be given time to attend medical appointments as well as the time and privacy to self-test and administer medicines in a clean and safe environment.
- Create or participate in a representative patient organisation and seek the support for that organisation from health and health-related bodies and civil society.

4. Responsibilities

People with diabetes have a responsibility to:

- Share information with their healthcare providers on their current state of health, all types of medicines they are using, allergies, social setting, lifestyle behaviour and any other information that would be relevant in a health provider determining the most suitable treatment and advice.
- Manage their agreed care and treatment plan.
- Adopt, implement and monitor healthy lifestyle behaviours as part of their self-management of diabetes.
- Share with their healthcare providers any problems they experience with their recommended treatment plan, including any barriers to its successful implementation.
- Inform family, school, work and social colleagues they have diabetes so that they can be supportive to people with diabetes, if and when needed.
- Show consideration and respect for the rights of other people with diabetes and their healthcare providers.

Source: International Diabetes Federation.

Available at: http://www.idf.org/webdata/docs/advocacy-kit/Charter-of-rights-ES.pdf

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11.2. Support groups for people with diabetes

Name	Phone	Address	Postal Code
Federación de Diabéticos Españoles (FEDE)	916 908 840	Calle de la Habana, 35 (posterior)	28945
Asociación Cántabra de Diabéticos (ACD)	942 274 022	Plaza Rubén Darío, s/n	39005
Asociación de Diabéticos de Melilla (ADIMEL)	952 679 626 690 826 328	Prolongación Paseo de Ronda Edif. Mar de Alborán, 3.bajo Aptdo. Correos n.° 67	52080
Asociación de Diabéticos Principado de Asturias (ADPA)	985 88 14 97 696 295 026	Isla de Erbosa, 17	33440
Asociación de personas con diabetes de les illes Balears	971 723 243	De la Rosa, 3-2°	07003
Asociación Navarra de Diabéticos (ANADI)	948 207 704	Calderería 1-entreplanta drcha.	31001
Associació de Diabetics de Catalunya (ADC)	934 513 676	Pere Vergés 1-11.er piso Hotel dentitats de la Pau-Serveis	08020
Diabéticos Asociados Riojanos (DAR)	941 231 278	Avda. Pío XII, 10-1.°C	26003
Federación Asociaciones Diabéticos de Extremadura (FADEX)	924 844 311	Pl. España 4, 1,a pta-Centro Cívico-Aptdo. 249	06700
Federación de Asociaciones de Diabetes de Canarias (FADICAN)	922 253 906	Santiago Cuadrado, 7	38201
Federación de asociaciones de Diabéticos Andalucía (FDA)	959 284 634	Vázquez López, 50-2.° izda.	21001
Federación de Asociaciones de Diabéticos de Aragón (ADEARAGON)	976 301 519	Moncasi, 3.°-2.°C	50006
Federación de Asociaciones de Diabéticos de la Comunidad Autónoma de Madrid (FADCAM)	656 443 718	Alvaro de Bazán 12, bajo-local 4	28902
Federación de Asociaciones de Diabéticos de Euskadi (FADE)	944 446 606	Iparraguirre 46, 3.°-1.a	48010
Federación de Castilla la Mancha de Asociaciones de Diabéticos (FEDICAM)	619 516 115	Mediodía 27	13600
Federación de Diabéticos Comunidad Valenciana (FEDICOVA)	965 257 493	Aiún, 21-local 12	03210
Federación de Diabéticos de Castilla y León (FADCYL)	923 123 612	Corregidor Caballero Llanes 15-19	37005
Federación Gallega de Asociaciones de Diabéticos (FEGADI)	986 431 582	Ronda Don Bosco, 41-bajo-oficina 12	36202
Federación Murciana de Diabéticos (FREMUD)	968 52 90 14 968 52 99 31	Tolosa Latour, 4-6.°A	30201

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Locality	Province	Community Autonomous	Web	Email
Fuenlabrada	Madrid	Madrid	www.fedesp.es	fede@fedesp.es
Santander	Cantabria	Cantabria	www.diabetescantabria.org	asoc.acd@terra.es
Melilla	Melilla	Melilla	www.adimel.org	clubadimel@hotmail.com
Luanco	Asturias	Asturias	www.asdipas.org	info@asdipas.org
Palma de Mallorca	Islas Baleares	Islas Baleares	www.adiba.es	adiba@adiba.es
Pamplona	Navarra	Navarra	www.anadi.es	anadi.correo@gmail.com
Barcelona	Barcelona	Cataluña	www.adc.cat	adc@adc.cat
Logroño	La Rioja	La Rioja	www.diabeticosriojanos.org	dar@eniac.es
Villanueva de la Serena	Badajoz	Extremadura	www.fadex.org	fadex@extremadura.es
La laguna	Santa Cruz de Tenerife	Islas Canarias	www.diabetesencanarias.org	info@diabetetenerife.org
Huelva	Huelva	Andalucía	www.diabeticosandaluciua.org	huelvadiabetes@hotmail.com
Zaragoza	Zaragoza	Aragón	www.adezaragoza.org	asociación@adezaragoza.org
Getafe	Madrid	Madrid	www.fedcam.com	fedcam@yahoo.es
Bilbao	Vizcaya	País Vasco		AVD1@euskalnet.net
Alcázar de San Juan	Ciudad Real	Castilla-La Mancha	www.fedicam.org	domingocamacho@terra.es
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Appendix 12. Glossary

Angiotensin converting enzyme inhibitors (ACE): drugs, which exert their main action by inhibiting the transformation of the angiotensin I enzyme to the angiotensin II enzyme, thus obtaining a limitation of the vasoconstrictor effect of this enzyme at peripheral level.

Ankle-arm index: systolic pressure ratio in the ankle and the arm.

Antagonists of angiotensin II receptors (ARBs), exert their vasodilatory action by blocking the enzyme angiotensin II at its receptors AT1 levels.

Anti-21-hydroxylase antibodies: autoantibodies recognizing the 21-hydroxylase enzyme, which are associated with Addison's disease.

Anti-GAD antibodies (GAD =*glutamic acid decarboxylase*): autoantibodies associated with the autoimmune response of DM1, which recognize the glutamic acid decarboxylase enzyme.

Anti-IA2 antibodies: autoantibodies associated with the autoimmune response of DM1, which recognize the tyrosine phosphatase.

Anti-Insulin antibodies (AIA =*insulin autoantibodies*): autoantibodies associated with the autoimmune response of DM1, which recognise insulin.

Anti-Islet cell antibodies (ICA =*islet cell antibodies*): autoantibodies associated with the autoimmune response of DM1, detected by immunofluorescence that recognize antigens of pancreatic islets.

Anti-TPO antibodies: circulating autoantibodies that recognize the thyroid peroxidase enzyme, which is associated with the autoimmune thyroid disease.

Anti-transglutaminase antibodies (ATA): autoantibodies that recognise human transglutaminase, and are associated with celiac disease.

Anti-zinc transporter antibodies (ZnT8): autoantibodies associated with the autoimmune response of DM1, which recognizes a Zn transporter protein in the beta cells and plays a crucial role in its maturation and thus also in the secretion of insulin.

ASR Scale (Achenbach-scale): instrument to assess the skills and behavioural problems in children.

Biomicroscopy: Examination of living tissues under a microscope. In ophthalmology, eye examination with a microscope (anterior chamber, lens, vitreous), using special lighting focused with the slit lamp.

Case-control study: a study that identifies people with a disease (cases), i.e. lung cancer, and is compared with a group without the disease (control). The relationship between one or more factors (i.e. smoking) related to the disease is examined by comparing the frequency of exposure to this or other factors between the cases and the controls.

Clinical Prediction Rule: is a clinical tool that quantifies the individual contribution of various components of the clinical history, physical examination, and laboratory results and other variables on the diagnosis, prognosis or likely response to a treatment in a particular patient.

Cochrane Library: database on effectiveness created by the Cochrane Collaboration, composed among others by original systematic reviews of this organization.

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Cognitive behavioural therapy or cognitive therapy: a psychotherapeutic intervention, which highlights prominently cognitive restructuring, the promotion of a collaborative therapeutic alliance and associated behavioural and emotional methods using a structured framework. Its working hypothesis is that thought patterns, called cognitive distortions, have adverse effects on the emotions and behaviour and therefore its restructuring, through psycho-educational interventions and continuous practice, can improve the state of the patient.

Cohort study: consists of monitoring one or more cohorts of individuals who have different degrees of exposure to a risk factor, and in whom the onset of the disease or the condition being studied is measured.

Confidence interval is the range, which lies within the true magnitude of the effect (never known with absolute exactitude) with a predetermined degree of security or confidence. The most common phrase used is the "confidence interval at 95%" (or "confidence limits at 95%"). This means that within that range, the true value would be found in 95% of the cases.

Conventional insulin syringe: 1 ml syringe, graduated to be able to administer insulin in units.

Copper IUD: intrauterine device used as a non-hormonal contraceptive. The copper acts as a spermicide and prevents the union of sperm and egg.

Cost minimization analysis: Economic analysis in which the costs are expressed in monetary units and the health effects are identical.

Cost-utility analysis: Economic analysis in which the costs are expressed in monetary units and the benefits in QALY (years of quality-adjusted life). The result, expressed as a cost/QALY ratio, can be used to compare different interventions.

C-Peptide: peptide secreted in equimolar amounts with insulin, which is used as a marker for the role of the cells.

DTSQ *(Diabetes Treatment Satisfaction Questionnaire)*: questionnaire assessing the quality of life for people with diabetes

Embase: European Database (Dutch) created by Excerpta Médica containing clinical medicine and pharmacology.

Endomysial antibody: immunoglobulin A antibodies which act directly against the interfibrillar substance of the smooth muscle (endomysium).

FDA: Food and Drug Administration (USA).

Formal Education: that which is based on regulated or structured programs

Glucagon: contra-insular hormone with a hyperglycaemic effect.

Glucose real time reading systems: Data generated from an initial latency period and the first calibration. It includes alarm systems in case of hypoglycaemia and hyperglycaemia, and some models have predictive alarms. The "real time" information is used by the patient (previously trained) interactively. This information is downloaded by the patient himself; these devices are designed to be used by the patient.

Glucose retrospective reading systems (Holter): Glucose data are downloaded to the end of the record using all the calibration points for its adjustment; they are placed by physicians/nurses, are blind to the patient and the data is downloaded afterwards so that the appropriate changes can be decided on.

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Glycated haemoglobin (also glycosylated haemoglobin) reflects the percentage of glucose binding to haemoglobin. Higher blood glucose levels are associated with higher glycated haemoglobin levels. Taking into account the average life of the erythrocyte, this measurement reflects the elevation of blood glucose over a period of approximately 3 months.

Heterogeneity: See 'Homogeneity'.

HLA *(human leukocyte antigen region)*: group of localised genes in the major histocompatibility complex on chromosome 6p21.

Homogeneity: means 'similarity'. Some studies are considered homogeneous if the results do not vary among themselves more than what can be expected by chance. The opposite of homogeneity is heterogeneity.

Intensive therapy: elements that are part of intensive therapy in DM1:

1. Multiple doses of insulin.
2. Careful balance between food intake, physical activity and insulin doses.
3. Daily monitoring of blood glucose.
4. Self-adjustment plan in the treatment (diet, exercise, insulin).
5. Define optimum glucose levels for each patient.
6. Frequent visits to the monitoring team.
7. Patient and health care team education and motivation.
8. Psychological support.
9. Quarterly assessment of HbA_{1c} levels.

Ketonemia: presence of ketones in the blood.

Ketonuria: presence of urine ketones (acetone, beta-hydroxybutyric acid and acetoacetic acid).

LNG-IUD: levonorgestrel-releasing intrauterine device for birth control used by producing endometrial atrophy, also acting on the cervical mucus and the ovary, preventing fertilization and the progressive decrease of bleeding.

Medline: Predominantly clinical database produced by the US National Library of Medicine.

Meta-analysis: A statistical technique used to integrate the results of different studies (studies of diagnostic tests, clinical trials, cohort studies, etc.) in a single endpoint, giving more importance to the results obtained in larger studies.

MODY diabetes *(Maturity-onset diabetes of the young)* adult diabetes that appears early in life and which nowadays tends to be included in the group of monogenic diabetes.

NICE: Part of the NHS (National Health Service, UK). Its role is to provide physicians, patients and the general public with the best evidence available, primarily in the form of clinical guidelines.

Non-mydriatic camera: a camera that can take pictures of the retina and generally of the fundus of the eye without inducing mydriasis.

Odds Ratio (OR): Is a measure of the effectiveness of a treatment. If equal to 1, the effect of the treatment does not differ from that of the control effect. If the OR is greater (or smaller) than 1, the treatment effect is higher (or lower) than the control effect. It must be noted that the effect being measured may be adverse (e.g., death, disability) or desirable (e.g. quit smoking).

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Ophthalmoscope: An optical instrument with a special lighting system used to observe the position of the eye, particularly the retina and its components e. g. vessels, parenchyma and optic nerve.

Ophthalmoscopy or fundus of the eye check-up: is the process of exploration of the retina. It can be done by direct or indirect ophthalmoscopy or with different lenses such as the Goldaman lenses, Bayadi lens, Hurbi lens, among others.

Prefilled syringes or prefilled pens: insulin injection systems with a capacity of 300 IU, p en-shaped and which includes the possibility of fractionated dosing and scale variations of 1 or 2 IU.

Randomized clinical trial: a study design in which people are randomly assigned to two groups: one (the experimental group) receives the treatment that is being tested and the other (comparison or control group) receives the standard treatment (or sometimes placebo). The two groups are monitored to observe any difference in the results. This is how the efficacy of a treatment is assessed.

Refractory arterial hypertension: lack of adequate control of blood pressure despite using a treatment with three drugs at maximum doses.

Relative Risk (RR): The ratio between the event rate in the treatment group and the control group. Its value follows the same interpretation as the OR.

SIGN: Scottish multidisciplinary agency that develops clinical practice guidelines based on evidence and on methodological documents about their design.

Sliding scales or phased demand: Managing fast acting insulin before meals or every 4-6 hours depending on the blood glucose levels.

Specificity: the proportion (or percentage) of really healthy people who obtain a negative result in the test. That is, the proportion of true negatives.

Spontaneous Remission: period that may appear after the diagnosis of DM1 that leads to a reduction in the need for exogenous insulin at doses lower than 0.3 IU/kg/day with improved metabolic control in HbA_{1c} levels at 6% or less (36 mmol/mol).

Starch: food reserve polysaccharide predominant in plants, consisting of amylose and amylopectin.

Structured or regulated educational program: one that provides knowledge and skills through a planned and progressive program, which includes coherent objectives, is flexible in content, covers the individual clinical and psychological needs, and is adaptable to the cultural context.

Sucrose: (table sugar) disaccharide of glucose and fructose.

Survival Education: initial acquisition of the basic knowledge and skills by the person with diabetes that make him/her able to cope with the diseases, by applying the care and treatment effectively.

Systematic review (SR): A review, in which the evidence on an issue has been systematically identified, evaluated and summarized according to predetermined criteria. It can include the meta-analysis or not.

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Appendix 13. Abbreviations

21-OH:	21-hydroxylase
Ac. Anti-Tg:	thyroglobulin antibodies
Ac. Anti-TPO:	thyroid peroxidase antibodies
Anti-ZnT8:	zinc antibodies antiporter
ACA:	adrenocortical antibodies
ACE:	angiotensin converting enzyme inhibitors
ADA:	*American Diabetes Association*
AMI:	AMI
Anti-IA2:	anti tyrosine phosphatase antibodies
BMI:	body mass index
CD:	celiac disease
CGM:	Continuous Glucose Monitoring
CH:	carbohydrates
CIBERDEM:	Biomedical Research Centre in Diabetes and Associated Metabolic Disorders
CPG:	Clinical Practice Guidelines
CPR:	Clinical prediction rule
CRF:	Chronic renal failure
CSII:	Continuous subcutaneous insulin infusion
CV:	cardiovascular
DCCT:	Diabetes Control and Complication Trial
DESIGN:	erectile dysfunction
1.	Diabetes mellitus Type 1
2.	Diabetes mellitus Type 2
DM:	diabetes mellitus
DN:	diabetic neuropathy
DR:	Diabetic Retinopathy
DTSQ:	*Diabetes Treatment Satisfaction Questionnaire*
DVC:	Vacuum devices
EAG:	Estimated average glucose
EMA:	endomysial antibodies
EMEA:	European Medicines Agency
GADA:	glutamic acid decarboxylase antibodies
GCK:	glucokinase
GEG:	Group to create the Clinical Practice Guideline
GF:	glomerular filtration
GIK:	glucose, insulin and potassium infusion
HbA_{IC}:	Glycosylated haemoglobin
IAA:	insulin antibodies
ICA:	islet cell antibodies
ICI:	intracavernous injection

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ICU:	intensive care unit
IFCC:	International Federation of Clinical Chemistry and Laboratory Medicine
IgA:	Immunoglobulin A
IIC:	intracavernous injection
IIEF:	*International Index of Erectile Function*
IM:	intramuscular
ISPAD:	*International Society of Paediatric and Adolescent Diabetes*
IUDs:	intrauterine device
IV:	intravenous
JAS/JSCC:	Japanese Diabetes Society/Japanese Society for Clinical Chemistry
JDRF:	*Juvenile Diabetes Research Foundation*
LDL:	low-density lipoprotein
LMP:	lidocaine plaster
MA:	meta-analysis
MDI:	multiple doses of insulin
MODY:	*Maturity Onset Diabetes of the Young*
NEFA:	non-esterified fatty acids
NGSP:	National Glycohemoglobin Standardization Program
NICE:	*National Institute for Clinical Excellence* (UK)
NNH:	number of patients needed to be treated for one patient to suffer an adverse event.
NNT:	number of cases to try to get a unit of effectiveness
PCP:	preconception care program
PDE5:	phosphodiesterase
QALY:	years of quality-adjusted life
RCT:	randomized
SBP:	Systolic blood pressure
SC:	subcutaneous
SD:	standard deviation
SEP:	*Sexual Encounter Profile*
SFQ:	sexual function questionnaire
SR:	spontaneous remission
SR:	systematic review
SSRIs:	selective serotonin reuptake inhibitors
UAEN:	specialized care units nephrology
WBQ:	*Well-Being Questionnaire*
WMD:	weighted mean difference

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Appendix 14. Declaration of interest

They following people have declared no conflicts of interest:

David Cantero Gonzalez, Ignacio Conget Donlo, Lorea Cañibano Garcia, Ricardo V. Garcia-Mayor, John Adrian Girbés Borrás, Alberto Goday Arno, Itziar Güemes Careaga, Virginia Guillen Cañas, M. Iruretagoiena Luisa Sánchez, Paloma Jimenez Huertas, Pedro Mª García Latorre, Argumedo Marta Lopez, Eduardo Millán Ortuondo, Ana M.ª Pedrueza Ortiz, M. Dolores González Ramírez, Mercedes Rigual Rodriguez, Jose Ramon Santos Martinez Rueda, Joseba Soloeta Eraso, Jorge Taboada Gomez, Gemma Villanueva Hernandez.

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