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Italian Standards for Diabetes Mellitus

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FOREWORD

We are very pleased and proud to present this paper, which defines Italian Standards for Diabetes for the first time. It has been firmly promoted by Diabete Italia.

You may wonder why we need treatment standards.

We shall answer with the phrase of an anonymous Medieval merchant: "*We selected the most beautiful and precious goods, the strongest and most resistant horses, the best clothing, the provisions for the journey and, the safest weapons; we wished our wives, children and friends farewell… but we knew not where to go….*"

Italian Standards based on evidence provided by scientific literature are clinical goals that must be achieved; they are the landmarks we must focus on to ensure optimal therapeutic efficacy and, they are a concise "global" paper on diabetes care.

Italian Standards offer an opportunity to develop healthcare provided to diabetics in Italy by defining the essential conditions and goals of care pathways and, by ensuring clinical efficacy combined with a correct use of available resources.

Hence, they are an important professional tool for diabetologists, other specialists (i.e. cardiologists, nephrologists…) and general practitioners. They will also enable healthcare facilities to design, schedule and organise healthcare with steady focus on both the health-related needs of diabetics and the rational use of resources.

This important work issues from the professional commitment of a team of diabetologists coordinated by Graziella Bruno, Luca Monge, Alberto De Micheli and Domenico Fedele. It is the result of a happy intuition – the need to define Italian standards for diabetes care by first analysing literature and then integrating it with recommendations that have been deemed the best suited and most useful to our country's framework.

Hence, we thank Graziella, Luca, Alberto, Domenico and the entire team that worked on this project, on behalf of Diabete Italia. Considering the ongoing evolution of care pathways and therapies, we also hope that this initiative will continue and that this document will be the first of a series focused on promoting the growth and improvement of quality care provided to diabetic patients in Italy.

Riccardo Vigneri ***Umberto Valentini,***

Adolfo Arcangeli ***Paolo Cavallo Perin***

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INTRODUCTION

Diabetes mellitus is a complex chronic disease that requires:

• multiple ongoing interventions on blood glucose concentration and cardiovascular risk factors to prevent both acute and chronic complications;

• educational initiatives targeted at diabetic patients to provide the knowledge required to self-manage the disease;

• treatment for the disease's complications, when present.

The efficacy of such interventions in improving the disease's outcome is backed by extensive scientific evidence.

The *Italian Treatment Standards for Diabetes* proposed herein have been drafted by two Italian scientific diabetes societies (AMD and SID) to provide clinicians, patients, researchers and those involved in diabetes care with recommendations for the diagnosis and management of diabetes and its complications. They also propose treatment goals – substantiated by extensive scientific evidence – on which therapeutic decisions can be based and, treatment quality evaluation tools adapted to the Italian framework. They are the scientific reference model for diabetes care, both concerning goals and processes. The project proposes to share common treatment models and goals for the care of diabetic patients in our practical national framework with Italian diabetologists and all medical and non medical professionals involved in diabetes care. *Italian Treatment Standards for Diabetes* can be deemed as a scientific landmark for integrated management, disease management, professional accreditation and, hospitals' daily need to create effective and efficient diagnostic and care pathways.

The level of scientific tests behind every recommendation has been classified, as envisaged by the *National Plan for Guidelines* (www.pnlg.it) (Table 1). The document enlarges on "desirable" goals in the management of most diabetics; individual preferences, comorbidity and other factors related to the individual patient can, however, justify the various decisions. Moreover, the *Standards* are not designed to prevent either further diagnostic investigations or patient management by other specialists, when required. For detailed information, please refer both to the mentioned guidelines and to references listed in each chapter.

Table 1. Evidence Levels and Recommendation Strength

EVIDENCE LEVELS	
Evidence	**Types**
I	Evidence obtained from many controlled randomised clinical trials and/or from systematic reviews of randomised trials.
II	Evidence obtained from one randomised trial with an appropriate pattern.
III	Evidence obtained from non-randomised cohort studies with either concurrent or historical controls or their metanalysis.
IV	Evidence obtained from either retrospective case-control studies or their metanalysis.

V	Evidence obtained from case studies ("series of cases") without a control group.
VI	Evidence based on the opinions of either authoritative experts or expert committees, as specified in both the guidelines and consensus conference, or based on the opinions of team members that drafted these guidelines.
RECOMMENDATION STRENGTH	
Strength	
A	The performance of a special procedure or diagnostic investigation is highly recommended. This strength indicates a special recommendation backed by scientific evidence of good quality, though not necessarily type I or II.
B	It is based on the doubt that the special procedure or intervention in question must always be recommended, but it is deemed that its performance must be carefully considered.
C	There is a basic uncertainty either for or against the recommendation to perform the procedure or intervention.
D	The procedure's performance is not recommended.
E	There are strong recommendations against the procedure.

METHODOLOGY

There are many international guidelines for diabetes mellitus: specifically, *Standards of Medical Care* published by the American Diabetes Association (ADA) has long been a landmark for diabetologists due to its pragmatic features, systematic updates and recommendations furnished with evidence levels. However, not always can treatment standards, which suit other populations and social and healthcare situations, be applied to the Italian framework; moreover, there are certain divergent views in the international diabetes community and, a national stand concerning the clinical application of these points is required.

On the basis of indications provided by the International Diabetes Federation (The IDF does not recommend 'reinventing the wheel', but does strongly encourage the redesign of the wheel to suit local circumstances), derived guidelines have thus been drafted for obvious reasons related to the rational use of both human and economic resources. Furnished with levels of evidence and recommendations, they are based on the critical evaluation of the ADA's original 2006 paper, other international guidelines and, when necessary, the primary sources available in literature, adapting them and targeting them at the Italian framework. Moreover, the paper integrates previously existing Italian guidelines, data and notes on the specific Italian situation and aspects that are not developed in the ADA's paper. Process and outcome indicators have been added to the recommendations whenever possible – they have already been tested in the AMD data file – to provide assessment tools.

The Consensus Conference Method, which requires a jury to discuss and evaluate a proposal presented by a team of experts appointed by both AMD and SID, was chosen to reach the paper's final draft.

THE PROCESS

The process that led to the *Italian Standards for Diabetes* is briefly described below.

• The project was commissioned by AMD and SID's National Steering Committees with Diabete Italia's approval. They requested a technical document drafted by experts and discussed by a jury, which they could approve as an official document on the views of scientific societies.

• The Editorial Team, which numbered 20 diabetologists with a Coordinating Committee of four diabetologists, edited the draft of the text's specific topics. The Editorial Team resorted to the contribution of expert consultants in methodology, EBM and quality issues and, of a consultant paediatric diabetologist recommended by the Italian Society of Paediatric Endocrinology and Diabetology.

• A highly interdisciplinary jury numbering diabetologists and members of other healthcare professions dedicated to diabetes care and lay members was created to guarantee the paper's best applicative efficacy. It counted seven diabetologists appointed by the AMD, seven diabetologists appointed by the SID, one dietician, one neurologist, one nephrologist, one cardiologist, one paediatrician, two general practitioners, one expert in therapeutic education, one nurse, one podiatrist, one dietician, one lawyer, one expert in bioethics, one representative of the Ministry of Health, one epidemiologist, one expert in healthcare economics, one member of the Tribunal of Patients' Rights, one quality expert and, one expert in political-organisational issues.

• The Jury received the document's preliminary text and heard the presentations of single topics and some queries on the document's controversial aspects at the *Consensus* meeting held in Frascati on 8-9 November 2006. The meeting was open to both National Steering Committees and to Presidents of the AMD and the SID's regional branches. The Jury later met behind closed doors to analytically assess the document and, a final plenary session presented and motivated criticisms, remarks and proposals in view of the document's first review.

• On the basis of these conclusions, the Editorial Team edited a second version of the document. The critical contribution of experts and leaders of AMD and SID study groups was requested during this reviewing phase.

• The Jury's reappraisal of the paper's second version enabled the Coordinating Committee to draft the final paper, whose version presented herein was finally approved by the AMD and the SID's National Steering Committees.

The names of all participants are listed above.

The paper will be published in this hardcopy version and in a pocket edition, besides an electronic version for the Web and palmtop PCs.

Regional initiatives focused on circulating, sharing and systematically implementing *Italian Standards* and

inserted in the framework and goals of ministerial initiatives for the organisation of diabetes care and for integrated management with general medicine are scheduled to be held in 2007.
As with all guidelines, the document will be periodically updated by a Committee that is specially appointed for this purpose.

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I. CLASSIFICATION AND DIAGNOSIS

A. DIAGNOSTIC CRITERIA

R E C O M M E N D A T I O N S

> Diabetes is diagnosed if:

• Fasting Blood Glucose is ≥ 126 mg/dl (after at least an 8 hours fasting);

or

• Random Blood Glucose is ≥ 200 mg/dl (irrespective of the intake of food);

or

• Blood Glucose is ≥ 200 mg/dl 2 hours after a 75 g oral glucose load. (**VI, B**)

> Blood glucose testing for diagnostic and screening purposes must be performed on venous plasma and confirmed in two different tests, if abnormal; the use of glucometer is not recommended as testing modes are hard to standardise. (**VI, B**)

> The following tests are not required for diabetes diagnosis:

- HbA_{1c};
- basal insulinemia and during OGTT insulinemia;
- postprandial glucose and diurnal glycemic profile. (**VI, E**)

> Blood glucose alterations that are not diagnostic for diabetes must be classified as:

- Impaired Fasting Glucose (IFG) (Fasting Blood Glucose: 100-125 mg/dl);
- Impaired Glucose Tolerance (IGT) (blood glucose concentration two hours after an oral glucose load ≥ 140 and <200 mg/dl). (**VI, B**)

> In subjects with IFG and IGT all cardiovascular risk factors must be examined to plan an appropriate care pathway. (**VI, B**)

> In subjects with IFG and either abdominal obesity or metabolic syndrome it could be useful to perform an OGTT for better diagnostic and prognostic definition. (**VI, C**)

B. CLASSIFICATION

Diabetes type 1 *is* characterised by β-cell destruction on an autoimmune or idiopathic background, leading to absolute insulin deficiency.

Diabetes type 2 *is* characterised by an insulin secretion disorder, gradually worsening over time and overlapping with a condition of insulin resistance.

Other specific types of diabetes are due to abnormalities in β-cell function and insulin action due to genetic defects, drugs, chemical substances (drugs used to treat AIDS or after an organ transplant), diseases of the exocrine pancreas

Gestational diabetes is first diagnosed during pregnancy, with a potential return to normal glucose tolerance after delivery.

COMMENT

Currently applied diagnostic criteria were approved by the World Health Organisation (WHO) in 1999. On that occasion the *blood glucose threshold for the diagnosis of diabetes was lowered from 140 to 126 mg/dl*. The change was suggested on the basis of observational studies, showing that risk of diabetic retinopathy (the most specific diabetes-related complication) is already increased with blood glucose <140 mg/dl and nearing 126 mg/dl. Criteria must be applied irrespective of sex and age; hence, they apply both to children and the elderly. (1-4)

The American Diabetes Association (ADA) has introduced − along with the Impaired Glucose Tolerance (IGT) category already envisaged in the former classification − a new diagnostic category called Impaired Fasting Glucose (IFG) and characterised by Fasting Glucose between 110 and 125 mg/dl. The ADA has recently proposed to bring down the IFG diagnostic threshold from 110 to 100 mg/dl. (5)

Table 2. Metabolic Syndrome: International Definitions

	WHO (1998)	EGIR (1999)	NCEP (2001-2005)	IDF (2005)
Definition	IGT, IFG, type 2 diabetes or low insulin sensitivity and ≥2 of the following risk factors	Fasting blood glucose >75th percentile and ≥2 of the following risk factors	≥3 of the following risk factors	Abdominal circumference: >94 cm (men); >80 cm (women) and >2 of the following risk factors
Obesity	BMI >30 kg/m^2 and/or waist/hips ratio >0.90 cm (men), >0.85 cm (women)	Abdominal circumference >0.94 cm (men); >0.80 cm (women)	Abdominal circumference ≥102 cm (men); ≥88 cm (women)	
Lipids	Triglycerides ≥150 mg/dl and/or HDL <35 mg/dl (men); <39 mg/dl (women)	Triglycerides ≥180 mg/dl and/or HDL <39 mg/dl	Triglycerides ≥150 mg/dl, HDL <40 mg/dl (men); <50 mg/dl (women)	Triglycerides ≥150 mg/dl or HDL <40 mg/dl (men); <50 mg/dl (women) or antidyslipidemic treatment
Glucose	IGT, IFG or type 2 diabetes	IGT or IFG, excluding type 2 diabetes	≥100 mg/dl*	>100 mg/dl
Blood pressure	≥140/90 mmHg	≥140/90 mmHg and/or antihypertensive treatment	≥130/85 mmHg	≥130 SBP or >85 DBP mmHg and/or antihypertensive treatment
Other	Microalbuminuria			

* Modified.

Table 3. Clinical Characteristics of Type 1 and Type 2 Diabetes

	TYPE 1	TYPE 2
Prevalence	0.3%	3-5%
Symptoms	Always present Often acute	Often moderate or absent
Tendency to ketosis	Present	Absent
Weight	Generally normal	Generally high (either overweight or obese)
Age at onset	Generally <30 years	Generally >30 years
Onset of chronic complications	Years after the onset of diabetes	Often present on diagnosis
Plasma insulin	Reduced or absent	Normal or increased
Autoimmunity	Present	Absent
Treatment	Insulin from the onset	Diet, oral hypoglycaemic agents, insulin (less often)

The cost/efficacy ratio of this definition has not been assessed (6); however, the variation proposed is currently applied in clinical practice and has been approved by the IDF (International Diabetes Federation), though it still awaits the WHO's approval.

IFG and IGT are neither a disease nor do they present any clinical symptoms, but they are of medical relevance due to the high risk of diabetes and cardiovascular diseases (6). It is, hence, of great importance to seek other cardiovascular risk factors in subjects with IFG and IGT to speedily establish the appropriate care pathway. IFG and IGT can coexist in the same individual, but they are often found in an isolated form. It can be useful to perform an OGTT in subjects with IFG and abdominal obesity or metabolic syndrome to provide a better diagnostic and prognostic picture; indeed, in a considerable number of these subjects OGTT test confirms the diagnosis of diabetes. (7-9)

The ADA has proposed the term *pre-diabetes* to designate IFG and IGT conditions (5). However, a high percentage of subjects with IFG/IGT do not develop diabetes; moreover, the use of this term could have negative impact on both the individual and the healthcare system. Hence, in clinical practice IFG and IGT are preferably defined as conditions of "impaired glucose tolerance", rather than as pre-diabetes.

The term pre-diabetes is, instead, adopted in Italy in the paediatric framework to define children and adolescents with evidence of β-cell autoimmunity, genetic susceptibility to type 1 diabetes and impaired insulin secretion. As in adulthood, even at a paediatric age the presence of Fasting Blood Glucose ≥100 mg/dl enables to diagnose IFG. In this case, the investigation can be completed with immunological, genetic (high-risk HLA) and metabolic data (OGTT and IVGTT to evaluate the early phase of insulin response) and in long term follow-up to monitor blood glucose concentrations. The physiopathological premise of this detailed diagnostic investigation lies in evidence, found in Italian case studies too, of an increased risk of its evolution into type 1 diabetes mellitus when associated with β-cell autoimmunity (anti-insulin, anti-GAD, anti-IA2), (10-11). However, since no therapeutic approach that stops damage to insular β-cells is currently available, the implementation of this approach can cause anxiety; hence, there is some divergence of opinion on this issue. Moreover, it must be mentioned that many Italian areas lack laboratories equipped to perform HLA allele susceptibility typing and autoantibody dosage.

Type 1 and type 2 diabetes are the most common forms in clinical practice. In Italy, the prevalence of known diabetes was approx. 2.5% at the close of the '80s, while undiagnosed diabetes numbered approx. 30% of all cases of diabetes (12-13). A recent study conducted in Turin in 2003 highlighted that the prevalence of known diabetes is 4.9% (14). Even the study promoted by Health Search – the research institute formed by *Società Italiana di Medicina Generale* (SIMG) – and based on patients treated by 320 general practitioners distributed all over the country, reports a 5.4% prevalence of diabetes mellitus in 2003 (15). The incidence of type 2 diabetes mellitus was estimated in the Brunico study–one of the few population-based studies conducted in Europe (16); the rate/1,000 person-years was 7.6 in subjects aged 40-79 years; the incidence was, however, 11 times higher in subjects with IFG, 4 times higher in those with IGT, 3 times higher in overweight subjects and 10 times higher in obese ones; moreover, the incidence was approx. 2 times higher in hypertensive and dyslipidaemic patients. Studies conducted in Cremona and Brunico revealed that the prevalence of Impaired Glucose Tolerance is 6-8% in women and 9% in men (12,16)

It is estimated that type 1 diabetes comprises 3-6% of all cases of diabetes in Italy. The incidence is approx. 10-11/100,000 person-years, with rates that are however 3-4 times higher than the national average in Sardinia. The risk of type 1 diabetes is increasing throughout the national and international territory, though the causes of this phenomenon have yet to be defined (17-18). The diagnostic picture of the two types of diabetes – whose clinical features are reported in Table 3 − has important prognostic and therapeutic indications. Though the patient's case history and the onset of the disease often allow to define the type of diabetes, in some cases the definition of autoimmunity markers (GADA, ICA, IA-2) and insular β-cell secretion tests (dosage of plasma C-peptide at fasting and after stimulus) can provide additional information. In practice, approx. 5-10% of patients initially defined as type 2 diabetics suffer from a form of latent autoimmune diabetes that develops into insulin dependence. The condition is called Latent Autoimmune Diabetes in the Adult (LADA) or Non Insulin Requiring Autoimmune Diabetes (NIRAD). Generally, clinical criteria defines patients as type 2 diabetics, but β-insular function progressively deteriorates over a period of 2-6 years and, patients require insulin treatment. Epidemiological, genetic and physiopathological aspects of this condition have not been entirely explained and, some authors believe that LADA is, in practice, nothing but type 1 diabetes in the adult (19-21). In Italy the incidence of type 1 diabetes in the 30-49 year age group – defined by the presence of β-insular autoimmunity markers on diagnosis – was comparable to that in youth, thus confirming how far this condition is underestimated in normal clinical practice (22). A population study conducted in Lombardy reported that approx. 2% of patients were GADA positive (24). In a multicentre study involving approx. 900 diabetics aged >40 years cared for in diabetes care centres, 6.7% were GADA positive (24), while a population-based study conducted on young patients with normal body weight reported a 22% incidence of ICA and/or GADA positivity at diabetes diagnosis (25).

The main problem of LADA epidemiological studies is the lack of standardised diagnostic criteria. From a clinical perspective, the condition must be suspected if one or more of the following characteristics are present:

• age <50 years;

• BMI <25 kg/m^2;

• family history positive for type 1 diabetes or autoimmune diseases;
• case history positive for autoimmune diseases;
• inadequate glycaemic control with oral hypoglycaemic agents 6-12 months after diagnosis.

Age at onset >50 years and overweight must, however, not rule out the diagnosis of LADA in advance, when the other criteria are met (24). Useful diagnostic tests confirming clinical suspicion of LADA are:
• positivity of autoimmunity markers (GADA, ICA);
• impaired β-cell function (basal C-peptide and/or after the Glucagon Stimulation Test).

The Glucagon Stimulation Test (1 mg IV) must be performed while fasting. Blood Glucose >180 mg/dl is a contraindication to the test, as the resulting β-cell hyperstimulation would lead to an overestimation of the real insulin secretion. After a basal sample to measure plasma C-peptide and the administration of 1 mg of glucagon IV, a new sample must be taken after a 6-minute interval. Basal values <0.07 ng/ml or values after stimulus <0.20 ng/ml indicate serious insulin secretion deficiency and, hence, the need for insulin treatment. The test is useful to form the diagnostic and prognostic picture of cases, whose classification is uncertain, but it is not the only criteria on which the therapeutic decision is based. (27-28)
MODY (Maturity-Onset Diabetes of the Young) is a relatively rare monogenic form of diabetes (less than 1% of cases initially defined as type 2 diabetes), characterised by dominant autosomic transmission. Six different genetic traits have been described leading to different functional alteration of pancreatic cells. Clinical detection criteria for MODY are listed below:
• age of onset <25 years;
• good glycemic control maintained without insulin for over 2 years;
• dominant autosomic hereditability (at least three generations);
• no evidence of autoimmunity.

When there is a founded clinical suspicion of MODY, it is useful to contact reference laboratories for the genetic characterisation (29). The diagnosis of MODY is important to provide patient's prognosis.

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II. SCREENING FOR TYPE 2 DIABETES

RECOMMENDATIONS

> Screening programmes are recommended for people at high risk of diabetes (selective screening, Table 2) identified during a medical check up (opportunistic screening). (**VI, B**)

> Screening programmes based on Fasting Blood Glucose have a more favourable cost/efficacy ratio than those based on OGTT. (**VI, B**)

> An OGTT can be performed in high risk subjects to better define the individual risk of diabetes and cardiovascular diseases. (**VI, B**)

> In case of normal screening tests, high risk subjects should be re-examined after 2-3 years; moreover, they must be provided with useful instructions to both change their lifestyle and to reduce diabetes risk factors. (**VI, B**)

Table 4. Subjects with a high risk of diabetes

IFG, IGT or past gestational diabetes
Age <45 years, especially with BMI ≥25 kg/m^2 or abdominal obesity
Age <45 years, overweight (BMI ≥25 kg/m^2) and one or more of the following conditions: • first degree relative with type 2 diabetes; • members of a high risk ethnic group; • arterial hypertension (≥140/90 mmHg) and/or antihypertensive treatment; • low levels of HDL cholesterol (≤35 mg/dl) and/or high triglyceride concentration (≥250 mg/dl); • clinical evidence of cardiovascular diseases; • low level of physical activity; • polycystic ovarian syndrome or other insulin-resistant conditions like Acanthosis nigricans; • women who delivered a baby weighting >4 kg.
Children aged >10 years, with BMI >85th percentile and two of the following conditions: • first or second degree relative with type 2 diabetes; • mother with gestational diabetes; • signs of insulin-resistance or associated conditions (hypertension, dyslipidaemia, acanthosis nigricans, polycystic ovarian syndrome); • members of a high risk ethnic group.

COMMENT

Screening is an evaluation process targeted at asymptomatic subjects, while the diagnostic test is performed to confirm a clinical suspicion formulated during a medical examination of the patient. If the screening test is positive, further diagnostic tests must be performed to confirm the diagnosis. According to WHO a screening test is useful if the test is easy to perform, easy to interpret, acceptable to the person to whom it is proposed, ensures high diagnostic precision, is repeatable in time and has an acceptable cost/benefit ratio (1).

An extensive debate is internationally in progress on the usefulness and method of implementation of screening programmes for type 2 diabetes (2-11). The theme is up to date considering the temporal increase of the disease–both in developing areas and in industrialised ones like Italy–and its high social cost. Some believe that the most effective strategy in reducing diabetes-related costs should target the population, focusing on lifestyle-oriented information campaigns; indeed, even a very small reduction in blood glucose concentration applied to a vast number of non diabetics could induce remarkable benefits in absolute terms (reduced number of new cases of diabetes and cardiovascular events). Observational data support the finding that even a moderate reduction in blood glucose concentration plays a significant role when it is extended to the entire population. For instance, a study conducted in Israel on males aged 26-45 years with basal blood glucose <100 mg/dl showed that blood glucose 91-99 mg/dl and triglycerides ≥150 mg/dl, compared to blood glucose <86 mg/dl and triglycerides <150 mg/dl, produced an 8-fold increase in the risk of diabetes over a 12-year follow-up; a similar increase was reported for blood glucose 91-99 mg/dl and BMI ≥30 mg/k^2, compared to blood glucose <86 and BMI <25 kg/m^2 (12).

It is estimated that the clinical diagnosis of diabetes is generally preceded by an asymptomatic phase of about 7 years, during which hyperglycaemia has harmful effects on target tissues; hence, complications of the disease are already present when the clinical diagnosis is made. It must be mentioned that Fasting Blood Glucose, which is diagnostic for diabetes, has been arbitrarily defined on the basis of the risk of diabetic retinopathy; no threshold effect has, however, been defined concerning the risk of cardiovascular complications. This indicates the importance of maintaining low Fasting Blood Glucose concentrations for preventive purposes. According to the DECODE (Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe) study − that enrolled approx. 30,000 individuals from 20 different European countries − values of fasting blood glucose of 81-89 mg/dl and 90-99 mg/dl are associated with the lowest risk of all-cause and cardiovascular mortality, respectively (13-14). The DECODE study also revealed that subjects with normal Fasting Blood Glucose and asymptomatic diabetes defined only by abnormal plasma glucose values 2 hours after OGTT (31% of cases of asymptomatic diabetes) are different with respect to subjects who are, defined diabetics on the basis of Fasting Blood Glucose and normal blood glucose concentrations 2 hours after OGTT (40%); only 28% of cases of diabetes meet both criteria. The death rate of subjects with hyperglycaemia 2 hours after OGTT was high, irrespective of fasting blood glucose concentrations. Considering these points, recent EASD/ESC guidelines consider OGTT an important screening test for patients with risk of diabetes and, an essential one for those with cardiovascular diseases (15). Even ADA guidelines underline that the OGTT test is useful to better define individual risk (2).

Economic evaluations based on simulation systems have indicated that the cost/benefit ratio of mass screening for diabetes is unacceptable. In fact, a simulation based on the most favourable scenario establishes that the necessary number of people who must undergo screening (NNS) is 500 to prevent cardiovascular events with hypertensive treatment (undiagnosed diabetes rate =6%; onset time brought forward by 5 years; antihypertensive treatment =50%). If we assume a basal rate of 3% and bring forward the onset by 2.5 years, the NNS rises to 3,600. (5)

Table 5. Diabetes Risk Score

	POINTS		SCORE
1. Age	<45 years ..... 0 p. 45-54 years..... 2 p. 55-64 years..... 3 p. >64 years ..... 4 p.		
2. BMI (Body Mass Index) If you do not know your BMI, ask your doctor for help	<25 kg/m^2..... 0 p. 25-30 kg/m^2 ..... 1 p. >30 kg/m^2..... 3 p.		
3. Abdominal circumference	**Men / Women** <94 cm <80 cm..... 0 p. 94-102 cm 80-88 cm..... 3 p. >102 cm >88 cm..... 4 p.		
4. Do you do physical exercise during your leisure time or physically demanding work for at least 30 minutes almost every day?	YES..... 0 p. NO ..... 2 p.		
5. How frequently do you eat fruit and vegetables?	Every day..... 0 p. Not every day ..... 1 p.		
6. Have you ever used anti-hypertensive drugs?	NO ..... 0 p. YES..... 2 p.		
7. Has any doctor ever told you that your blood glucose (glycaemia) is too high (i.e. during a medical follow up examination or during either a disease or pregnancy? 8. Has any of your family members got diabetes?	NO ..... 0 p. YES. ..... 5 p. NO ..... 0 p. YES: grandparents, uncles or cousins ..... 3 p. YES: biological father or mother, brothers or issue..... 5 p.		
Total DIABETES RISK SCORE (add up the scores of all questions, 1-8)			
Your risk of developing diabetes over the next 10 years is:	Score <7 7-11 12-14 15-20 >20	Risk **Low:** 1 on 100 **Slightly high:** 1 on 25 **Moderate:** 1 on 6 **High:** 1 on 3 **Very high:** 1 on 2	

The NNS required to prevent mono-ocular blindness is even higher and data are scarce concerning other potential interventions to allow simulations. Considering the above mentioned points, mass screening for diabetes is currently not recommended. Similar evaluations applied to either opportunistic screening procedures or screening procedures targeted at high risk subjects, instead, reveal that the implementation of these strategies ensures more advantages than potential disadvantages. In fact, achieving optimal risk

factor levels reduces cardiovascular events, thus involving a considerable advantage for both the individual and society (3). However, literature offers no data concerning the optimal frequency of diabetes screening procedures.

Recent studies have defined scores to facilitate the detection of subjects at risk of diabetes. The advantage of tools based on these scores lies in their easy administration to the general population during normal outpatients' visits. Self-assessment questionnaires, for instance, encourage the patient to personally calculate the risk score and to report it to the attending physician if it is high. These scores number the Diabetes Risk Score, which was applied to the Finnish population (16). The IGLOO study conducted in Italy on 1,377 subjects aged 55-75 years confirmed that this tool can be applied to the Italian population presenting one or more cardiovascular risk factors (86% sensitivity, 93% negative predictive power). In this study, a Fasting Blood Glucose test in subjects with scores >9, and OGTT in those with 100-125 mg/dl Fasting Blood Glucose led to the detection of 83% of cases of diabetes and of 57% of cases of IGT (Fasting Blood Glucose tested in 64% of subjects and OGTT in 38%) (17) (Table 5).

The advantages of early detection and diagnosis of asymptomatic diabetics have yet to be proved. A Cochrane protocol was recently published to especially define the efficacy of screening for type 2 diabetes in reducing both morbidity and death rate; its secondary goal is to assess the effects of screening on adverse events, on the use of healthcare services, on the quality of life and on economic costs. (9)

Key factors in the current debate on diabetes screening can be summarised as follows:

Factors favouring diabetes screening:

• type 2 diabetes presents a long asymptomatic phase during which the disease can be diagnosed only if it is actively sought through a screening procedure;

• simple and cheap non invasive screening tests are available;

• the percentage of undiagnosed diabetes ranges from 30 to 50% of cases with type 2 diabetes and, the pre-clinical phase is not benign; indeed, patients often already have complications of the disease when symptoms that allow the diagnosis set in;

• it has been proved that optimal glycemic control from the early phases of diabetes and the correction of cardiovascular risk factors effectively reduce the incidence and progression of diabetes complications;

• acute and chronic complications of diabetes seriously affect quality of life and public health;

• screening for diabetes detects people, whose blood glucose alterations are not diagnostic for diabetes (IGT and IFG); interventions on their lifestyle can prevent/delay the full-blown disease's development.

Factors against diabetes screening:

• low prevalence of the disease;

• waste of time and energy to perform follow-up visits and additional tests required to confirm the diagnosis;

• possible adverse effects of treatments of the disease;

• increased costs caused by treating the disease in advance, compared to its natural evolution;

• lack of evidence concerning the higher efficacy of interventions implemented during the pre-clinical phase of the disease, compared to those prescribed after clinical diagnosis.

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III. SCREENING AND DIAGNOSIS OF GESTATIONAL DIABETES

R E C O M M E N D A T I O N S

> Risk of gestational diabetes must be assessed during the initial evaluation of a pregnant woman (Table 3): an OGTT must be performed at the 24th -28th week of gestation when there is an intermediate risk; if the risk is high, the test must be performed as early as possible. (**V, B**)

> The screening procedure suggested is the two-phase oral glucose load test (50 g Glucose Challenge Test and diagnostic test with 100 g of glucose. (**VI, B**)

> Glucose tolerance should be reassessed in all women with gestational diabetes six weeks after delivery with an OGTT. (**VI, B**)

Risk Profiles

Low risk. Screening is not required when all the following characteristics are present:

- age <25 years;
- normal pre-pregnancy weight;
- negative family history for diabetes mellitus;
- negative case history for impaired glucose tolerance;
- obstetric history with no unfavourable outcome;
- ethnic group with a low prevalence of gestational diabetes.

Medium risk. Women with intermediate characteristics between low and high risk: the Glucose Tolerance Test should be performed between the 24th and 28th week.

High risk. Screening must be performed as early as possible (and repeated between the 24th and 28th week of gestation, if the first test is normal), if one or more of the following characteristics is present:

- positive family history for diabetes in first degree relatives;
- previous diagnosis of impaired glucose tolerance;
- foetal macrosomia during past pregnancies;
- obesity (BMI >30 kg/m^2);
- pronounced glycosuria during the current pregnancy.

Glucose Load Testing Mode

- The oral glucose load test must be performed in the morning, while fasting.
- The woman must be seated and abstain from both eating and smoking during the test.
- The diet must be free and comprise at least 150 g of carbohydrates/day a few days before the test.
- The glucose dosage must be tested on plasma with enzymic methods, while the use of glucometer is not recommended.
- The glucose load test must not be performed during intercurrent diseases (flu, fever, etc.).

Screening Test Interpretation Criteria (50 g Glucose Challenge Test)

- Negative: plasma glucose values <140 mg/dl after 1 hour.
- Positive: plasma glucose ≥140 mg/dl after 1 hour
- Diagnostic for gestational diabetes: plasma glucose ≥198 mg/dl after 1 hour

A positive screening test must be followed by a diagnostic test with OGTT 100 g.

Interpretation Criteria for the Diagnostic Test

TIME	DIAGNOSTIC OGTT (100 g) PLASMA GLUCOSE mg/dl
0 min	≥95 mg/dl
1 hour	≥180 mg/dl
3 hour	≥140 mg/dl
2 hour	≥155 mg/d

COMMENT

Undiagnosed gestational diabetes involves considerable risks for the mother (hypertensive complications, increased incidence of caesarean delivery, etc.), the foetus and the newborn (increased incidence of macrosomia, hyperbilirubinaemia, hypocalcaemia, polycythemia, and hypoglycaemia) (2-4). The diagnosis of gestational diabetes is, hence, essential for the outcome of pregnancy and, it is also an important opportunity to prevent the onset of diabetes in the mother (5). Unfortunately, the procedures have yet to be standardised and clarified to date and, many issues are still unsolved.

Extension of the population to be investigated

Leading Italian and international scientific institutions have long declared that screening should be extended to all pregnant women, but an approach based on risk stratification has prevailed. The currently recommended stand − which surfaced at the 4th International Workshop-Conference on Gestational Diabetes Mellitus held in Chicago in 1997 − is a reasonable compromise, which envisages that only low risk pregnant women will be excluded from screening (1). The indication to perform large scale screening outside this category remains unchanged.

Diagnosis

Generally, the premise for a two-phase diagnostic track first envisages a simple fast and sensitive test that is not very specific; the need to resort to the diagnostic test, which is usually longer, costly and less tolerated, is thus reduced. However, the two-phase procedure requires more investigations and, if it is positive, delays the diagnosis and commencement of treatment.

Concerning the diagnostic test, the discussion has developed in these years along two directives: on the one hand, it envisages a diagnostic OGTT with 100 g of glucose − proposed by O'Sullivan in 1964 (6), and accepted by the National Diabetes Data Group (7) and by the International Workshop Conference on Gestational Diabetes Mellitus in 1980, 1985 and 1991 (8-10); on the other hand, it envisages a 75 g glucose OGTT proposed by the OMS in 1985 (11). The first stand, with a subsequent series of adjustments − the last of which was introduced by Carpenter and Coustan (12) − was extensively applied in the USA and in Italy, where it was adopted both by the *Italian Society of Diabetology* (SID) and by the *Società italiana di ginecologia e ostetricia* (Italian Society of Gynaecology and Obstetrics - SIGO). (13)

The indication of the WHO was in turn widely applied and basically accepted also by the European Association for the Study of Diabetes (EASD). (14)

The 4th Workshop held in Chicago in 1997 attempted to reach a synthesis (5); the stand that surfaced on that occasion and was later applied by the ADA is currently a landmark. The results of the international study (HAPO Study*, Hyperglycaemia and Adverse Pregnancy Outcome*) should provide a final indication on the recommended diagnostic strategy.

A 2-phase diagnostic track with the 50 g Glucose Challenge Test (GCT) is the most reliable screening methods (15). Its recommended performance period is between the 24th and 28th week of pregnancy, except in "high risk" subjects on whom the test must be performed as soon as possible.

The test is considered positive if blood glucose is ≥140 mg/dl after 60 minutes: this level has 79% sensitivity and 87% specificity in predicting gestational diabetes (15-16). A positive test must always be followed by a diagnostic test. Gestational diabetes can also be diagnosed on the basis of blood glucose concentrations by adopting the same diagnostic criteria implemented in the general population (plasma blood glucose≥126 mg/dl or random blood glucose >200 mg/dl confirmed in at least two tests) (17).

The diagnostic track recommended by the Diabetes and Pregnancy Study Group of the SID and based on the above summarised evidence is reported in the enclosed flow-chart. (Figure 1) (18)

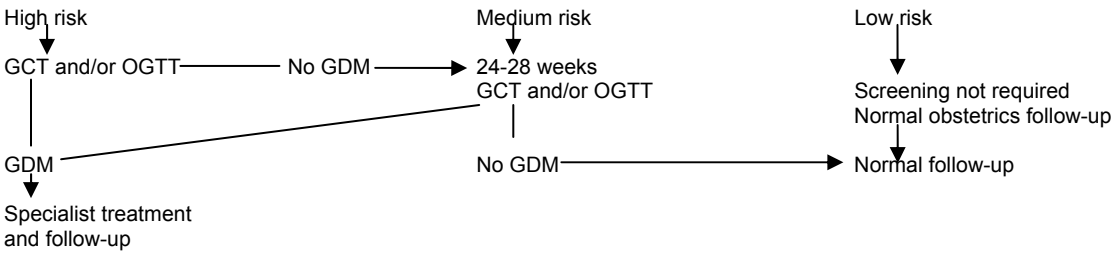

Figure 1. Diagnostic course for the screening and diagnosis of gestational diabetes
GDM: Gestational Diabetes Mellitus
GCT: Glucose Challenge Test (50 g)
OGTT: Oral Glucose Tolerance Test

Studies evaluating the prevalence of gestational diabetes in Italy are few and, especially, cannot be immediately compared due to methodological differences concerning both the screening methods employed and the recruited sample. Prevalence range from 2 to 12%. On the basis of studies published so far, we can estimate a prevalence of 7% of gestational diabetes, which is likely overestimated; indeed, in most studies screening was targeted at women with one or more risk factors for gestational diabetes, rather than at a non selected population (19).

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IV. PRIMARY PREVENTION OF TYPE 2 DIABETES

RECOMMENDATIONS

> Avoiding overweight and performing regular physical exercise (20-30 minutes a day or 150 minutes a week) is the most appropriate way of reducing the risk of type 2 diabetes mellitus in subjects with impaired glucose tolerance (IGT). (**I, A**)

> Subjects with IGT must be given counselling concerning weight loss and indications to increase physical exercise. (**I, A**)

> Subjects with IGT must be encouraged to change their diet habits: reduce the total intake of fat (<30% of the daily energy intake) and especially of saturated fatty acids (less than 10% of the daily calorie intake); increase the intake of vegetable fibre (at least 15 g/1,000 Kcal). (**I, A**)

> Pharmacological treatment though less effective, can be considered for obese subjects with IGT in whom the lifestyle interventions have either failed or cannot be applied. (**I, B**)

> When other strategies have proved ineffective, bariatric surgery can be considered a therapeutic option allowing preventing the onset of type 2 diabetes in subjects with severe obesity and IGT. (**I, C**)

COMMENT

In subjects with Impaired Glucose Tolerance (IGT) these recommendations are based on the results of more than one randomised clinical trial. Hence they belong to the Recommendation Strength A group, in line also with nutritional recommendations for diabetes prevention and treatment given by the EASD study group (1). It is reasonable to hypothesize that proposed interventions are also effective in other categories at risk of diabetes (i.e. subjects with IFG, obesity, family history of diabetes, etc.); however, no data are available on cost-benefit ratio of implementing prevention programmes for categories other than IGT. We must stress that recommendations are the outcome of a result analysis of clinical studies conducted in high risk subjects (down-stream strategies).

There is, instead, no evidence concerning the efficacy of large scale interventions (upstream strategies) targeted at the general population and, theoretically characterised by a possible greater impact in terms of prevention.

The investigational pattern of studies that have implemented midstream strategies − with interventions targeted either at defined population groups or at communities at risk − have limitations.

Lifestyle

Observational epidemiological studies *(Nurses' Health Study)* (2) and both uncontrolled and controlled intervention studies (3-6) have reached similar conclusions. Interventions designed to improve lifestyle and which envisage moderately intense aerobic physical exercise for at least 20-30 minutes a day or 150 minutes a week with a subsequent 5% weight loss, reduce the incidence of type 2 diabetes mellitus by

approx 60%. Hence, they are highly effective preventive and therapeutic tools in either stopping or slowing down the diabetes epidemic. Therapeutic educational programmes, which regularly gauge the level of physical exercise performed, can facilitate the steady implementation of a physical exercise programme. (7)

Concerning dietary habits, many epidemiological studies have attempted to evaluate relations between the quantity/quality of fatty acids in the diet and the risk of type 2 diabetes. Most evidence indicates that quality is more important than the total quantity of nutrients: specifically, saturated fatty acids increase the risk of type 2 diabetes, while their partial replacement with unsaturated fatty acids (poly- and monounsaturated fatty acids) reduces it (8). In the latter framework, fatty acids n-3 and/or the consumption of fish should be included, since most studies have provided evidence that fish has a protective effect against type 2 diabetes.

Concerning carbohydrates, most observational epidemiological studies suggest that a diet rich in fibre and food with a low Glycemic Index protects against the risk of type 2 diabetes. The two most recent studies on primary prevention against type 2 diabetes, DPS (Finnish Diabetes Prevention Study) (9) and DPP (Diabetes Prevention Program) (5) deem that, besides weight loss and increased physical exercise, a reduced intake of saturated fatty acids and an increase in vegetable fibres is the foundation of a multifactor intervention on lifestyle. It is most likely that the lower incidence of type 2 diabetes obtained in these studies also partly depends on diet changes (9). How far the results were obtained from the implementation of single interventions cannot, however, be defined. Recent DPS analyses show that, irrespective of physical exercise and initial blood glucose concentrations, subjects that followed a low fat diet with a high content of fibre showed better weight reduction and lower incidence of diabetes, compared to those who followed a diet rich in fat and poor in fibre.

Intervention with Hypoglycaemic Agents

The DPP (Diabetes Prevention Program) study enrolled 2,155 subjects with IGT who were examined yearly with an OGTT and six-monthly with Fasting Blood Glucose tests. At the end of a mean follow-up period of 2.8 years, the incidence of diabetes was 7.8% in patients treated with placebo and 4.8% in patients treated with metformin, with a 31% lower relative risk of developing the disease (5). Later, an Indian study too evaluated the use of metformin, obtaining qualitative results that resemble those of the DPP study (6). It is interesting to notice that in this study the combined administration of metformin and lifestyle changes was not more effective than the separate administration of the two interventions.

Concerning other insulin-sensitising drugs, three studies analysed the effect of glytazones in preventing type 2 diabetes: DPP, which also had a troglytazone arm, the TRIPOD study (Troglytazone in Diabetes Prevention) (10) conducted in women with previous gestational diabetes and, the DREAM study (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) (11), whose results have been recently reported.

Both DPP (arm with troglytazone) and TRIPOD were interrupted early after report of fatal cases of liver toxicity caused by troglytazone; TRIPOD continued in the open mode replacing troglytazone with pioglitazone (10). However, the perspective analysis of subjects treated before the study was ended suggests the high efficacy of the drug in preventing progression towards diabetes.

Lastly, the recent DREAM study evaluated the effect of rosiglitazone on incidence of diabetes over a three

years period. The DREAM study enrolled 5,269 subjects (aged >30 years) with no cardiovascular disease, and with Impaired Glucose Tolerance (IGT) or Impaired Fasting Glucose (IFG). Subjects were assigned to either the placebo group or the rosiglitazone group (4 mg/day for the first 4 months and then 8 mg/day). Compared to placebo, rosiglitazone significantly reduced the risk of developing diabetes by 60%. No reduction was, instead, highlighted either in the death rate or in the total number of cardiovascular events, while the risk of heart failure increased from 0.1% in the placebo group to 0.5% in the rosiglitazone group. The long term effects of discontinuing rosiglitazone are still not known. (11)

The STOP-NIDDM study (Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus) tested the feasibility of preventing the onset of type 2 diabetes with acarbose treatment over a 3.3 years study period. This trial randomised 1,429 subjects with IGT; 715 of them were treated with acarbose (100 mg 3 times a day) and 714 with placebo. The incidence of diabetes during the 39 months of observation was 32% in the acarbose group and 42% in the placebo group, with a 25% lower relative risk. Patients were re-evaluated after an approx. 3-month period of discontinuation of treatment (either drug or placebo) during which 15% of patients treated with acarbose developed diabetes, compared to 10.5% of control patients. These results suggested that a pharmacological intervention with acarbose in patients with IGT can delay progression towards diabetes mellitus. Effect, however, disappear when treatment is discontinued. We must also mention that a significant percentage of patients (approx. 25%) abandoned the study before its completion due to the side effects of acarbose on the gastrointestinal system. (12)

Pharmacological Intervention with Other Drugs

XENDOS (XENical in the prevention of Diabetes in Obese Subjects) is an important intervention study based on orlistat. It achieved an overall 37% reduction in the risk of diabetes, reaching 45% in subjects with IGT after 4 years of treatment. (13)

The positive effects of orlistat on glycaemia were later confirmed by the XXL study (Xenical ExtraLarge study) conducted on over 15,000 obese patients with and without type 2 diabetes. It revealed an overall 7.5% reduction in Fasting Blood Glucose, especially 5.1% in the non diabetic group and 15.0% in the diabetic group. (14)

The efficacy of treatment with statin in preventing the onset of type 2 diabetes in subjects at risk has yet to be proved. In the WOSCOPS study (West Of Scotland Coronary Prevention Study) (15), pravastatin reduced the incidence of type 2 diabetes by 30%, suggesting an important pleiotropic effect: it was hypothesized that the effect on glucose metabolism can be related to the significant reduction in circulating triglycerides (-12%), compared to controls. As alternative explanations, pravastatin could either reduce inflammatory cytokines (IL-6, TNF-α) that are directly involved in generating insulin-resistance or improve endothelial function, increase perfusion of muscle and adipose tissues and increase glucose uptake.

Other studies, however,–HPS with simvastatin (16), ASCOT-LLA with atorvastatin (17) and, LIPID with pravastatin–did not confirm the findings of the WOSCOPS study. (18)

The beneficial effect of chlofibrate on insulin sensitivity was already highlighted in the ‘80s. Studies have pointed out improved glucose tolerance in dyslipidaemic subjects with IGT, significantly reduced FFA levels and insulin resistance, reduced incidence of new cases of diabetes (from 54% to 42%) and slower progression of glucose intolerance.

There is, to date, no convincing evidence that some antihypertensive drug categories can be useful in preventing the onset of type 2 diabetes in subjects at risk. Compared to the non diabetic population, prevalence of hypertension is higher in patients with type 2 diabetes. Similarly, subjects with insulin resistance, metabolic syndrome or impaired glucose metabolism have a higher risk of developing both hypertension and cardiovascular diseases. The large-scale use of antihypertensive drugs in the diabetic population has long encouraged research on the possible influence of these drugs on glucose metabolism. Unlike reports on non-selective diuretics and beta-blockers, which have moderately worsened the glucose balance in very extensive population studies, active ingredients marketed in recent years have, instead, proved their null or slightly improving effect on metabolic control (calcium antagonists, ACE-inhibitors, AT-III inhibitors). Considering the over 200 studies published in literature on the possible protective effect of antihypertensive drugs on the incidence of diabetes, only 14 met inclusion criteria for metanalysis (i.e. randomised controlled trials), though none of them considered the incidence of diabetes as primary endpoint (19). A general conclusion is that the impact of antihypertensive treatment on the risk of diabetes in subjects who are prone to it is rather neutral, with a tendency to worsen when diuretics and beta-blockers are used and, neutral or moderately favourable when ACE-inhibitors, AT-II receptor blockers or calcium antagonists are prescribed. The recent DREAM study, whose primary endpoint was the onset of diabetes, also evaluated the effect of ramipril, noticing that the incidence of diabetes did not differ in the ramipril and placebo arms. However, ramipril produced a higher regression to normal blood glucose concentrations, which was the secondary endpoint of the study. At the end of the study, average Fasting Blood Glucose concentrations did not differ in the ramipril and placebo groups, but blood glucose tested 120 minutes after an OGTT was lower in the group treated with the ACE inhibitor. A secondary endpoint, which considered myocardial infarction, stroke, congestive heart failure, cardiovascular death, recent onset of angina and revascularisation, did not differ between ramipril and the placebo. However, the fact that enrolled subjects did not present a cardiovascular disease must be mentioned. Hence, ramipril cannot reduce either the incidence of diabetes or the death rate in subjects with IFG or IGT (11).

The Effects of Bariatric Surgery

Some studies have compared the efficacy of bariatric surgery and low calorie diets in preventing the onset of type 2 diabetes in severely obese subjects with IGT (BMI >40) (19-21). A Swedish study (21) on a large number of subjects, observed a reduced incidence of type 2 diabetes over a 2-10 years study period, which was associated with a BMI reduction in the group treated with gastric surgery, compared to the group that was administered traditional treatment. In the four-year follow-up Italian study (22) conducted on fewer subjects, the application of a gastric bandage reduced the BMI from 46 to 38 kg/m^2 and caused no new cases of diabetes, while the group on traditional treatment recorded a 17% incidence of diabetes.

Lifestyle or Drug Treatment?

The DPP study compared the two therapeutic intervention arms, revealing that lifestyle changes are almost twice as effective in preventing diabetes as the administration of metformin (58% and 31% relative reduction, respectively). Intervention studies centred on diabetes preventing lifestyle and drugs in patients with poor glucose tolerance were recently evaluated by a systematic review and metanalysis, which proved

that lifestyle interventions were at least as effective as pharmacological ones (23). Recommended goals include moderate weight loss (5-10% of body weight) and moderate physical exercise (30 minutes a day). Since this therapeutic approach has proved effective in either preventing or delaying the onset of diabetes, besides ensuring other beneficial effects too, doctors and nurses must encourage all overweight or sedentary subjects to adopt these lifestyle changes. Current evidence does not allow to recommend pharmacological treatment as either an alternative or routine addition to diabetes preventing lifestyle changes; hence, doctors, healthcare professionals, the NHS at large and all those who are socially involved must encourage a healthier lifestyle model, while waiting for research to find more effective and efficient primary prevention programmes for type 2 diabetes. (24)

Pharmacoeconomic Notes

A recent systematic review of literature (25) evaluated the economic aspects of type 2 diabetes mellitus prevention. The analysis revealed that, despite the few available studies, strategies designed to intensively prevent type 2 diabetes through lifestyle changes (i.e. DPP and DPS studies) are highly *cost-effective*, which means that implementation costs cut down healthcare expenses in the long term. However, the DPP programme would be very costly, if applied to the general population. Hence, cheaper methods should be identified to achieve the same degree of weight loss observed in the DPP study. Even the use of drugs that reduce both body weight and hyperglycaemia is effective, compared to traditional interventions. The implementation of prevention strategies must also take into account the importance of creating an integrated network between general and specialist care-giving levels to optimise both screening and prevention of type 2 diabetes.

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V. DIABETES CARE

R E C O M M E N D A T I O N S

> Diabetics must be cared for by both the general practitioner and the diabetes team, which, coordinated by a diabetologist, comprises doctors, nurses, dieticians, podiatrists and mental health professionals skilled in implementing an integrated disease management approach designed to treat a chronic disease. (**VI, B**)

> Diabetics must actively participate in the care plan, which is drafted like a personalised therapeutic alliance between the patient, his/her family and diabetes team members. The patient's age, education and employment, physical exercise practised, diet habits, social and economic conditions, personality, cultural factors and the presence of other diseases or complications of diabetes will be focused. (**VI, B**)

> The care plan must comprise an education program centred on self-management of diabetes to provide − by applying diversified strategies and techniques to suit the patient's age, social status and cultural level − appropriate knowledge on problem-solving methods applied to disease management. The care plan implementation requires every aspect to be clarified and agreed on between the patient and the diabetes team, besides the definition of achievable goals. (**VI, B**)

A. INITIAL EVALUATION

R E C O M M E N D A T I O N S

> A diabetic patient's first evaluation envisages a complete medical check up that also seeks chronic complications typical of the disease and laboratory tests to define the patient's general clinical conditions. If diabetes had already been diagnosed, the treatment established and the degree of glycemic control obtained must be reassessed and the disease management plan must be redrafted, if necessary, once key points have been defined. (**VI, B**)

Overall evaluation parameters are illustrated in Table 6.

Table 6. The Diabetic Patient Initial Evaluation

FAMILY HISTORY • Family history of diabetes, arterial hypertension, dyslipidaemia, cardiovascular diseases and other endocrine diseases.
PHYSIOLOGICAL HISTORY • Physical exercise practised. • Lifestyle and cultural, psychosocial, educational and economic factors that can influence diabetes management. • Use of tobacco, alcohol and narcotics. • Evaluate diet habits, nutritional condition, weight history, growth and development in children and adolescents. • Contraception, sexual history and reproduction.
PAST MEDICAL HISTORY • History and treatment of other diseases, including endocrine ones and eating disorders. • Cardiovascular risk factors: smoking, hypertension, obesity and dyslipidaemia. • Past HbA_{1c} values. • Frequency, severity and causes of acute complications (i.e. ketoacidosis and hypoglycaemia). • Evaluate in detail past therapeutic programmes, prescribed diet, extent of education on the self management of diabetes and approach to the disease.
RECENT MEDICAL HISTORY • Symptoms related to the diagnosis of diabetes. • Symptoms related to diseases that can cause secondary diabetes (i.e. haemochromatosis, pancreatic diseases). • Current diabetes treatment: drugs, diet plan, self-monitoring. • Past and current infections of skin, feet, teeth or the genitourinary system. . Symptoms of diabetes complications in eyes, kidneys, peripheral nerves, genitourinary system (including sexual diseases), bladder and gastrointestinal function (including celiac disease in type 1 diabetes), heart, cardiovascular system and feet, and current treatment • Use of drugs that can interfere with blood glucose concentrations • Evaluate mood disorders.

PHYSICAL EXAMINATION

- Height and weight (related to normal age parameters in children and adolescents).
- Abdominal circumference.
- Sexual maturation (if in peripuberty).
- Lying and standing blood pressure (compare with normal age parameters in children and adolescents).
- Ophthalmological examination of *fundus oculi*.
- Examination of the oral cavity.
- Palpation of the thyroid.
- Heart and lung semiotics.
- Abdominal palpation (to highlight hepatomegaly).
- Palpation and auscultation to evaluate pulses and detect any vascular murmurs.
- Evaluate hands.
- Examine feet.
- Examine the skin (especially insulin injection sites).
- Neurological examination.

LABORATORY TESTS

- HbA_{1c}.
- Fasting lipid profile, comprising total cholesterol, HDL cholesterol, triglycerides and LDL cholesterol.
- Liver function test and further investigations for suspected liver steatosis.
- Test microalbuminuria in all type 2 diabetics and in type 1 diabetics with disease duration >5 years.
- Serum creatinine and estimated glomerular filtration.
- On diagnosis of type 1 diabetics: screen for autoimmune thyroiditis and celiac disease: TSH, FT4, anti-thyroid antibodies, EMA or anti-transglutaminase* and IgA.
- Urine tests to evaluate ketonuria, proteinuria and urinary sediment.

DIAGNOSTIC INVESTIGATIONS AND SPECIALIST CONSULTATIONS

- ECG in the adult, if clinically required.
- Ophthalmological examination, if required.
- Family planning for women of childbearing age.
- Nutritional Medical Treatment, if required.
- Specialist consultation on educational therapy, if it is not provided by either the doctor or other diabetes team members.
- Specialist consultation on behavioural therapy, if required.
- Specialist consultation for feet, if required.
- Other specialist consultations and services, if required.

* If normal, yearly check TSH, antithyroid antibodies, EMA or antitransglutaminase in paediatric patients. If EMA or antitransglutaminase are positive on 2 occasions, perform an intestinal biopsy to confirm the diagnosis of celiac disease with a histological examination.

B. GLYCEMIC CONTROL

1. Evaluating Glycemic Control

a. Glycated Haemoglobin (HbA_{1c})

R E C O M M E N D A T I O N S

> Evaluation of glycemic control achieved by a diabetic envisages periodical HbA_{1c} testing. (**VI, B**)

> HbA_{1c} dosage must be tested at least twice a year in all diabetics, even when glycemic control is stable within the therapeutic goal. (**VI, B**)

> HbA_{1c} dosage must be tested every three months in patients, whose hypoglycaemic treatment has been changed or whose therapeutic goal has either not been reached or is not stable in time. (**VI, B**)

COMMENT

HbA_{1c} testing enables to estimate the Mean Blood Glucose concentration over the past 2-3 months to evaluate the efficacy of current treatment. The dosage should be regularly tested in all diabetic patients, especially to document the degree of glycemic compensation on the initial evaluation and, then, as part of the treatment.

Since HbA_{1c} mirrors Mean Blood Glucose over the past 2-3 months, 3-monthly testing is required to decide whether metabolic control has been achieved and maintained within the goal. Regular HbA_{1c} testing enables to speedily detect values outside the therapeutic goal. The individual patient's HbA_{1c} dosage testing frequency should depend on the clinical condition, the type of treatment implemented and, the attending physician's opinion.

Glycemic control can be better assessed by combining the results of self monitored blood glucose and HbA_{1c}; the latter should, in fact, not only be used to evaluate glycemic control over the past 2-3 months, but also to check the accuracy of the reflectometer used, the patient's diary and the self-monitoring plan's adequacy. Table 7 reports the correspondence between HbA_{1c} and mean basal glycaemia levels obtained by the DCCT study. (1)

If, however, the HbA_{1c} result does not correspond to the patient's clinical condition and to self-monitored blood glucose values, conditions that change erythrocyte turnover (i.e. haemolysis, haemorrhages) and haemoglobin variants must be taken into account. (2)

However the attending physician must know the limits of HbA_{1c} dosage; for instance, conditions that alter erythrocyte turnover (i.e. haemolysis and haemorrhages), and haemoglobin variants that can cause high HbA_{1c} levels, which do not correspond to the patient's clinical condition. (13)

Table 7. Correlation between HbA_{1c} Levels and Mean Plasma Glucose in Multiple Tests Performed in a 2-3-month period in the DCCT study's framework

HbA_{1c} (%)	MEAN PLASMA GLUCOSE (mg/dl)
6	135 mg/dl
7	170 mg/dl
8	205 mg/dl
9	240 mg/dl
10	275 mg/dl
11	310 mg/dl
12	345 mg/dl

b. Self-monitoring of Blood Glucose (SMBG)

R E C O M M E N D A T I O N S

> Blood glucose self-monitoring with the diabetes team check is an essential factor in the self management of diabetes both to achieve the therapeutic goals and to reduce the risk of acute hypoglycaemia. (**VI, B**)

> Daily self-monitoring (at least 3-4 checks/day) is essential for type 1 diabetics under intensive insulin therapy. (**II, A**)

> Blood glucose self-monitoring–by varying frequency and testing modes–is useful for type 2 diabetics under insulin therapy. (**III, B**)

> Discontinuous blood glucose self-monitoring is potentially useful for type 2 diabetics on either oral or diet therapy, but no clear evidence is available concerning its efficacy on glycemic control. (**VI, C**)

> Self-monitoring of post-prandial blood glucose can be useful to both obtain good glycemic control and to achieve the target post- prandial blood glucose concentration. (**VI, B**)

> Self-monitoring frequency must be adjusted to intercurrent events and increased in clinical conditions, such as an intercurrent disease, unnoticed episodes of hypoglycaemia, hypoglycaemia at night and changes in hypoglycaemic treatment. (**VI, B**)

> The patient must be taught to self-monitor blood glucose; moreover, glucometer accuracy must be periodically checked and treatment must be adjusted to suit measured values, even resorting to a commonly agreed algorithm. (**VI, B**)

> Patient training to self-monitor blood glucose must be added to an educational programme that is both conducted and controlled in the middle and long term by nursing personnel experienced in the field of diabetes. (**VI, B**)

COMMENT

Leading clinical trials on the role played by glycemic control in the development of complications in type 1 diabetes made use of blood glucose self-monitoring in the therapeutic strategy (3). The role of self-monitoring is, instead, controversial in type 2 diabetes; many metanalysis have, in fact, shown inadequate evidence (4-7), while a metanalysis conducted by the Cochrane Collaboration in 2005 detected the positive effect of self-monitoring on HbA_{1c} (8). Similar conclusions were reached by another metanalysis conducted in 2005, which proved that blood glucose self-monitoring in type 2 diabetics who are not treated with insulin leads to a moderate improvement in glycemic control only if it is part of an educational programme focused on disease management (9). Data published by the Italian study QuED (*Qualità della cura ed Esito in Diabetologia* - Care Quality and Outcome in Diabetology) suggests that blood glucose self-monitoring in patients who are not insulin treated does not improve glycemic control, while it can be a source of stress (10). Concerning the effect of self-monitoring on clinical endpoints (diabetes related morbidity and mortality), the only evidence available is provided by the non randomised retrospective ROSSO study, which associated self- monitoring with reduced morbidity even in a non insulin treated patient group (12).

In 2003 the AMD and the SID issued recommendations for diabetics whose glycemic compensation was stable within the therapeutic goal. These recommendations were diversified by the hypoglycaemic treatment administered (11) (Table 8), but regional laws and local circular letters on their implementation in therapeutic plans often do not comply with these indications; hence, the geographically heterogeneous features of medical prescriptions. The survey on the consumption of reactive strips in European countries – published along with AMD-SID Guidelines – reveals that the Italian per capita consumption is under 25-29%, compared to the European average (11). The survey conducted in the framework of the QUADRI study (*Qualità dell'Assistenza alle persone Diabetiche nelle Regioni Italiane* - Quality of Care for Diabetics in Italian Regions) revealed that only 62% of patients under insulin therapy daily checked their blood glucose in 2004, while 53% reported performing repeated daily checks.

Anyhow, the key function of self-monitoring in good blood glucose control requires the implementation of periodical reliability checks. To ensure effective self-monitoring procedures, patients must be instructed how to make use of data obtained to adjust diet, physical exercise and drug therapy. Healthcare professionals should periodically evaluate the patient's skill in using self-monitoring as a treatment management tool. (7,11)

Table 8. Recommendations on the Use and Frequency of Self-Monitoring

The following patient classes are defined by treatment: 1) intensive insulin therapy; 2) traditional or combined insulin therapy; 3) oral hypoglycaemic therapy with secretagogues; 4) diet therapy and/or therapy with insulin-sensitizing drugs.

Recommendations for the above-listed classes
Class 1 a) 4 checks/ day are the rule in routine conditions. b) Unlimited number of checks in case of poor glycemic control or intercurrent diseases and only for limited periods till the event is resolved.
Class 2 a) The number of daily checks must equal the number of injections ± 20% as a routine. b) Unlimited number of checks in case of poor glycemic control or intercurrent diseases and only for limited periods till the event is resolved.
Class 3 a) The number of checks must equal the weekly profile on 4 routine points. b) Up to 2 checks/day when there is a high risk of hypoglycaemia or its potentially serious consequences (coronary heart disease, cerebral vascular disease, and proliferating retinopathy). c) Unlimited number of checks in case of poor glycemic control or intercurrent diseases and only for limited periods till the event is resolved.
Class 4 The efficacy of blood glucose self-monitoring has yet to be proved in this class of patients. We find an exception in gestational diabetes, which requires blood glucose self-monitoring at home to decide when to start insulin therapy. The diabetologist must establish testing frequency to suit individual clinical conditions. Glucometers must be deemed essential in implementing self-monitoring at home. Lancers – one per envisaged check – and lancing devices must equally be deemed essential.
Recommendations for checks Check the monitoring technique at regular intervals. Check result accuracy. Check the patient's skill to use the results.

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2. Glycemic Goals

R E C O M M E N D A T I O N S

> Diabetes treatment must be speedily adjusted in every patient to obtain near normal blood glucose concentrations and stable HbA_{1c} values under 7% (Table 5). These values will enable prevention of both the incidence and progression of micro- and macrovascular complications. (**I, A**)

> Lower glycemic control goals (HbA_{1c} <6.5%) can be considered for individual patients. (**III, B**)

> Slightly higher glycemic control can be considered in both small children and patients with acute episodes of hypoglycaemia, reduced life expectancy or comorbid conditions. (**VI, B**)

> Algorithms for insulin therapy are recommended for Intensive Care patients as they facilitate the achievement of glycemic goals. (**II, B**)

Table 9. **Glycemic Goals in Type 1 and 2 Diabetic Adults**

HbA_{1c} <7.0%* (<6.5% in individual patients)
Fasting and pre-prandial blood glucose 90-130 mg/dl°
Post-prandial blood glucose† <180 mg/dl°

* Referring to 4.0-6.0% in the non diabetic population with the method adopted by the DCCT study.
† Post-prandial blood glucose must be tested 2 hours after the meal's start.
° Fasting blood glucose <110mg/dl and post-prandial blood glucose <145 mg/dl must be pursued in type 2 diabetes (IDF 2005).

COMMENT

Blood glucose control is essential in the management of diabetes mellitus. Randomised controlled clinical trials like DCCT and UKPDS have proved that improved glycemic control (mean HbA_{1c} =7%, around 1% above the normal range) is associated with a reduced incidence of microangiopathic (retinopathy, nephropathy and neuropathy) and cardiovascular complications (1-6). The EDIC study (an observational study of patients enrolled in the DCCT study) also proved that the protective effects of intensive treatment on the risk of cardiovascular diseases lasts in type 1 diabetics even 11 years after the trial's conclusion (8). Concerning type 2 diabetes, UKPDS has highlighted a borderline reduction in the cardiovascular risk of intensive care patients compared to traditional treatment patients (RR 0.81, IC 95% 0.71-1.00, p=0.052). This most likely mirrors the multifactor pathogenesis of cardiovascular diseases (3). The STENO-2 study, in fact, proved that along with good glycemic compensation, it would be appropriate to introduce effective control of dyslipidaemia and hypertension, besides treatment with aspirin and ACE-inhibitors in diabetics with microalbuminuria (9,10).

Epidemiological studies have highlighted no threshold values for HbA_{1c}; hence, lower glycemic goals (HbA1c <6%) can be pursued in individual patients. However, there is no data available to detect diabetics with a high risk of acute hypoglycaemic episodes, whose frequency is increased by intensive insulin treatment. Frequent acute hypoglycaemic episodes are an indication to change treatment and raising glycemic goals. The absolute risk and advantages of HbA_{1c} <6% are currently being evaluated by the study on type 2 diabetes [ACCORD (Action to Control Cardiovascular Risk in Diabetes)]. Higher treatment goals would better suit diabetics with reduced life expectancy and those with comorbidity. European guidelines recommend HbA_{1c} values between 7.5% and 8.5% for type 2 diabetes in the elderly and frail patients who are not self sufficient, have multisystem diseases, are living in nursing homes or suffering of dementia. The optimal level of glycemic compensation is also not defined for children aged less than 13 years. Some epidemiological studies associated high blood glucose after an oral load (2-h OGTT) with an increased cardiovascular risk, irrespective of basal glycaemia (11). Post-prandial blood glucose >140 mg/dl is unusual in non diabetic subjects, though large evening meals can be followed by blood glucose concentrations up to180 mg/dl. New drugs that mainly control post-prandial blood glucose, while reducing HbA_{1c}, are currently available; hence, diabetics with optimal values of pre-prandial blood glucose, but not of HbA_{1c}, can, most likely, obtain a further reduction in HbA_{1c} with treatment targeted at post-prandial blood glucose (1-2 hours after the meal's start) <180 mg/dl or less. It must however be stressed that the effect of this approach on micro and macrovascular complications has yet to be defined (12). Even the increased variability of fasting blood glucose in the long term increases general mortality and, especially, cardiovascular mortality in type 2 diabetics, as documented by the Verona Study (13,14).

Achieving glycemic goals depends on both the patient and the doctor's targets as highlighted by the QuEd study (15). The study − conducted on a sample of 342 doctors distributed throughout the Italian regions – revealed a specific link between the level of HbA_{1c} deemed as therapeutic goal and the level reached by patients. This data stresses the relevance of the doctor's awareness on achieving near normal blood glucose concentrations to obtain proper primary and secondary prevention of micro and macroangiopathic complications.

In Italy, AMD file data showed that 25.5% of type 1 diabetics and 43.1% of type 2 diabetics has HbA_{1c} <7%, while 20.3% of type 1 diabetics and 13% of type 2 diabetics has HbA_{1c} >9% (16). The Casale Monferrato Study, however, proved that mean compensation has decidedly improved in time: while only 36.8% of diabetics had HbA_{1c} <7% in 1991, in 2000 the proportion had risen to 54.6%. (17)

The QUADRI study – an epidemiological study coordinated by the National Health Institute in almost all Italian regions in 2004 – gave information about patients' perception of care quality (interview with 3,116 patients aged 18-64 years randomly enrolled) (18). Concerning glycemic control, the study highlighted that HbA_{1c} had been tested over the past 4 months only in 65% of diabetics. Moreover, 68% of diabetics reported that they had been instructed on how to manage a possible hypoglycaemic crisis and 56% of patients treated with insulin declared that they performed self-monitoring at home.

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C. MEDICAL NUTRITION THERAPY

RECOMMENDATIONS

General Recommendations

> To achieve therapeutic goals, people with diabetes or impaired glucose tolerance must be administered personalised medical nutrition therapy by a dietician, preferably a diabetes team member trained in the diabetes field. (**III, B**)

> Nutrition consultation must consider people with Impaired Glucose Tolerance or diabetes mellitus' personal requirements and intention to change. (**VI, B**)

> Vegetables, beans, fruit and cereal typical of the Mediterranean diet must be added to the diet of people with type 1 and 2 diabetes mellitus. The intake of fibre rich food with a low Glycemic Index must be encouraged especially when a diet is rich in carbohydrates. (**I, A**)

> There is no evidence to recommend the use of "diet" foods for diabetics. (**VI, D**)

Overweight and Obesity

Weight loss is recommended in all overweight (BMI 25.0-29.9 kg/m^2) or obese (≥30.0 kg/m^2) adults. (**I, A**)

> The main approach to weight loss is a change in lifestyle, which involves reducing calorie intake and increasing physical exercise. A moderate reduction in calorie intake (300-500 kcal/day) and a moderate increase in energy consumption (200-300 kcal/day) ensure slow but progressive weight loss (0.45-0.90 kg/ week). (**I, A**)

> Moderate physical exercise must be recommended to suit the patient's inclination and capacity when the program starts. This exercise must then gradually increase in duration and frequency to 30-45 minutes a day of moderate aerobic exercise for 3-5 days a week (goal: 150 min/week). Higher levels of physical exercise – at least one hour a day of moderate activity (walking) or 30 minutes a day of more vigorous exercise (jogging) – can be required to obtain effective long term weight loss. (**VI, B**)

Carbohydrates

> The daily intake of carbohydrates with the diet must provide 45-60% of total daily calories. (**VI, C**)

> Considering these limits, the patient's metabolic features will suggest the most appropriate intake for type 1 and 2 diabetics. (**I, A**)

> Diets with a low carbohydrate content (specifically reduced below 130 g/day) are not recommended for diabetics. (**III, B**)

> Both the quantity and quality of carbohydrates in food can influence the glycemic response. Controlling total carbohydrate intake with either an exchange diet or the carbohydrate count is a key strategy to obtain glycemic control in patients under insulin therapy with a daily multidose pattern (basal-bolus). (**I, A**)

> Assessing the quantity, quality and distribution of the daily intake of carbohydrates can facilitate achieving optimal glycemic control. All patients treated with hypoglycaemic drugs, especially with insulin therapy, require the time of intake and drug dosage to be evaluated and adapted to the quantity and nature of carbohydrates taken. (**III, B**)

Sucrose

> As with the population at large, in diabetics too the total intake of sucrose should not exceed 10% of the total energy daily introduced with food. A more restrictive attitude can be useful for people who need to lose weight. (**I, A**)

Glycemic Index

> The Glycemic Index can be a useful indicator in the choice of food rich in carbohydrates to be added to the diet of diabetics. (**III, B**)

Fibre

> People with type 1 and 2 diabetes must be encouraged to introduce food with high fibre content. (**I, A**)

> The ideal fibre intake with the diet should be more than 40 g/day (or 20 g/1,000 kcal/day); most of it should be soluble. (**I, A**)

> Daily consumption of 5 portions of either vegetables or fruit and a weekly intake of 4 portions of beans can meet minimum fibre requirements. (**III, B**)

Proteins

> Individuals with any degree of chronic renal failure must limit protein intake to the recommended dose (0.6-0.8 g/kg) to reduce the risk of nephropathy developing any further. (**I, A**)

> In patients with no history of nephropathy, the protein intake should provide 10-20% of the total energy daily supplied by food. (**VI, B**)

Fat

> Fat intake must not contribute over 30% of the total energy daily supplied by food. (**III, B**)

> The daily intake of saturated fat must be less than 10% of total calories. A lesser amount (<7%) can be useful if LDL cholesterol is >100 mg/dl. (**I, A**)

> Oils rich in monounsaturated fatty acids (MUFA) are an important source of fat. Depending on the patient's preferences, they can provide 10-20% of the total energy daily introduced with food. (**III, B**)

> The intake of trans fatty acids must be minimised (<1%). (**VI, B**)

> Polyunsaturated fatty acids (PUFA) must not contribute over 10% of the total energy daily supplied by food. (**III, B**)

> Cholesterol introduced with the diet must not exceed 300 mg/day. It can be further reduced if LDL cholesterol is >100 mg/dl. (**I, A**)

> In overweight patients, a fat intake below 30% of the total energy daily introduced can facilitate weight loss. (**IV, C**)

Alcohol

> A moderate intake of alcohol (up to 10 g/day in women and 20 g/day in men) is acceptable, if the patient wishes to take alcoholic drinks. (**III, B**)

> Patients treated with insulin may take alcohol only with meals comprising food containing carbohydrates to prevent the risk of dangerous prolonged episodes of hypoglycaemia. (**VI, B**)

Sweeteners

> Calorie-free sweeteners (i.e. saccharin, aspartame, acesulfame-K, sucralose) are safe when taken in moderate daily doses. (**I, A**)

Diet Supplements

> Habitual intake of supplements, such as antioxidants (i.e. vitamin E, C and β-carotene) is not recommended when there is no evidence of their long term efficacy and safety. (**I, D**)

> The intake of food that is naturally rich in antioxidants, microelements and other vitamins must be encouraged. Hence diabetics must be encouraged to daily eating fruit and vegetables. (**III, B**)

Salt

> Like the population at large, diabetics must be recommended to take less than 6 g/day of salt. (**I, A**)

Specific Nutritional Interventions in Type 1 Diabetics

> Patients treated with either short acting insulin analogues or insulin pumps must adjust the pre-prandial insulin bolus to suit carbohydrates contained in meals. (**I, A**)

> Patients treated with fixed doses of insulin must maintain carbohydrate intake at meals constant both concerning quantity and time. (**III, B**)

COMMENT

Medical Nutrition Therapy is an essential aspect in diabetes management and in education to self management. Besides its role in diabetes prevention and control, both the EASD and the ADA acknowledge that nutrition is an essential factor in a basically healthy lifestyle.

Guidelines and recommendations are a lot. Reviews of scientific evidence and detailed information on this topic can be found in the document published by the EASD's Diabetes and Nutrition Study Group in 2004 (1), in the ADA's *Position Statement* published in September 2006 (2) and, in the ADA's *Technical Review* published in 2002 (3). These documents are, however, not homogeneous concerning the degree of evidence proposed for certain recommendations.

The ADA and the EASD have different views concerning recommendations for carbohydrates. The EASD focuses on the origin and characteristics of carbohydrates introduced, numbering slow absorption, rich fibre content and low glycemic index. On the other hand, the ADA puts the glycemic index's role in the right

perspective by highlighting the relevance of the quantity of carbohydrates taken and assigning evidence level A (ADA classification), typical of key strategies in obtaining glycemic control, to the recommendation on controlling the total carbohydrate intake with exchange diets or the carbohydrate count (1). The EASD, instead, assigns evidence level C (EASD classification) to adjusting the dosage and administration time of hypoglycaemic agents to suit the diet's carbohydrate intake. (2)

The ADA proposes a more moderate attitude towards the intake of sucrose. In fact, it stresses that, since sucrose does not cause a higher increase in blood glucose than an isocaloric quantity of starch, there is no reason to reduce the intake of sucrose in diabetics. Hence the suggestion that a diabetic who wishes to take sucrose can either use it to replace other food containing carbohydrates envisaged by the diet or increases the dose of the pre-prandial insulin bolus (Evidence Level A). The latest *Position Statement* integrates these indications, inviting more attention on avoiding the intake of an excessive calorie amount. (1)

As stressed in the European recommendations letter of presentation (4), "national scientific societies and healthcare professionals must turn these recommendations into appropriate guidelines for the various nations and population groups." Hence the decision to mainly present recommendations given in the paper drafted by the EASD's Diabetes and Nutrition Study Group (2). They will be easier to apply in our framework and daily clinical practice. The Italian stand concerning recommendations on Medical Nutrition Therapy for diabetes mellitus is declared in the consensus paper drafted by the Diabetes and Nutrition Group formed by the *Associazione Italiana di Dietetica e Nutrizione Clinica* (Italian Association of Dietetics and Clinical Nutrition - ADI) and by the *Associazione Medici Diabetologi* (AMD). This paper refers to recommendations given by the EASD's Diabetes and Nutrition Study Group in 1999, adapting them to the Italian framework. (5)

The GISED presented data on nutrition therapy in the Italian diabetes framework at the 2005 National AMD Congress held in Genoa; the study highlighted the lack of dieticians in diabetes teams (i.e. 0.3 dieticians/1,000 patients) (6). This information confirms data processed by the AMD Study Group on Healthcare Models: it highlighted that dieticians − either full time or part time − were only present in 58% of Italian diabetes departments in 2003. This percentage dropped to 49% in smaller diabetes clinics and, to 22% in territorial ones. (7)

Lastly, AMD data file provides information on the diabetic population body mass index in a representative sample of 123,863 Italian diabetics in 86 diabetes clinics. The mean BMI of type 2 diabetics was 29.2+/-5.0 kg/m^2, while over 37% of type 2 diabetics had BMI >30 kg/m^2. (8)

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D. PHARMACOLOGICAL TREATMENT

1. Type 1 Diabetes

R E C O M M E N D A T I O N S

> Keep close control of blood glucose to reduce the risk of chronic complications. (**I, A**)

> The first choice treatment pattern is the basal-bolus. (**IV, B**)

> The prescription of self management algorithms for insulin therapy can facilitate the achievement of glycemic goals. (**II, B**)

> When HbA_{1c} values are higher than the goal, appropriate treatment variations should be speedily implemented to rapidly reach and maintain good glycemic control in time. (**VI, B)**

> Take into account the patient's possible poor adhesion to the prescribed therapy. (**I, A**)

> Treatment with insulin pumps should be prescribed to patients, whose educational evaluation and basal-bolus insulin therapy pattern (with rapid and slow acting analogues) have failed to achieve good metabolic control and, if there are frequent and/or asymptomatic hypoglycaemic episodes. (**I, B**)

COMMENT

Basic Evidence

There is some essential clinical evidence every doctor should follow in his prescriptive approach; specifically, in type 1 diabetes the close control of glycaemia reduces the risk of onset and/ or the progression of diabetic retinopathy and nephropathy (1,2,3) and the cardiovascular risk has been reduced even after the period of close monitoring is discontinued (4); however, this involves an increase in the risk of hypoglycaemic episodes; in fact, the DCCT study's group under intensive treatment reported thrice the number of acute hypoglycaemic episodes. (3)

Since the DCCT study, it has been widely acknowledged that multi- injection therapy is the best therapeutic approach (1,3) to reduce the risk of both micro- (4) and macrovascular complications (5), even 8 years after the study's interruption, but with a higher risk of hypoglycaemia (1). The first choice treatment is the basal-bolus, which can be administered with human insulin, analogues and pump devices. It is hard to establish which insulin type can obtain the best glycemic control, while involving a lower risk of hypoglycaemia;

despite a number of papers focused on proving that rapid-acting analogues ensure a more flexible administration, a recent metanalysis (6) did not detect basic differences in metabolic control,
compared to regular human insulin. A metanalysis (which however combines type 1 and 2 diabetes) has proved with considerable evidence that insulin glargine considerably reduces the risk of hypoglycaemia, compared to NPH insulin (7). Insulin detemir has been recently introduced as basal insulin (whose duration of action is less than 24 hours) (8); early studies on this insulin type seem to detect a reduced risk of hypoglycaemia at night, compared with NPH insulin. (9,10)
Though these analogues are more expensive than NPH insulin, a moderate improvement in glycemic control (11) and, especially, the cost/ benefit ratio (including also fewer episodes of hypoglycaemia with a subsequent improvement in the quality of life) give evidence to support their use. (12)
The controlled DAFNE study reveals that an educational course, which combines intensive insulin treatment with a free diet and self management algorithms for insulin therapy improves the quality of life and glycemic control without increasing the number of either acute hypoglycaemic episodes or the cardiovascular risk. (13)
CSII therapy (Continuous Subcutaneous Insulin Infusion) can be a valid alternative in type 1 diabetics who fail to maintain good metabolic control for various reasons (14-16). The main advantages in using the microinfusion device, compared to multi-injection treatment based on NPH insulin, are better glycemic control assessed as lower glycated haemoglobin and glycemic variability, fewer hypoglycaemic episodes and patients' perception of a better quality of life (15). A recent survey conducted in Italy found that the pump device is used by 2,702 patients (97% type 1 diabetics); this number does not reach 5% of the national type 1 diabetic population, which records a 1.8-fold growth in 39 months, compared to the previous survey. (17)
An insulin type that can be administered by inhalation (18) and which is also effective in type 1 diabetes has been recently introduced (19). However, the British National Institute for Health and Clinical Excellence recommended its use only in rare cases and for 6 months at most. (20)

2. Type 2 Diabetes

R E C O M M E N D A T I O N S

> Continue close monitoring of blood glucose to reduce the risk of chronic complications. (**I, A**)

>When HbA_{1c} concentrations are higher than the glycemic goal, appropriate treatment variations must be speedily implemented to rapidly reach and maintain good blood glucose control in time. (**VI, B**)

> The first choice drug is metformin when there is an overweight condition (BMI >25 kg/m^2). (**I, B**)

> Secretagogues, metformin, glytazones and insulin are equally effective in reducing glycated haemoglobin. (**I, A**)

> It is essential to combine two or more oral hypoglycaemic drugs in patients who lack good control with monotherapy. (**I, A**)

> It is essential to start either mono- or multi-injection insulin therapy when blood glucose control is inadequate even with multitherapy. (**I, A**)

> Take into account possible poor adhesion to the prescribed treatment. (**I, A**)

COMMENT

Basic Evidence

There is some basic clinical evidence listed herein that every doctor should take into account in his prescriptive approach.

Close glycemic control reduces the risk of the onset and/or progression of diabetic retinopathy (21,22) and nephropathy (21,22) in type 2 diabetics too (23). In the UKPDS study the endpoints related to diabetic microangiopathy (including retinopathy and nephropathy) were reduced by 37% for every 1% HbA_{1c} reduction without a minimum threshold (24). The lack of a threshold suggests that any HbA_{1c} reduction ensures a lower risk of microvascular complications. Evidence concerning macrovascular complications is, unfortunately, less strong; however, every percentage point reduction of HbA_{1c} involved a 14% drop in the risk of myocardial infarction, 12% in stroke, 16% in heart failure and 21% in diabetes-related deaths (24).

Close glycemic control involves an increased risk of hypoglycaemia. In the UKPDS study, the intensively treated group reported hypoglycaemic episodes in 1-2% of cases (21).

Close glycemic control involved an increase in body weight, which was more evident with insulin therapy than with oral therapy (21). In the UKPDS study, patients assigned to intensive treatment reported a higher weight increase in 10 years (3.1 kg); this was further enhanced in those treated with insulin (4.0 kg) but did not occur with metformin. (25,26,27)

Only too often adhesion to treatment is poor (more frequently with metformin) and, generally, drugs taken once a day improve the adhesion to treatment. (28,29,30,31)

Multitherapy is often an inevitable choice after some years. In the UKPDS study, half the patients required a second drug to control glycaemia after three years and 75% of patients achieving 7% HbA_{1c} were treated with multitherapy after 9 years (32,33).

There is no evidence that one drug or treatment must be preferred to others, with the only exclusion of metformin in overweight diabetics (34); hence, evidence related to individual drugs and even to drug categories will be reported individually.

Biguanides

Metformin is the first choice drug for both overweight and obese diabetics (BMI > 25.0 kg/m²) (32-34). In fact, in the UKPDS study metformin ensured the same glycemic control with a lower risk of complications, fewer hypoglycaemic episodes and no weight increase.

This evidence was anticipated and confirmed by extensive metanalysis (25-27). Metformin efficacy is also maintained in combination with secretagogues (35,36); it is dose-dependent and achieves maximum

efficacy with 2 g/day (37), a dose currently marketed sulfonylurea- metformin combinations cannot reach. Metformin is equally effective even when there is no overweight condition; in these patients it can, anyhow, be the first choice alternative to other drugs (secretagogues) (25,26).

When treatment starts, about 10% of patients complain of diarrhoea and other gastrointestinal disorders (25,26), but the percentage is lower when treatment starts with a low dosage for 4-6 weeks. Episodes of acute lactic acidosis have been reported with an estimated incidence of 3 cases in 100,000 patient-years (38), which contraindicates the drug's administration to patients with either chronic renal failure or at risk of acute renal failure (i.e. surgery, iodated contrast medium). However, the increased lactic acid concentration in metformin treated patients does not significantly differ from patients who are taking other treatments (39). The mechanism behind metformin hypoglycaemic action is still not clear (40). Considering its confirmed efficacy as monotherapy, the low risk profile concerning side effects and the very low cost metformin remains the first choice drug for type 2 diabetes. (41)

Phenformin is another biguanide with hypoglycaemic properties. It is equivalent to metformin, but has a much higher risk of lethal lactic acidosis (42); hence, its withdrawal from many countries' Pharmacopoeia. In Italy it is still available as combination treatment, though its use is not recommended.

Acarbose

Acarbose is an effective alternative oral treatment for type 2 diabetes, though it produces a lower reduction in glycated haemoglobin (0.6-0.7%) compared to other oral hypoglycaemic drugs (43). As metformin, and unlike other hypoglycaemic treatment, it has no negative effects on body weight. It can cause gastrointestinal side effects (i.e. diarrhoea, flatulence) that often interfere with the patient adhesion to treatment. It effectively prevents diabetes in patients at risk (44) and, most likely, also reduces cardiovascular risk (45). But such evidence has been criticised by some experts. (46)

Thiazolidinediones (glytazones)

Thiazolidinediones, commonly known as glytazones, are PPAR-gamma receptor agonists; PPAR-gamma is a nuclear receptor that is located in many tissues, especially in adipocytes. Rosiglitazone and pioglitazone are currently available. A moderate number of randomised controlled studies (47-54) have extensively proved that their efficacy resembles other oral treatment, both as monotherapy and in combination with metformin or secretagogues. However, maximum efficacy is achieved over a longer period (4-6 weeks) and, in Italy, the high cost has led to their prescription as monotherapy only after intolerance has been proved towards other monotherapies (55,56). The EMEA recently removed the contraindication against the combination of glytazones and insulin. The risk of developing heart failure, probably subsequent to water retention (57), contraindicates its use in patients at risk of this complication. (58)

To date there is no evidence that glytazones reduce the macrovascular complications of diabetes, but many clinical studies have revealed that they reduce many cardiovascular risk factors in diabetics (59). So far only one study on pioglitazone (PROactive) (60) has proved that it reduces the incidence of certain clinical cardiovascular events (the study's secondary endpoint) in secondary prevention, while increasing the number of even lethal heart failures. The multicentre study ADOPT (A *Diabetes Outcome Progression Trial*) (61) evaluated the efficacy of rosiglitazone, glibenclamide and metformin as first choice monotherapy in

patients recently diagnosed with type 2 diabetes. The study's primary endpoint was the monotherapy failure period, considering as failure confirmed fasting blood glucose > 180 mg/dl. After 5 years, when only 20% of the original cohort still participated in the study, the cumulative incidence of therapeutic failure was 15% in the group treated with rosiglitazone, 21% in the one treated with metformin and 34% in the one treated with glibenclamide. The reduced risk of monotherapy failure in patients treated with rosiglitazone was 32%, compared to those treated with metformin and 63% compared to those treated with glibenclamide. Results for HbA_{1c}, however, showed a less significant reduction in HbA_{1c} values after a 4-year follow-up: rosiglitazone, in fact, differed concerning HbA_{1c} values, compared to metformin (0.13%) and glibenclamide (0.42%). Moreover, at the end of the follow-up period, the percentage of patients still under treatment with the drug assigned at the time of randomisation maintaining HbA_{1c} <7% was 40% in the group treated with rosiglitazone, 36% in the one treated with metformin and, 26% in the glibenclamide one. These differences are statistically significant, but their clinical impact is likely limited (62). Other factors, such as the patient's age, risk of hypoglycaemic episodes, adverse events and the cost of treatment are relevant in the choice of the initial diabetes treatment drug. Moreover, recent observations report the increase d risk of atypical osteoporotic fractures (hands and feet) in women treated with glytazones. The cause of this increased risk has yet to be found. (63)

The *New England Journal of Medicine* recently published the results of a metanalysis of 42 trials with rosiglitazone (27,000 subjects, divided into two treatment arms) that reported, with only a 24-month follow-up, OR=1.43 (95% CI 1.03-1.98) of myocardial infarction and OR=1.64 (0.98-2.74) of cardiovascular mortality (64). Despite the limits of an analysis based on aggregated data – instead of individual data, provided by studies focused on evaluating glycemic compensation and of the limited number of events (myocardial infarction: n=86 *vs.* n=72; cardiovascular mortality: n=39 *vs.* n=22) and of the lack of standardised diagnostic criteria for these events, the study provides an important reflection regarding the indications for the use of a drug, whose effect on glycemic compensation is known (surrogate event) but whose effects on cardiovascular events have yet to be defined (65). The subsequent publication of an interim analysis of the RECORD study (66) (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) produced no conclusive results.

The EMEA and the AIFA's official notes mention that the drug has long been monitored for possible adverse effects on the cardiovascular system; hence, the need for prescribers' compliance with limitations for use established in the EU for some hearth diseases.

Some studies reviewed by the metanalysis had enrolled patients on whom such limitations were not applied. Patients were, hence, invited not to discontinue treatment and to discuss the issue with their attending doctor during a follow up visit.

Rimonabant

Rimonabant is the first drug listed in a new therapeutic category called "CB1 antagonists", which are designed to inhibit appetite- regulating endocannabinoid system receptors with various peripheral actions too, especially on adipocytes (67); the drug is not marketed in Italy at the time this paper is published. The four reference studies, Rio-Lipids (68), Rio-North America (69), Rio-Europe (70) and Rio-Diabetes (71) agree on results concerning weight loss, variations in abdominal circumference, HDL cholesterol,

triglycerides and the prevalence of the metabolic syndrome. In type 2 diabetics enrolled in the RIO-Diabetes study (71) and already under treatment with metformin or sulfonylureas, the study has proved that the drug is effective on glycated haemoglobin levels, waist circumference, body weight and other cardiometabolic risk factors (i.e. dyslipidaemia and blood pressure). However, there are no comparative data between rimonabant and other drugs, neither hypoglycaemic agents nor obesity treatment drugs; moreover, the metanalysis of four studies (72) reveals an evident presence of side effects, especially involving psychiatric disorders. The drug real role in diabetes care has yet to be defined.

Secretagogues

Only recently marketed drugs are backed by published randomised controlled studies that prove their efficacy. Comparative drug-related metanalysis are also very few. We can, however, say that all drugs can reduce HbA_{1c} by about 1-1.5% (21,73) and, subsequently, the risk of both microvascular and cardiovascular complications (24). There are various comparative studies on glimepiride and glibenclamide (also called gliburide), which, however, agree on the drugs' equivalent efficacy (74). Other secretagogues (i.e. repaglinide and nateglinide – the latter not marketed in Italy) with faster drug dynamics that simulate the normal early stages of insulin secretion have also been marketed in recent years (75,76). Repaglinide efficacy resembles sulfonylureas (77) with an enhanced effect on post-prandial hyperglycaemia and a lower risk of hypoglycaemic episodes (78). This would suggest its choice for patients with mainly post- prandial hyperglycaemia, but there are no studies in this regard. Repaglinide efficacy is also maintained when it is combined with glytazones (79). All secretagogues (sulfonylureas and glinides) stimulate insulin secretion by binding a specific receptor that is located in beta-cells (*Sulfonylurea Receptor 1*) in isoforms that can also be found on both smooth arterial muscles and cardiac muscle (80). The various secretagogues' specificity for the cardiac receptor varies [highest in glibenclamide; lowest in gliclazide (81)]; only one retrospective study (82), however, detected an increased mortality in patients treated with glibenclamide.

Incretins

The term incretin refers to a peptide hormone substance produced in the gastroenteric system; it directly stimulates insulin secretion and enhances the secretagogue effect of glucose (83). No drug belonging to this group is marketed in Italy at the time this paper is published. GIP is produced in the small intestine proximal region (K cells), while GLP1 is produced in the distal one (L cells); both have their own receptor and are rapidly degraded by the enzyme dipeptidil-peptidase 4. Experimental evidence reveals that incretins can stimulate the glucose- induced biosynthesis and secretion of insulin (thus reducing the risk of hypoglycaemia) and they inhibit the secretion of glucagon, gastric empting and acid secretion. It is worth noting that hormones could reduce food intake and, especially, have a trophic effect on the beta-cell mass. (84,85)

Two incretin mimetic therapeutic approaches are currently being developed: GLP-1 analogues (exenatide and liraglutide, which can currently only be administered subcutaneously) and DDP-4 inhibitors (sitagliptin and vildagliptin, which inhibit the incretin-degrading enzyme) (86).

Exenatide is a peptide with 39 amino acids, an exendin-4 derivate extracted from the saliva of a large lizard that lives in Arizona, the *Gila Monster*. Some clinical trials have proved its efficacy when administered in

addition to metformin (87) or sulfonylureas (88) and to the combination of the two drugs (89). It is as effective as glargine (90) and rapid acting pre-mixed insulin analogs (91) in reducing glycated haemoglobin; it produces a significant reduction in body weight but also increases gastrointestinal side effects.
Liraglutide is a GLP1 analogue. A fatty acid molecule bound to it allows its binding with albumin at the site of injection to ensure slow release (half life: 11-15 hours) (92). It also effectively reduces glycaemia (93). These analogues, instead, only produce a moderate increase in the risk of iatrogenic hypoglycaemia (87-89,91) probably less evident than the risk of insulin induced hypoglycaemia (90).
Vildagliptin and sitagliptin provide another ways of increasing GLP1 concentrations, specifically, inhibiting the enzyme DPP-4 action. These drugs administered to type 2 diabetics are associated with a significant improvement in glycemic control in monotherapy (94,95), in addition to metformin (96,97) or pioglitazone (98), but there are currently no comparative studies with other drug categories to prove their real efficacy. Compared to GLP-1 analogues, gliptins have the doubtless advantage of oral administration, but they lack the body weight reducing effect (86). Gliptins also offer the advantage of a lower risk of iatrogenic hypoglycaemia, which was practically the same as in the placebo group in many studies. (96-98)

Insulin

Insulin therapy is one of the “intensive” therapies in the UKPDS study (21) and it is as effective as other therapies in preventing complications, despite the higher number of hypoglycaemic episodes it causes. It is hard to establish which insulin type can obtain good glycemic control with a lower risk of hypoglycaemic episodes; however, a recent metanalysis revealed rather evidently that insulin glargine reduces the risk of hypoglycaemia, compared to NPH insulin, in type 2 diabetes (99). Even insulin detemir has produced a more significant reduction in the risk of hypoglycaemia at night, compared to insulin NPH. (9,100)
Comparative studies on the use of rapid acting analogues of human insulin in type 2 diabetes have especially (101-102) found an improvement in post-prandial hyperglycaemia with the analogue, with no significant advantages on glycated haemoglobin.

Table 10. Oral Hypoglycaemic Treatment

1. Start oral pharmacological treatment when lifestyle interventions are unable to maintain glycemic control at desired values (HbA_{1c} <7%). However, always encourage maintaining lifestyle changes. Evaluate any initial oral drug dosage or an increase of the same every 2-6 months to reach and maintain HbA_{1c} <7% in time.
2. Start with metformin (first choice), unless there is a risk of renal failure. Start with low doses that can be increased in time – this will avoid gastrointestinal intolerance. Periodically check renal function and the risk of renal failure (glomerular filtrate <60 ml/min/1.73 m^2); if there are contraindications or intolerance, move on directly to the next paragraph.

3. Add a drug (secretagogue/ glytazone) when metformin alone cannot maintain good glycemic control, is not tolerated or is contraindicated. Secretagogues reach the target faster, but they can also lead to secondary failure more rapidly; glytazones induce water retention and involve an increased risk of heart failure in patients already at risk of this disease, but they ensure maintenance of good glycemic control for a longer period than secretagogues. Start therapeutic education: if secretagogues are prescribed, warn the patient of the risk of hypoglycaemia; if glytazones are prescribed, warn patients of the risk of water retention. If appropriate, prescribe the use of self-monitoring devices. When compliance could be a problem, prefer once- a day drugs. Rapid-acting secretagogues can become a valid alternative in patients with a variable lifestyle.
4. Triple combination therapy can be used when combinations of metformin-secretagogues or metformin-glytazones cannot maintain glycemic control (HbA_{1c} <7%); anyhow, consider the option of directly starting insulin therapy.
5. Acarbose can be another option, especially in patients who are intolerant towards other drugs.
6. Either increase doses or add other drugs, always checking metabolic control at frequent intervals (no longer than 3-6 months) till the goal is achieved. When conditions undergo rapid deterioration, evaluate the option of starting insulin therapy at an early stage.

Despite evidence that treating post-prandial hyperglycaemia improves glycemic control and reduces the progress of atherosclerosis and cardiovascular events (103), the advantage of specifically reducing post-prandial hyperglycaemia must be supported by targeted randomised, controlled, well-designed studies (104). There are no substantial differences in clinical terms between the three currently marketed rapid-acting analogues (105). Insulin therapy is initially added to oral treatment in type 2 diabetes (i.e. by adding NPH, glargine or detemir in the evening or small boluses of a rapid-acting analogue at mealtime); it is later either adjusted or increased to suit the basal-bolus pattern (106) or, if necessary – in rare selected cases – with premixed drugs. Both patients and doctors' hesitation to start insulin therapy (107,108), even multi-injection therapy, has led to the development of alternative routes of administration for the hormone. The first of these to be marketed is pulmonary insulin (18). Various clinical trials have proved its efficacy as monotherapy (109), either in addition or in replacement of metformin and/or sulfonylureas (110,111), comparing the effect with human insulin or its analogues (112,113). The NICE, however, recommended against its use in type 2 diabetes, unless in rare cases and for at most 6 months. (20)
For a summary of the therapeutic approach to type 2 diabetes refer to a version of 'IDF Guidelines for Oral Therapy (Table 10) and Insulin Therapy in Type 2 Diabetes' that has been modified for the Italian framework. (Table 11)

Table 11. Insulin Therapy in Type 2 Diabetes

1. Start treatment with insulin when oral therapy and intervention on lifestyle cannot achieve glycemic control. However, always encourage maintaining lifestyle changes. Consider either starting or increasing insulin every 2-6 months to reach and maintain HbA_{1c} <7% in time.

2. After the diagnosis, tell the diabetic that insulin is, anyhow, one of the possible treatments and that it can prove to be either the best or the only one that can either achieve or maintain glycemic control.
3. Start therapeutic education and prescribe the use of self-monitoring devices. Explain that doses can be low in the first prescription, but that they can reach 50-100 units/day in some cases.
4. Start insulin therapy before the onset of metabolic failure, especially when, despite maximal therapy, HbA_{1c} (DCCT study standard dosage) exceeds 7.5%. However, continue with metformin. The use of secretagogues can be continued, at least on a temporary basis during insulin therapy, unless insulin or a rapid acting analogue is administered at mealtimes. Acarbose too can be continued.
5. When you start insulin therapy: 5.1 use a basal insulin like detemir, glargine or NPH (the risk of hypoglycaemia is higher with NPH); *or* 5.2 use a rapid-acting analogue at mealtime; *or* 5.3 directly use a basal-bolus pattern; *or* 5.4 when there are serious and evident compliance problems, use a dual administration of premixed insulin (biphasic), attempting, anyhow, to educate the patient to follow a basal-bolus pattern.
6. Start insulin therapy by prescribing a self titration pattern (increase 2 units every 3 days till the goal is achieved) or through weekly contacts (always using a similar pattern). Establish the goals fasting and pre-prandial glycaemia <110 mg/dl; post-prandial <145 mg/dl. Check blood glucose at other times to identify other possible causes of bad control.
7. Encourage the patient even over the telephone till the glycemic goal is achieved.
8. Prescribe both the pen (either rechargeable or disposable) and normal syringes, leaving the patient free to choose.
9. Encourage administering insulin in abdominal (fast absorption) and thigh (slow absorption) subcutaneous tissue, considering arm and buttocks as valid alternatives. Always remember that some patients may not prefer the abdominal administration for cultural reasons.

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E. THERAPEUTIC EDUCATION

RECOMMENDATIONS

> People with diabetes must be instructed to self-manage their disease both at the time of diagnosis and later, to suit requirements. (**III, B**)

> Education on the self-management of diabetes must be guaranteed by the team's healthcare personnel that are specially qualified with ongoing professional training to conduct educational activities. (**VI, B**)

> All diabetes teams must have at least one healthcare operator who is specifically trained in therapeutic education. (**VI, B**)

> When there is no educator, we encourage other team members to acquire this competence. (**VI, B**)

> Education on the self-management of diabetes must also focus on psychosocial issues because emotional wellness is strongly associated with the positive outcome of treatment. (**III, B**)

> Education on the self-management of diabetes must be appropriately acknowledged and paid as an integrated intervention system in the framework of NHS services. (**VI, B**)

COMMENT

The current didactic approach focuses on enhancing diabetics' competence to make informed decisions concerning self-management. The wording *Diabetes Self-Management Education* (DSME) adopted both by the ADA and the IDF mirrors their acknowledgement that 95% of diabetes care is self-provided by diabetics and their families. Education has been an integral part of intensive care in type 1 diabetes in the DCCT study, just as diet education had a significant impact on the UKPDS study (type 2 diabetes) before randomisation; education is subsequently deemed an essential part of diabetes care.

Systematic reviews of educational therapy in diabetes observe the heterogeneous methods and result-reporting ways adopted by the mentioned studies as critical aspects in study assessments. Research in the educational field is complex due to the many variables involved and because it is impossible to conduct controlled studies. Often the implemented educational interventions are not adequately described; hence, it is hard to evaluate their transferability.

Most literature has only evaluated either the knowledge-based outcome or the result of glycemic control. Many studies have found that education on the self-management of diabetes is associated with improved knowledge of diabetes (1), improved self-care mode (1) and improved outcomes, such as reduced HbA_{1c} (3,4,6,7), reduced reported body weight (1) and better quality of life (5). The best outcomes in the middle term have been reported when education on the self-management of diabetes was provided for a longer period, including strengthened education during the follow-up phase (1), was adapted to meet individual requirements and preferences (2) and focused on psychosocial issues too (1,2,6). Current evidence on specific educational models, techniques and the frequency of meetings are not sufficient to provide specific recommendations (8). However, recent reviews indicate that the group educational-therapeutic model approach has proved effective in type 2 diabetes by improving certain control parameters (i.e. HbA_{1c} and blood pressure), besides knowledge on diabetes (9,10). According to the NICE review, the cost-effectiveness ratio depends on the type of educational programme; despite the scarce evidence concerning the cost of education at large, it is deemed that, considering the low cost of such programmes, even moderate improvements in terms of morbidity or quality of life are sufficient to make educational interventions cost-effective. (8)

Educational interventions are more effective when they are organised in an integrated diversified training system targeted at healthcare professionals and focused on organisation (12-13). Involving nursing staff in

coordinating educational interventions increases the short term efficacy of the same, but there are no middle-long term studies, except for special patient types (i.e. those with chronic complications) (11).
The *Gruppo Italiano di Studio per l'Educazione e Diabete* - GISED [Italian Study Group for Diabetes Education) – the Italian correspondent of the European study group DESG (Diabetes Education Study Group) – operates in the framework of research and training focused on the therapeutic education of diabetics. The Permanent Training School formed by *Associazione Medici Diabetologi* (AMD) and the Permanent Training School formed by the Nurses Association OSDI and the work group Structured Therapeutic Education are actively involved in ongoing training. The preliminary survey promoted by the GISED in 2004 (14) reports that diabetes clinics, which answered the questionnaire sent to them, provided the following information:
– about 200 of the 650 clinics considered in the AMD's census declared that they provide therapeutic education and that its clinical application still involves considerable difficulties;
– the time various healthcare professionals dedicate to educational activities covers a very small part of the weekly schedule;
– in many cases education is provided in a disorganised manner;
– only just over half the centres that provide therapeutic education implement group interventions but they do not always envisage dedicated hours and/or spaces;
– healthcare professionals seem to lack training; hence the failure to know and use appropriate methodological techniques;
– often educational activities are neither evaluated nor recorded.

Considering this situation, clinics that still do not envisage structured space and time for therapeutic education should provide healthcare professionals with training on tools (i.e. methods, strategies, etc.) by resorting to the assistance and competence of the GISED and of training schools formed by the AMD and the *Associazione Operatori Sanitari di Diabetologia Italiani* - OSDI (Association of Italian Diabetological Healthcare Professionals).
The GISED offers some training tools on therapeutic education to healthcare professionals:
a) educational packets for diabetes teams (first packet: prevention of foot lesions);
b) training courses for diabetes healthcare professionals based on the DESG (the European Diabetes Education Study Group) curriculum;
c) training courses for diabetes teams to educate patients to use insulin pump therapy.

We must notice that though "collective educational therapy" and "individual educational therapy" services are envisaged in the nomenclature and price list, in many Italian regions they are either not free from prescription charges or they are paid for at trivial rates by the National Health System. These administrative aspects require an urgent corrective intervention by the competent institutions (i.e. Ministry of Health, Regional Administration).

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F. PHYSICAL EXERCISE

R E C O M M E N D A T I O N S

> At least 150 min/week of moderately intense aerobic physical exercise (50-70% of the maximum heart rate) and/or at least 90 min/week of intensive physical exercise (>70% of the maximum heart rate) are recommended to improve glycemic control, encourage maintenance of optimal body weight and reduce the risk of cardiovascular diseases. Physical exercise must be distributed in at least 3 days/week with intervals that do not exceed two consecutive days. (**I, A**)

> Failing contraindications, type 2 diabetics must be encouraged to perform physical exercise against resistance thrice a week following a programme defined with the diabetologist and targeted at all major muscle groups.(**I, A**)

> Introducing subjects who are out of training and have various degrees of relative sarcopoenia to a physical exercise programme − through gradual exercises against the resistance of small weights − can enable them to start aerobic exercises that strengthen muscles and increase aerobic capacity and weight loss. (**VI, B**)

> The treadmill test is not recommended in asymptomatic subjects with a low risk of coronary heart disease who wish to start a physical exercise programme (risk of a cardiac event after 10 years <10%). (**VI, D**)

> It is advisable to increase blood glucose self-monitoring before, during (exercise duration >1 h) and after

physical exercise. Instructions must be provided concerning the need for carbohydrate integration and the management of hypoglycaemic therapy. Physical exercise is not recommended with ketosis. Instructions must also be provided concerning the risk of hypoglycaemic episodes during exercise and the risk of delayed hypoglycaemia after physical exercise. (**VI, B**)

COMMENT

These recommendations are mainly supported by metanalyses of studies conducted in type 2 diabetics on the role of aerobic physical exercise and resistance on glycemic control, irrespective of variations in body weight. (1,2)

Cohort studies have confirmed that ongoing intensive physical exercise is associated with a significant reduction in both cardiovascular and general mortality. (3-5)

Various studies have agreed on the long term efficacy of counselling activities on physical exercise, of physical exercise on cardiovascular risk and on the parallel reduction in treatment costs. (6)

In type 2 diabetes, physical exercise against resistance associated with moderate weight loss has proved effective in improving glycemic control and certain metabolic syndrome parameters and in preventing the loss of muscle mass (7-9).

A recent metanalysis conducted on type 2 diabetics confirmed an improved glycemic control during aerobic physical exercise programmes, both against resistance and in a combined mode. Programmes that combine aerobic activity and exercise against resistance give a small additional advantage on glycemic control and on some risk factors in type 2 diabetes (10).

An investigation conducted on a sample group of type 2 diabetics highlighted the importance of social and psychological factors on the practice of physical exercise, documenting how young age, high cultural level, the absence of motivational barriers and a good degree of perceived health and expected performance are related with the degree of physical exercise practised (11).

Before starting physical exercise that is more intensive than fast walking, one must rule out conditions involving a high cardiovascular risk (especially uncontrolled hypertension) and the presence of complications that contraindicate the practice of certain exercises due to the high risk of the disease evolution (i.e. severe vegetative or peripheral neuropathy, preproliferating or proliferating retinopathy and macular oedema) (13).

In *Diabete Italia*'s framework, the *Gruppo di Studio Diabete Attività Fisica* - GAF (Study Group on Diabetes and Physical Exercise) is implementing a programme of research, training (for diabetologists and metabolic fitness trainers) and activities targeted at patients. The GAF's recent investigation on diabetics attending Diabetes Clinics highlighted how about all type 2 diabetics (89.8%) deem it possible to improve their health with physical exercise, especially if male, young and with a high level of education (12). Physical exercise is practised ≥3 times/week by subjects who deem it useful for their health (53% vs. 25%). Perceived obstacles to the regular practice of physical exercise are a sense of physical inadequacy, lack of time, laziness and the presence of respiratory disorders. Anyhow, most patients (77%) deem that the figure of the metabolic fitness trainer is useful in the framework of diabetes services, while 94% would use devices to practise physical exercise if the facility were equipped with them.

Main reference documents on the frequency of physical exercise refer to the population at large and have

been produced by the American College of Sports and the US Department of Health and Human Services (14,15).

DEFINITIONS

Definitions are based on the Surgeon General's report Physical Exercise and Health published in 1996. (13)

Physical Activity: body movement produced by the contraction of skeletal muscles; it achieves higher energy expenditure than energy spent at rest.

Physical Exercise: scheduled, organised and repeated body movement performed to either improve or maintain one or more body components in good physical form.

Aerobic Exercise: repeated continuous rhythmic movements of the same large muscle groups for at least 10 minutes each. Examples comprise walking, cycling, jogging, swimming, aerobic exercise in water and various sports.

Exercise Against Resistance: activities that make use of muscular strength to either move a weight or work against a resistant weight.

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G. PSYCHOSOCIAL EVALUATION APPLIED TO DIABETES CARE

R E C O M M E N D A T I O N S

> A preliminary evaluation of the psychological and social condition must be performed at the first examination and, anyhow, when adherence to the therapeutic regime is inadequate. (**VI, B**)

> The psychosocial evaluation should study the attitude towards the disease and subsequent expectations, diabetes- related complications, medical management and quality of life (both in a broad sense and related to the disease), economic, social and emotional resources and the patient's psychiatric history, if any. (**VI, B**)

> Psychological treatment is better inserted in the framework of routine treatment than administered only when a specific problem or worsening in the psychic condition are detected. (**VI, B**)

COMMENT

Both psychological situation and social condition can influence the patient's ability to correctly follow diabetes treatment and to adopt the appropriate lifestyle for the disease (1-6). Family conflicts triggered by the need for care are frequent and may interfere with the outcome of treatment (7); hence the need for the clinician to speedily and efficiently evaluate the psychosocial condition in certain situations to provide personalised counselling and/or to request an appropriate consultation. (8)

Patients often reveal their psychosocial vulnerability on diagnosis and when the medical condition changes: the end of the "honeymoon" period, when more intensive treatment is required, and when a new complication is diagnosed. (4,6)

Psychosocial screening must also evaluate the attitude towards the disease, expectations concerning medical management and complications, affectivity/ mood, quality of life (both in a broad sense and related to diabetes), financial, social and emotional resources (9) and the psychiatric history (6-11). Cases of gross therapeutic non compliance (either by the patient or others) (1,6), depression involving possible self-harm (2,3), diet disorder symptoms (12), organic problems and the onset of a cognitive condition that significantly impairs judgement (3) require special focus.

Such cases need a consultation with a psychiatrist who is familiar with diabetes-related problems.

Psychological treatment is better inserted in the framework of routine treatment than administered only when a specific problem or deterioration in the psychic condition are detected (13). Screening tools (questionnaires) can facilitate the achievement of this goal; even if the clinician does not feel qualified to treat psychological problems, good doctor-patient relations enhance the patient's inclination to accept advice to attend other consultation services.

It is essential to establish the point that emotional well being is part of diabetes management. (10)

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H. INTERCURRENT DISEASES

R E C O M M E N D A T I O N S

> When there is an intercurrent disease, pharmacological treatment must be reviewed and adjusted to suit either concomitant blood glucose alterations or the new risk profile induced by the disease in progress. (**III, B**)

COMMENT

Stress induced by diseases, traumas and/or surgery often worsens glycemic control, precipitating either diabetic ketoacidosis or a hyperosmolar non-ketotic condition (or even the combination of the two). Any condition that leads to the worsening of glycemic control requires frequent monitoring of both blood glucose and ketones in urine. A disease that involves vomiting and ketosis can indicate diabetic ketoacidosis, which is a life threatening condition that requires immediate medical intervention to prevent complications and death (1). Very high blood glucose concentrations require temporary treatment adjustments and frequent contact with the diabetologist, if they are associated with ketosis.

Patients treated with either oral hypoglycaemic agents or only with nutrition therapy may require temporary treatment with insulin; an appropriate intake of fluids and calories must also be ensured.

Compared to healthy people, it is more likely that either an infection or dehydration will make hospitalisation necessary for a diabetic. The hospitalised patient must be treated by a doctor who is experienced in diabetes management. Recent studies suggest that achieving close glycemic control with insulin can reduce morbidity in subjects with an acute disease (2) and mortality in the period that closely follows myocardial infarction (3). For further information on the management of patients with ketoacidosis or a hyperosmolar non-ketotic condition in hospital, refer to the related chapter.

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I. HYPOGLYCAEMIA

RECOMMENDATIONS

> Oral glucose (15 g) is the choice treatment for mild and moderate hypoglycaemia, though equivalent doses of any form of carbohydrates containing glucose can be used for this purpose; the effects of treatment should be evident within 15 minutes after ingestion. (VI, B)

> The effect of treatment during a hypoglycaemic condition can only be temporary. Hence, blood glucose must be tested every 15 minutes till at least two normal values are found without the administration of further treatment between two tests. (**VI, B**)

> The intravenous administration of hypertonic glucose solutions (20-33%) is the choice treatment for acute hypoglycaemia when there is venous access, failing which, either intramuscular or subcutaneous administration of glucagon is recommended. (**VI, B**).

> Glucagon must be available for all patients with a significant risk of acute hypoglycaemic episodes (i.e. diabetics under insulin therapy who lack good glycemic control due to either unstable blood glucose concentrations or the onset of sudden hypoglycaemic episodes with no forewarning). The administration of glucagon does not require the attendance of a healthcare professional. (**VI, B**)

COMMENT

Hypoglycaemia (blood glucose <70 mg/dl), especially in patients treated with insulin, is the main limiting factor in the management of type 1 and 2 diabetes. (1)

Three degrees of hypoglycaemia have been defined: mild with only neurogenic symptoms (i.e. tremors, palpitation and perspiration), a problem the individual can self manage; moderate, when these symptoms are joined by neuroglycopenic ones (i.e. mental confusion, weakness), but the subject can self-manage the problem; severe, when the subject's awareness is altered and another person assistance and care is required to treat the hypoglycaemic episode. (2)

The management of mild and moderate hypoglycaemia requires the intake of food containing either glucose or carbohydrates. The acute glycemic response depends on the glucose or starch content and all carbohydrates containing glucose increase blood glucose concentrations, but hypoglycaemia must preferably be corrected with simple sugars that allow easy quantification and faster absorption: 15 g of glucose increase blood glucose by about 38 mg/dl after 20 minutes (3).

According to the well known "15 Rule", hypoglycaemia should be treated with 15 g of carbohydrates (preferably glucose tablets or sucrose granules dissolved in water, 125 ml of a sugared drink or fruit juice, or 1 tablespoon of honey), retesting blood glucose levels after 15 minutes and repeating treatment with another 15 g of carbohydrates till the blood glucose concentration rises above 100 mg/dl (2). The effect of treatment on hypoglycaemia can only be temporary. Hence, blood glucose must be tested every 15 minutes till two normal values are found without further administration of treatment between the two tests.

The treatment of acute episodes of hypoglycaemia (i.e. when the subject can take nothing by mouth) requires the assistance of another person for systemic treatment:

- when a situation arises outside the hospital and there is no IV access available, use pre-filled glucagon syringes (1 mg) for adults and children aged over 12 years; the dose is 0.5 mg for children aged less than 12 years (4). Caregivers and people living in close contact with diabetics must know the problem and be instructed on how to administer the drug either intramuscularly or subcutaneously; the Emergency Department should however be informed;
- when rapid IV access is available, a 1-3 minute infusion of 15-20 g of glucose in a 20-33% hypertonic solution is recommended (i.e. 80 ml of 20% glucose solution or 50 ml of 33% glucose solution). A dose of 200-500 mg/kg is recommended in children (4). Subsequent treatment strategies must consider the specific causes of the hypoglycaemic episode.

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J. VACCINATIONS

RECOMMENDATIONS

> Yearly administer the anti-flu vaccine to diabetics aged over 6 months. (**III, B**)

> Administer the pneumococcal vaccine to diabetic adults at least once in a lifetime. A single revaccination is recommended for subjects aged >64 years who had their first vaccination at least 5 years before. Other indications for revaccination are nephrotic syndrome, chronic renal failure and other immunocompromised conditions (i.e. organ transplant). (**III, B**)

COMMENT

Flu and pneumonia are common infectious diseases that can be prevented. They are associated with high mortality and morbidity rates in the elderly and in patients with chronic diseases.

There are few studies on the morbidity and mortality of flu and pneumococcal pneumonia, specifically in diabetics. Observational studies on patients with various chronic diseases, including diabetes, reveal that these conditions are associated with an increased number of admissions to hospital for flu and its complications. One case control study noticed that the anti-flu vaccine reduced diabetes-related admissions to hospital by 79% during flu epidemics. (1)

Diabetics have a higher risk of pneumococcal sepsis; their high risk of hospital sepsis has recorded a 50% mortality rate.

Safe effective vaccines that considerably reduce the risk of these diseases' serious complications are currently available (2,3) and there is sufficient evidence to prove that diabetics have an appropriate serological and clinical response to these vaccinations.

Anti-flu vaccine administration to the Italian population is increasing, but there are no prevalence data for diabetics.

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K. DIABETES MANAGED CARE

RECOMMENDATIONS

> Achieving diabetes care goals envisages cooperation between the diabetes team, the general practitioner and, in a broad sense, the specialist in territorial medicine, in the framework of well defined care pathways based on an integrated multidisciplinary and multiprofessional approach that is implemented with the patient's informed consent. (**III, B**)

> It is to be hoped that facilities directly involved in diabetes care have appropriate information systems with a special data storage system designed to store common basic data by format and plot to encourage data sharing and the definition and use of clinical indicators. (**VI, B**)

> Either a specialised team or a diabetologist should be consulted when there is:

- newly diagnosed diabetes;
- insulin-treated diabetes;
- diabetes without good glycemic control;
- gestational diabetes either during pregnancy or in view of a pregnancy;
- diabetes developing either acute or chronic complications. (**III, B**)

COMMENT

For various reasons many diabetics fail to achieve the therapeutic goals established by their general practitioners and specialists. Some Italian studies have noticed a drop in cardiovascular mortality and the onset of complications and better metabolic control when diabetic patients are controlled by either a specialist or a diabetes team (1,2). International studies have proved that integrated management provided by general practitioners and specialist services is effective in achieving therapeutic goals (3-6).

Hence the need for diabetes clinics and general practitioners to draft integrated management plans. In this regard, diabetologists (i.e. the scientific societies AMD and SID) and general practitioners (i.e. the scientific society SIMG) have agreed on recommendations for diabetes management (7). Recommendations issued in 2001 are summarised below, since they are the only ones published so far. The IGEA project is drafting organisational guidelines based on reliable evidence of efficacy to better implement the integrated management of diabetes. (3-6)

They envisage that the diabetologist must:

1) provide direct clinical management, cooperating with GPs, for diabetic patients with:
– type 1 diabetes;
– acute metabolic instability;
– evolving chronic complications;
– continuous treatment with subcutaneous insulin pumps;

2) frame newly diagnosed diabetic patients by drafting a personalised mutually agreed management plan;

3) periodically evaluate type 2 diabetics followed by GPs according with the managed care protocol;

4) provide clinical management, cooperating with GPs, for diabetic patients:
– with type 2 diabetes presenting a severe metabolic imbalance, for any reason;
– who plan on starting a pregnancy;
– who are pregnant;
– with gestational diabetes;
– who are either awaiting or preparing for major surgery;

5) update GPs on the complications of diabetes (i.e. erectile dysfunction, autonomic neuropathy, acute retinopathy…) that require an integrated multispecialist approach;

6) plan nutrition therapy;

7) provide educational therapy;

8) coordinate clinical, training, epidemiological and management activities related to diabetes care.

The GP's duties towards diabetic patients can be defined as specified below:

1) screen the population at risk to detect:
– undiagnosed cases of diabetes;

– cases of gestational diabetes;
– cases with Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG);

2) diagnose diabetes;

3) provide healthcare education and counselling to both subjects at risk and diabetic patients;

4) correct wrong diet habits and manage the diet prescribed by the Diabetes Clinic in close collaboration with the same;

5) manage the pharmacological treatment of type 1 and 2 diabetics, in close collaboration with the Diabetes Clinic;

6) monitor side effects and any interference with hypoglycaemic treatment;

7) ensure integrated follow-up management for diabetics with the Diabetes Clinic to achieve good metabolic control and early diagnosis of complications;

8) contact the Diabetes Unit to both frame newly diagnosed diabetics and schedule their periodical visits, according to the management plan;

9) organise the medical practice (i.e. patient access, equipment, and staff) to ensure optimal management of diabetic patients;

10) establish a clinical data collection sheet with the competent Diabetes Clinic (i.e. either hard copy or digital case records).

11) cooperate with the Diabetes Clinic in diabetes research.

Recent years have witnessed a progressive increase in the number of general medicine associations and an extensive territorial involvement in trials centred on new healthcare management models based on the concept of ascertaining and reviewing quality; healthcare professional right and duty to work by goals and to be paid by the established results achieved has been acknowledged everywhere. The dialogue between GPs and diabetologists has never been interrupted, despite the many bureaucratic, administrative and, at times, even cultural obstacles found on its path.
Project IGEA (*Integrazione Gestione e Assistenza del diabete* - Diabetes Integration, Management and Care), coordinated by the National Health Institute and designed to implement diabetes managed care in the framework of the *National Prevention Plan*, has been implemented in various Italian regions since 2006.

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VI. PREVENTION AND MANAGEMENT OF DIABETIC COMPLICATIONS

A. CARDIOVASCULAR DISEASES

Cardiovascular diseases are the main cause of mortality and morbidity in diabetics (1). The Italian diabetic population's mortality rate is 30-40% higher than the non diabetic population (2,3), but the gap seems to reduce when there is specialist organised care (4). Cardiovascular diseases are the cause over 50% of deaths. Probably diabetics have the same risk of cardiovascular events as the non diabetic population of cardiopathics, though not all evidence agrees on this point. The diagnosis of diabetes is generally preceded by about 7-year phase during which the disease is silent, though the cardiovascular risk is already comparable to that of known diabetes.

Type 2 is an independent risk factor for macrovascular diseases and coexisting conditions; hypertension and hyperlipidemia are also risk factors. Clinical studies have proved that a reduction in cardiovascular risk factors effectively prevents or slows down the onset of cardiovascular complications. Evidence is summarised and commented in the sections below. In fact, recent evidence, such as the one provided by the Steno-2 study, suggests adopting a more aggressive approach both to diabetes and to all associated risk factors (5). Only a global approach to the disease, that does not only seeks glycemic control but also considers the various risk factors, can lead to a reduction in the disease's impact on the diabetic population.

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1. Hypertension Management

R E C O M M E N D A T I O N S

Screening, diagnosis and monitoring

> Blood pressure must be tested at every visit. Systolic pressure ≥130 mmHg or diastolic pressure ≥80 mmHg must be confirmed on various days for one month. (**V, B**)

> Blood pressure must be checked every 3 months in patients under hypertensive treatment and every 4-8 weeks during the dose adjustment phase unless therapeutic goals are achieved. (**VI, B**)

Goals

> Antihypertensive treatment administered to diabetics focuses on achieving systolic pressure <130 mmHg. (**III, B**)

> Antihypertensive treatment administered to diabetics is designed to achieve diastolic pressure <80 mmHg. (**II, B**)

> Pressure goals <125/75 mmHg are recommended for diabetics with proteinuria >1 g/day. (**II, B**)

Therapy

> Patients with either systolic pressure 130-139 mmHg or diastolic pressure 80-89 mmHg must change their lifestyle (i.e. reduce body weight if they are overweight, perform regular aerobic physical exercise, follow a low salt diet and reduce alcohol intake) and follow behavioural therapy for no more than 3 months. Start pharmacological treatment, if goals have not been achieved at the close of the said period. (**VI, B**)

> Besides behavioural therapy and advice on lifestyle, hypertensive patients (systolic pressure ≥140 mmHg or diastolic pressure ≥90 mmHg) must be administered intensive pharmacological therapy designed to achieve therapeutic goals. (**I, A**)

Frontline Pharmacological Treatment

> The choice of initial pharmacological treatment must consider comorbidities indicating either the use or exclusion of a certain drug category. (**VI, B**)

> Patients with diabetic nephropathy (reduced estimated glomerular filtration rate or micro/macroalbuminuria) must be administered either ACE-inhibitors or ARBs, excepting pregnant women. (See diabetic nephropathy). (**I, A**)

> Failing a comorbid condition, frontline pharmacological treatment for patients with blood pressure >140/90 mmHg must envisage a drug category that can reduce cardiovascular events in diabetic patients (i.e. ACE-inhibitors, ARBs, diuretics, calcium antagonists and beta-blockers). (**I, A**)

> Alpha- lytics are not recommended as frontline drugs for hypertension with diabetes. (**I, E**)

> Treatment with ACE-inhibitors, ARBs or diuretics requires kidney function and serum potassium testing either 1-2 weeks after the treatment's start or after an increase in dosage; testing will then be performed either once a year or more frequently in patients with impaired kidney function. (**VI, B**)

> Treatment with ACE-inhibitors and ARBs is contraindicated in pregnancy. (**VI, E**)

> Standing blood pressure must be checked in people with diabetes and hypertension, when it is clinically indicated. (**VI, B**)

COMMENT

Introduction

Hypertension (blood pressure ≥140/90 mmHg) is a common comorbidity in diabetes; it affects most diabetics and depends on the type of diabetes, age, obesity and the ethnic group. Moreover, hypertension is a major risk factor for cardiovascular diseases and microvascular complications, such as retinopathy and nephropathy. In type 1 it is often the outcome of underlying nephropathy, while in type 2 it can be part of the metabolic syndrome (specifically, obesity, hyperglycaemia and hyperlipidemia) that is associated with a high cardiovascular risk.

The Italian DAI, Casale Monferrato and UDNH studies report an 80-85% prevalence of arterial hypertension (≥140/90 mmHg) in type 2. In these studies, the percentage of treated subjects fluctuated between 53% and 67% and, over 50% of subjects were administered monotherapy (1). Data recently obtained by Metascreen, an Italian observational study conducted on over 8,000 type 1 and 2 diabetics attending specialist centres, reveals that little over 10% of treated diabetic patients achieved satisfactory pressure control and, that multidrug antihypertensive therapy is underused in both types of diabetes (multitherapy type 1: 26%; type 2: 34%). The Italian QuED study also showed poor compliance with guidelines on blood pressure control in type 2 diabetics. Only 6% of subjects had blood pressure <130/85 mmHg, while 52% had blood pressure ≥160/90 mmHg. Moreover, only 12% of subjects were treated with more than one antihypertensive drug. The study highlighted that overall treatment quality is strongly influenced by organisational and structural factors, for instance the frequency of visits to the doctor, sex and the doctor's level of specific specialisation seem to considerably influence treatment quality. (2)

On the basis of the results of "Italian Diabetes Care Quality Indicators" defined by the AMD, 77.2% of type 2 diabetics and 66.2% of type 1 diabetics had their blood pressure checked at least once, with a rather limited variability between different centres.

Intermediate outcome indicators reveal that two thirds (65.5%) of type 1 diabetics and only one third of type 2 diabetics (36.6%) achieve the pressure target ≤130/80. The percentage of subjects under antihypertensive treatment is 27.6% in type 1 and 52.8% in type 2, but half those with type 1 and two thirds of those with type 2 fail to achieve appropriate pressure control.

Screening and Diagnosis

Failing real scientific evidence, the IDF paper recommends checking blood pressure with a mercury manometer or other efficient validated tool and a cuff the appropriate size and, recording blood pressure values in the patient's pressure book. Moreover, it recommends considering the possible secondary causes of arterial hypertension, if abnormal pressure values are found. Australian guidelines recommend frequent monitoring during the treatment's adjustment phase because data provided by the *Perindopril Therapeutic Safety Study* proved that the maximum antihypertensive effect after a dosage change is achieved after up to 6 weeks (3). Australian guidelines stress that it is useful to perform the pressure Holter test in subgroups of hypertensive diabetics. In fact, 24-hour dynamic blood pressure monitoring can rule out high pressure caused by fear of doctors, besides recognising "non dippers" with an increased risk of micro and macrovascular complications. Moreover, pressure Holter test results are better related with the cardiovascular risk, than results obtained by measuring blood pressure in the medical practice.

Goals

Randomised clinical studies have proved the positive effects (i.e. lower incidence of coronary events, stroke and nephropathy) of reducing systolic pressure <130 mmHg and diastolic pressure <80 mmHg in diabetics (4,5,6, and 7). The results of both *Hypertension Optimal Treatment* (HOT) and UKPDS-38 (*UK Prospective Diabetes Study*) studies back the recommendation to establish 80 mmHg as target diastolic pressure. In fact, both studies have proved a reduction in micro- and macrovascular complications and, in cardiovascular and diabetes-related mortality in patients with about 80 mmHg diastolic pressure. Evidence concerning systolic pressure <130 mmHg is less strong and issues from both prospective cohort studies (8) and ABCD studies. A 132 mmHg systolic pressure reduced the ABCD-HT study's overall mortality rate (9) and, a 128 mmHg systolic pressure reduced the incidence of stroke in the ABCD-NT study (10). Moreover, epidemiological analyses have proved that pressure >115/75 mmHg is associated with an increased percentage of cardiovascular events and an increased mortality rate in diabetics (4,11, and 12). According to this data, a pressure goal <130/80 mmHg seems reasonable and is recommended by most of the recent guidelines. ACCORD study (2009) results are pending concerning variations in recommendation strength for target systolic pressure. A pressure goal <125/75 mmHg is, instead, recommended for diabetics with proteinuria >1 g/day (see *Diabetic Nephropathy*).

Behavioural Therapy

Despite the lack of controlled studies on diet and physical exercise in the management of arterial hypertension in diabetics, such measures (i.e. low sodium diet, reduced body weight in overweight individuals, regular aerobic physical exercise, moderate reduction in alcohol intake, reduced intake of caffeine) have proved effective in reducing blood pressure in non diabetics (13). Moreover, these non pharmacological strategies can positively modify blood glucose levels and the lipid profile. Their effects on cardiovascular events are not well documented as yet.

Pharmacological Therapy

The primary goal is to achieve the pressure target, irrespective of the drug category used. Australian guidelines, the IDF paper and the recent NICE-BHS (National Institute for Health and Clinical Excellence-British Hypertension Society) guidelines stress the importance of evaluating whether the patient has a comorbidity that specifically indicates either the use or exclusion of a special category of antihypertensive drugs as choice frontline treatment. Beta-blockers are recommended for patients with angina; ACE-inhibitors or beta-blockers for patients with past myocardial infarction; ACE-inhibitors or diuretics for patients with heart failure; ACE-inhibitors or angiotensin receptor blockers (ARB) for patients with nephropathy (reduced estimated GFR or micro/macroalbuminuria). Beta-blockers are, instead, contraindicated in patients with peripheral vasculopathy or asthma and, ACE-inhibitors/ARBs are not recommended for patients with renal artery stenosis and pregnant women.

Failing a comorbid condition, the use of drugs that can reduce cardiovascular events in diabetic patients is recommended: ACE-inhibitors, ARBs, diuretics, calcium antagonists and beta-blockers. Australian and Canadian guidelines recommend against using alphalythics as frontline drugs to manage hypertension in diabetes. In fact, in the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study – an extensive randomised study on various pharmacological treatments for arterial

hypertension – the study arm with alphalythics was interrupted early because treatment with doxazosin increased the risk of stroke and heart failure, compared to that with chlortalidone. (14)

It is uncertain whether certain categories of antihypertensive drugs are superior to others in terms of reducing cardiovascular risk, and must thus be recommended as frontline treatment. However, it is a known fact that compared to placebos, ACE-inhibitors reduce the incidence of cardiovascular events in patients with a high cardiovascular risk, either with or without hypertension (15,16). Moreover, the ALLHAT study found no significant differences between frontline treatment with lisinopril, amlodipine and chlortalidone and cardiovascular risk, though diuretics were slightly more effective than other antihypertensive drugs in reducing the incidence of heart failure (17). The UKPDS study too observed no significant differences in terms of cardiovascular risk between captopril and atenolol. Instead in the LIFE (Losartan Intervention For Endpoint) study's subgroup of hypertensive diabetics with left ventricular hypertrophy, ARBs proved superior to beta-blockers in improving the cardiovascular outcome. (18)

Some studies have proved that ACE-inhibitors are superior to dihydropiridine calcium channel blockers (DCCB) in reducing the incidence of cardiovascular events (19,20). Moreover, data on diabetics with diabetic nephropathy has documented the superior efficacy of ARBs, compared to DCCBs in reducing cardiovascular events (21). On the other hand, the recent INVEST study (International Verapamil Study) involving over 22,000 subjects with coronary heart disease and arterial hypertension, proved that the efficacy of verapamil and non-dihydropiridine calcium channel blockers resembled that of beta-blockers in reducing cardiovascular mortality; this data was confirmed in the subgroup of diabetics (22). Lastly, the recent ASCOT-BPLA study (Anglo-Scandinavian Cardiac Outcome Trial-Blood Pressure Lowering Arm) proved that amlodipine, combined with perindopril, if necessary, had a superior effect than atenolol, combined with the diuretic, if necessary, on mortality and overall cardiovascular events in hypertensive patients with a moderate cardiovascular risk. This result was confirmed in the diabetic subgroup (23). On the basis of results obtained by the ASCOT-BPLA study, recent metanalyses performed by Lindholm LH et al. (24) and, the NICE study 2006, which highlight an increased risk of stroke in patients under treatment with beta-blockers, NICE-BHS guidelines recommend against using beta-blockers as frontline drugs to manage hypertension in both diabetics (25) and non diabetics. There is also some doubt over extending evidence obtained in a prevalently non diabetic population, to diabetics. Moreover, almost all the studies mentioned have methodological limits; besides, even minor differences in pressure levels obtained by administering various categories of antihypertensive drugs could partly justify the results. Hence, the discussion on the best frontline drug is partly academic, considering the fact that diabetics almost always require combined treatment to reach the therapeutic target and, that 29% of subjects randomised for intensive pressure control in the UKPDS study was treated with at least three different drugs at the close of the study (5). Concerning multitherapy, ADA guidelines recommend including an ACE-inhibitor or an ARB and, avoiding the combination of thiazide diuretics and beta-blockers – due to their risk of deteriorating metabolic control – in the multidrug therapeutic pattern of hypertensive diabetics.

Monitoring

Blood pressure must be rechecked within a month before starting treatment to confirm the presence of hypertension. Systolic pressure ≥140 mmHg and diastolic pressure ≥90 mmHg, anyhow require

pharmacological treatment. Hypertensive patients should be frequently monitored and the drug dose should be adjusted till recommended pressure goals are reached (7). Glycemic control and the presence of other cardiovascular risk factors, such as obesity, dyslipidaemia and smoking, microalbuminuria (tested before commencing treatment) should be carefully evaluated and treated.

Pregnant Women

Diabetic women with chronic arterial hypertension during pregnancy should achieve systolic pressure 110-129 mmHg and diastolic pressure 65-79 mmHg, to ensure a possible long term positive effect on maternal health. Lower pressure values can be associated with reduced foetal growth. Treatment with ACE-inhibitors and ARBs is contraindicated during pregnancy, because it can damage the fetus. The chronic use of diuretics during pregnancy has been associated with a drop in maternal plasma volume, which could reduce perfusion in the uterus and the placenta. Antihypertensives with known efficacy, whose administration is safe during pregnancy, are methyldopa, labetalol, diltiazem, clonidine and prazosin.

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2. Dyslipidaemia Management

R E C O M E N D A T I O N S

> A complete lipid profile (total cholesterol, HDL and triglycerides) must be run at least yearly and at closer intervals in case of failure to achieve the therapeutic goal. (**VI, B**)

> LDL cholesterol must be deemed the primary goal of treatment. (**I, A**)

> Non-HDL cholesterol can be a secondary goal in diabetics with blood triglycerides >200 mg/dl. (**III, B**) The apoB/apoA1 ratio can be a useful index of the cardiovascular risk in diabetics. (**III, B**)

> Lifestyle changes (diet with low saturated fat and cholesterol and high fibre content, increased physical exercise) and corrections concerning cardiovascular risk factors (optimisation of glycemic control and pressure values, discontinuation of the smoking habit) are essential in dyslipidaemic diabetics. (**I, A**)

> Hypolipidemic treatment has proved effective as primary and secondary prevention in reducing cardiovascular risk (i.e. fatal and non fatal AMI and coronary revascularization) in type 2 diabetics. (**I, A**)

> Statins are the first choice drugs in preventing cardiovascular diseases. (**I, A**)

> Treatment with statins and lifestyle changes are recommended for LDL cholesterol >130 mg/dl in diabetics aged <40 years with no additional cardiovascular risk factor. The therapeutic goal is to achieve LDL cholesterol <100 mg/dl. (**V, B**)

> In high risk diabetics (i.e. one or more cardiovascular risk factors) hypolipidemic treatment must start irrespective of the LDL cholesterol level. The therapeutic goal is to achieve LDL cholesterol <100 mg/dl. (**I, A**).

> LDL cholesterol <70 mg/dl can be a therapeutic goal for diabetics with cardiovascular diseases and multiple cardiovascular risk factors that cannot be corrected. (**VI, B**)

> Additional treatment goals can include achievement of plasma triglyceride levels <150 mg/dl and HDL cholesterol >40 mg/dl in men and >50 mg/dl in women. (**III, B**)

> Treatment with fibrates can be considered in diabetics with hypertriglyceridemia undergoing primary prevention treatment but with optimal LDL cholesterol levels. (**II, B**)

> The combination statin + fibrate can be taken into account to achieve the therapeutic goal, but it is not supported by intervention studies targeted at diabetics. (**VI, C**)

COMMENT

Diabetes and the cluster of associated cardiovascular risk factors are the cause of high cardiovascular morbidity and mortality rates in diabetics. Arteriosclerosis has a worse prognosis in diabetics and records a high mortality rate (1-2). Cardiovascular risk factors resemble those of the population at large, but their effect is enhanced in diabetes (3). The most common lipid profile alteration is hypertriglyceridemia, which is a likely marker of alterations (i.e. low HDL cholesterol, presence of small dense LDL lipoproteins, insulin-resistance) that are pathogenetically related to arteriosclerosis (4). Recent studies have revealed that the apoB/apoA1 ratio can be an accurate cardiovascular risk factor, especially in diabetes mellitus, since it is directly related to the number of atherogenic lipoprotein particles, rather than to their lipid content (5-7). International standards for ApoA1 and ApoB levels now enable the extensive use of such assays in clinical practice.

The 2006 *Annali AMD* report that Italian Diabetes Units have run a lipid profile on 63% of diabetics: only 30% of these had LDL cholesterol <100 mg. Moreover, 32% of diabetics who are administered hypolypidemic treatment have LDL cholesterol ≥130 mg. The DAI study pointed out that only 28% of Italian diabetics presenting a cardiovascular disease and attending the 201 Diabetes Units over the period 1998-1999 were treated with statins (8). However, a comparative analysis between the Casale Monferrato Study's 1988 cohort and the 2000 one reveals an improvement in time: in fact, diabetic patients' probability of presenting LDL cholesterol >100 mg/dl was 30% less in 2000, compared to 1988. (9)

Many clinical trials have provided epidemiological evidence on the efficacy of statin-based therapy in primary and secondary prevention in the population at large, while studies conducted on the diabetic population are fewer. Anyhow, a recent metanalysis has proved that the low incidence of major cardiovascular events during hypolidemic treatment is comparable in primary prevention of both diabetics (21%, IC 95% 11-30, p<0.0001) and non diabetics (23%, 12-33%; p=0.0003) (8). The reduced risk in secondary prevention was 21% in diabetics (IC 95%, 10-31%; p=0.0005) and 23% in non diabetics (IC

95%, 19-26; p<0.00001). In the multivariate analysis, adjustments made for other risk factors further increased the beneficial effects on diabetics. Moreover, diabetics recorded a 3-fold reduction in the absolute risk in secondary prevention. The *Number Needed to Treat* (NNT) with primary prevention was 37 diabetics and 44 non diabetics, while secondary prevention counted 15 diabetics and 16 non diabetics. (10)

Even the CARDS study (Collaborative Atorvastatin Diabetes Study) − the first trial designed for type 2 diabetics in primary prevention − highlighted that treatment with 10 mg/day of atorvastatin reduces the relative risk of major cardiovascular events by 37%. (11)

Table 12. Recommended Therapeutic Goals

	AMERICAN DIABETES ASSOCIATIO	THIRD EUROPEAN JOINT TASK FORCE	EASD/ESC GUIDELINES 2007
Cholesterol	***Normal***	<175 mg/dl	<175 mg/dl
LDL Cholesterol	<100 mg/dl In very high risk subjects <70 mg	<100 mg/dl	<97 mg/dl <70 mg/dl in secondary prevention
HDL Cholesterol	>40 mg/dl in males >50 mg/dl in females	>40 mg/dl	>40 mg/dl in males >46 mg/dl in females
Triglycerides	<150 mg/dl	<150 mg/dl	<150 mg/dl

International Guidelines: Therapeutic Goals and Treatment

Table 12 summarises therapeutic goals proposed by the main guidelines for diabetics (12-14). Detailed recommendations are provided by the National Cholesterol Education Program (NCEP-ATP III), which stresses that diabetes must be deemed an equally important risk factor, just as the cardiovascular risk associated with diabetes is equivalent to the one produced by the presence of a cardiovascular disease, at least in some populations. The Third European Joint Task Force especially focuses on subjects with a high risk of developing cardiovascular events, such as type 2 diabetics and type 1 diabetics with proteinuria; the latter's treatment goals are total cholesterol <175 mg and LDL cholesterol <100 mg. Low HDL cholesterol levels and high triglyceride levels are not proposed as therapeutic goals; they are deemed as markers of a very high cardiovascular risk. EASD/ESC joint guidelines on diabetes, prediabetes and cardiovascular diseases have been recently published. (15)

From a therapeutic perspective, the guidelines agree in considering statins as frontline treatment. A lower dose of statins combined with other hypolipidemic agents (i.e. ezetimibe) can achieve the therapeutic goal, but no intervention studies have so far proved this combination's superiority in preventing cardiovascular events.

Management of hypertriglyceridemia and low HDL cholesterol levels is a field that lacks reliable evidence. Fibrates are proposed as a therapeutic choice when triglyceride levels are high, but opinions still differ concerning the best level to commence treatment and, in which cases either monotherapy or statin combinations should be preferred. The FIELD study, which was specifically designed to evaluate fenofibrate

treatment vs. placebo in type 2 diabetics (total blood cholesterol 115-250 mg/dl; total cholesterol/HDL cholesterol ratio >4; triglycerides >90 mg/dl) (16), was recently published. A 5-year follow up period with fenofibrates significantly reduced the incidence of non fatal AMI, but not of other primary end points (i.e. coronary events and coronary death). Such results most likely depend on the more frequent administration of statins in the control arm than in the group treated with the active drug. However, the study provides no adequate evidence to support the role of fibrates in cardiovascular prevention in diabetics. Literature counts no clinical trials on the safety and efficacy of statins/ fibrates combination in subjects with diabetes mellitus. Centred on the population at large, the SAFARI study, which compared simvastatin 20 mg vs. simvastatin 20 mg + fenofibrate in 618 subjects aged 21-68 years presenting hyperlipidemia with multiple phenotypes, reported a statistically significant improvement in all lipid profiles in the arm that was administered the combined treatment for 12 weeks (17). No episodes of either clinical myopathy or serious liver function impairment were reported. However, this data requires further confirmation from more extensive studies that envisage a longer follow-up period.

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3. Use of Antiplatelet Drugs

RECOMMENDATIONS

> Antiplatelet treatment with acetylsalicylic acid is recommended for diabetics who have either experienced a past cardiovascular or cerebrovascular event or have peripheral arteriopathy. (**I, B**)

> Antiplatelet treatment with acetylsalicylic acid is recommended for either diabetics aged over 40 years or those with at least one cardiovascular risk factor (i.e. hypertension, cigarette smoking, dyslipidemia, family history of cardiovascular events, microalbuminuria). (**I, B**)

> Treatment with acetylsalicylic acid is best avoided in case of recent gastrointestinal bleeding, uncontrolled arterial hypertension, active liver disorders and drug allergies. (**I, A**)

> The combination of acetylsalicylic acid + clopidogrel can be recommended for very high risk diabetics (who have undergone revascularization surgery and have a history of past cerebral ischemic events or multiple vascular involvements). (**II, B**)

> There are no controlled studies on the use of acetylsalicylic acid in diabetics aged less than 30 years and in type 1 diabetics. (**VI, C**)

COMMENT

Haemostatic alterations can be found both in diabetes and in the insulin resistance syndrome (1-2). Specifically, the levels of plasma fibrinogen, PAI-1, factor VII and factor von Willebrand − which are predictive of ischemic heart disease in the population at large − were high in diabetic patients. (1-4)
The platelets of diabetics are hypersensitive to agglutinating agents *in vitro* (5). One process involved is the increased production and release of thromboxane, which is a vasoconstrictive and antiplatelet agent (6-7). Acetylsalicylic acid inhibits thromboxane synthesis and, this property leads to recommendations concerning the drug's use to prevent both primary and secondary cardiovascular events.

Aspirin and Diabetes

Considering the physiopathological remarks that back the use of ASA in the diabetic population, intervention trials have produced results that lack a univocal interpretation. (8-9)
The Primary Prevention Project (PPP) evaluated the efficacy of treatment with 100 mg ASA in 4,495 subjects with no cardiovascular disorders, but presenting at least one risk factor (10). The study observed a significant reduction in such events in the population at large, subsequent to the use of ASA: RR=0.69 (IC 95% 0.53-0.90) for cardiovascular events and 0.32 (IC 95% 0.14-0.72) for cardiovascular mortality. Results were, instead, less significant in the analysis of the diabetic subgroup (n=1,031), most likely due to the smaller cohort studied: RR =0.89 (IC 95% 0.62-1.26) for cardiovascular events and RR =1.23 (IC 95% 0.69-2.19) for cardiovascular mortality. (11)
In the ETDRS study conducted on 3,711 diabetics with a 7-year follow-up, the administration of 650 mg

ASA produced RR =0.91 (IC 99% 0.75-1.11) for general mortality and RR=0.83 (IC 99% 0.66-1.04) for both fatal and non fatal infarction (12). Specifically, the study provided no evidence concerning a higher risk of retinal, vitreous and gastrointestinal bleeding during treatment with high doses of ASA.

In the metanalysis performed by the Antithrombotic Trialists' Collaboration, the nine studies evaluated related to diabetic patients (n=4,961, including 3,711 in the ETDRS study) show a non significant 7% reduction in the cardiovascular risk. (13)

The Veterans Administration Cooperative Study observed that the administration of 650 mg ASA and dipiridamol to diabetics who had undergone amputation surgery or had critical ischemia in the lower limbs did not reduce the risk of either new amputation nor of cardiovascular mortality. (14)

In the *US* Physicians' Health Study's subgroup of 533 diabetics (15) − male doctors undergoing primary prevention and treated with 325 mg of aspirin vs. placebo with a 5-year follow up − 4% of subjects treated with ASA vs. 10.1% of those who were administered the placebo suffered a myocardial infarction ($p<0.01$). A possible explanation to the lesser efficacy of ASA in diabetics theorises a more frequent resistance to the action of aspirin, compared to non diabetics (20% in some studies). (16-17)

Other Antiplatelet Drugs

The combination ticlopidine̲ aspirin vs. aspirin and vs. aspirin̲ warfarin has proved superior in preventing thrombotic complications after coronary stent placement in non diabetics (18-21). But no studies are currently designed specifically for diabetics treated with ticlopidine.

The better safety profile of clopidogrel (a drug that belongs to the same family as ticlopidine and has the same mode of action), compared to ticlopidine, has drawn researchers and clinicians' attention to this drug. However the data available is not conclusive (22-25). The CHARISMA trial (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance), which has enrolled and randomised over 15,000 patients (6,000 diabetics) for treatment with aspirin̲ placebo or aspirin̲ clopidogrel, will provide more data in the future. (26)

International Guidelines

Though data published in literature provides no conclusive evidence on the efficacy of ASA treatment in diabetic patients, as stressed by recent editorials (27), almost all guidelines (28-34) strongly back this treatment, which is assigned high recommendation strength. Australian guidelines, for instance, recommend that all subjects with type 2 mellitus should be administered prophylactic treatment with aspirin (75-325 mg), failing contraindications (30). New Zealand guidelines recommend treatment with low doses of ASA (75-150 mg) for all diabetics with an over 15% cardiovascular risk 5 years after diagnosis (i.e. subjects with diabetes̲ hypercholesterolemia or low HDL or arterial hypertension). (31)

The ADA has recommended the use of aspirin, assigning it evidence level A:

• for primary prevention in type 2 diabetics aged over 40 years or with at least one risk factor (family history of cardiovascular diseases, arterial hypertension, cigarette smoke, hyperlipidemia, microalbuminuria);

• for primary prevention in type 1 diabetics aged over 40 years or with at least one risk factor (family history of cardiovascular diseases, arterial hypertension, cigarette smoking, hyperlipidemia, microalbuminuria);

• for secondary prevention in diabetics with a history of myocardial infarction, vascular bypass surgery,

ischemic stroke or transient ischemic attacks, peripheral vasculopathy, claudicatio and/or angina.

The ADA also suggests that alternative drugs to aspirin can be used in patients with contraindications to the drug's administration and evidence level E (32). Scottish and Canadian guidelines (28-29) and IDF recommendations basically agree with the above examples.

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4. Discontinuing the Smoking Habit

R E C O M M E N D A T I O N S

> Healthcare professionals must recommend all diabetics to discontinue cigarette smoking. (**I, A**)

> Counselling on giving up smoking, nicotine replacement therapy and other drug treatment should be deemed as therapeutic components of diabetes care. (**III, B**)

COMMENT

Smoking induces vasospasm, thus reducing blood flow; moreover, it increases blood viscosity and the concentration of coagulation factors. Its involvement in the atherogenic process is most likely due to damage to the intima caused by the local build up of carboxyhemoglobin and carbon monoxide (1). Cigarette smoke is also a powerful inhibitor of prostacyclin, which is both a vasodilator and anti-platelet drug. (2)

Smokers have an enhanced atherogenic lipid profile with higher concentrations of total cholesterol, triglycerides and VLDL and, lower levels of HDL. (3)

Considering the various coagulation-related alterations, we must mention: the increase in platelet aggregation, von Willebrand's factor and fibrinogen, besides the drop in the levels of plasminogen and its tissue activator. (4-5)

The prevalence of the smoking habit in the Italian diabetic population can be deduced from the DAI study conducted on 19,570 diabetics who were seen by the 201 Diabetes Units between September 1998 and March 1999 (6); 19% of men and 6% of women were smokers. Moreover, data published by the *2006 Annali AMD* reports that 29% of type 1 diabetics are smokers (11% of them smoke >20 cigarettes a day), while type 2 diabetics number 18% of smokers (20% of them smoke >20 cigarettes a day).

Many clinical trials, especially the Framingham Study, have highlighted relations between smoking and coronary heart disease, intermittent claudicatio and obliterative arteriopathy (7-8). Diabetics who are also smokers have a higher risk of morbidity and premature death associated with macroangiopathic complications; cigarette smoke is also involved in the onset of microvascular complications. (9-10)

Giving up smoking is hard and complex due to the physical and psychological addiction. A doctor's simple

request to give up smoking achieves a moderate 2.5-14.7% discontinuation rate and NNT=35 (11-12). Intensive educational interventions can obtain 19-38% discontinuation rates (13-14). Many randomised clinical studies have proved the efficacy of counselling on changes in the smoking habit. Nicotine replacement treatment effectively increases the rate of discontinuation 1.5-2-fold (15), but there is no evidence concerning its efficacy in those who smoke less than 15 cigarettes a day. Eight weeks of treatment seem to be as effective as longer treatment (12). Treatment with either clonidine or amitriptiline can increase the discontinuation rate of smoking, but it is not void of side effects (16-17). Acupuncture has proved ineffective in discontinuing smoking (18). The return to smoking, after discontinuation, fluctuates between 23% and 40% (19-20); hence, the importance of continuing the educational intervention, even after the patient has given up smoking.

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5. Coronary Heart Disease - Screening and Management

RECOMMENDATIONS

Screening

> We recommend yearly screening for all diabetics from the time the disease is diagnosed. (**III, B**)

> All diabetics, irrespective of the risk level, must yearly undergo:

– peripheral pulse examination and search for vascular bruits;

– basal ECG;

– Winsor Index (if normal it can be evaluated again after 3-5 years). (**VI, B**)

> The following diagnostic investigations are also recommended for diabetics with a high cardiovascular risk (they must be repeated every 1-3 years, depending on the results obtained):

– carotid Doppler ultrasound;

– Doppler ultrasound of the lower limbs (with Winsor Index <0.9 or if arteries are not compressible);

- ischemia provocative tests (exercise ECG or exercise stress scintigraphy/ echocardiography) (**VI, B**)

Treatment

> Diabetics with either a cardiovascular disease in progress or with high risk factor levels must be administered appropriate treatment unless all altered values are normalised. (**I, A**)

> Treatment with beta-blockers must be considered for diabetics with either past myocardial infarction or those who have undergone coronary revascularization surgery, irrespective of pressure values. (**I, A**)

> Treatment with ACE-inhibitors to prevent cardiovascular events must be considered for diabetics aged over 55 years presenting at least one cardiovascular risk factor, irrespective of pressure values. (**I, A**)

COMMENT

An Evaluation of the Global Cardiovascular Risk

In December 2002, a Committee of Experts representing Italian scientific societies of diabetology (AMD, SID), cardiology (SIIA, FIC, Forum for the prevention of cardiovascular diseases) and lipidology (SISA), of the SIMG, of Gruppo Cochrane Collaboration Italia and of the FAND, published the *Linee-guida per la prevenzione cardiovascolare nel paziente diabetico* [Guidelines for Cardiovascular Prevention in Diabetic Patients]; it is currently the only official Italian paper on the topic. (1)

Agreeing with recommendations issued by other guidelines (2-5), the paper stresses the importance of evaluating the global cardiovascular risk (i.e. age, sex, family history of coronary heart disease or sudden death, physical exercise, smoking, body weight and distribution of body fat, duration of the diabetic disease, glycemic control, blood pressure, microalbuminuria, plasma lipids) and of using algorithms to perform risk stratification. The paper – which says that risk factors and related cut-off rates are defined by a consensus conference and are thus not backed by specific data – highlights that the algorithms available are not optimal because they consider diabetes a dichotomous variable with no concern for the duration of the disease and the degree of glycemic control and, they have been designed for populations with a higher cardiovascular risk than Italians. New Zealand guidelines make similar considerations by saying that Framingham's algorithm cannot be applied to all ethnic groups, to diabetics with disease duration > 10 years and those with HbA_{1c} >8%, to patients with metabolic syndrome and to diabetics with

microalbuminuria. (3)

In early 2004 was presented to the scientific community and published on the website of the National Health Institute the documentation on the Italian cardiovascular and cerebrovascular risk, based on the 17 cohort studies conducted in our country in the '80s (www.cuore.iss.it). This documentation considers the presence/absence of diabetes, irrespective of the durations of the disease and control, despite avoiding an overestimate of the risk related to the ethnic group, is still not the optimal tool in the Italian diabetic population.

Many studies have documented the association between cardiovascular risk and glycemic control. The San Antonio Heart Study highlighted a positive trend between glycemic values and cardiovascular mortality. Subjects belonging to the highest glycemic quartile presented a risk that was 4.7-fold higher than those in the lower quartiles (6). Studies conducted in Finland documented a linear correlation between glycemic control and coronary risk in type 2 diabetics aged 45-74 years. (7-9)

A metanalysis of 10 observational studies conducted over the past two decades, numbering a total of 7,435 subjects with type 2, studied relations between HbA_{1c} and the cardiovascular risk: it surfaced that a 1% increase in HbA_{1c} is associated with RR = 1.8 (95% CI 1.10-1.26). Data is scarce due to a likely publication bias, the few studies conducted and the heterogeneous nature of the studies (10). Results, however, agree with those reported by the UKPDS trial, thus denoting an association between glycemic control and macroangiopathy, though to a lesser degree than was noticed with microangiopathy. Many studies, numbering the Nurses' Health Study, have reported the association between the duration of the disease and the cardiovascular risk. (11)

In 2001 UKPDS researchers formulated an algorithm taking into account both the duration of the disease and the HbA_{1c} level (UKPDS RISK ENGINE http://www.dtv.ox.ac.uk/index.php?maindoc=/riskengine/). New Zealand Guidelines (3) and those issued by the International Diabetes Federation (12), on the basis of the above considerations, deem this algorithm the most appropriate for the diabetic population.

The DAI study applied 3 functions derived from the Framingham Heart Study to a sample of 8,200 diabetics aged 40-74 years with no known vascular disease, attending 201 Italian diabetes clinics in 1998-1999; the trial proved that 65-70% of diabetics examined can be defined as high risk, irrespective of the formula used (13). However, in Italy type 2 diabetics seem to be exposed to a lower cardiovascular risk than diabetics belonging to populations in northern Europe or the United States. The Verona Diabetes Study − conducted on a cohort of 7,168 subjects with type 2 mellitus − reported that the SMRs *(Standardized Mortality Ratios)* of cardiovascular disease and ischemic heart disease were 1.34 and 1.41, respectively (14). Similar results were reported by the Casale Monferrato Study. (15)

Screening Methods for Cardiovascular Diseases in Diabetics

The most effective and efficient diagnostic approach for silent coronary heart disease in diabetics is still widely debated. (16)

In fact, while the accuracy of exercise ECG performed with chest pain is comparable in both diabetics and non diabetics, studies on asymptomatic subjects are still very few (17). Overall data published in literature suggests that 1/3 of asymptomatic diabetics with a high risk has a silent coronary heart disease. Janand-Delenne and coll. applied exercise ECG to evaluate 203 diabetics with no symptoms of angina and a

negative rest ECG. The test was positive in 16% of subjects, while angiography detected a coronary heart disease in 9% of them (16). Bacci and coll. consecutively evaluated 206 patients with either peripheral arteriopathy or at least two risk factors; 19% of them had a positive exercise test. Angiography highlighted a coronary disease in 29%; hence, the positive predictive value of exercise ECG was 79%. (18)

Stress echo is a diagnostic procedure that has proved to be more accurate than exercise ECG in the population at large (19,20). Data concerning the diagnostic value of the test in diabetics is rather scarce. A comparative study of stress echo, exercise ECG and myocardial scintigraphy in 56 asymptomatic diabetics presenting at least three additional risk factors and normal basal ECG documented a 69% positive predictive value for stress echo, 60% for exercise ECG and 75% for myocardial scintigraphy (21). Another group of researchers evaluated 563 diabetics with either known or suspected coronary heart disease who performed stress echo and had a mean 3-year follow-up period. Subjects with pathological stress echo had a higher incidence of cardiac events than subjects with a negative test (2% vs. 0% the first year; 12% vs. 2% the second year; 23% vs. 8% the third year). The ejection fraction at rest and the number of ischemic segments found during exercise provided further prognostic information. (22)

Stress myocardial scintigraphy ensures 88% sensitivity and 74% specificity in detecting coronary heart disease in the population at large and, a similar result has been documented in the diabetic population too. This test is very useful, especially towards risk stratification in high risk asymptomatic diabetics. A study conducted on a cohort of 1,427 asymptomatic diabetics, stratified into high, medium and low risk levels by their scintigraphy result, documented a significant difference in the three groups' yearly mortality rate (5.9% vs. 5% vs. 3.6%) (23). Another trial conducted on 180 asymptomatic subjects who underwent myocardial scintigraphy with pharmacological stress found that cardiac events (i.e. death and acute myocardial infarction) occurred in 3% of subjects who had no perfusion defects, in 10% of those with a perfusion defect in only one site and, in 31% of those with more extensive perfusion defects. (24)

The ADA (25) proposes performing ischemia inducing tests on diabetics with:

1) either typical or atypical cardiac symptoms;

2) resting ECG that suggests ischemia or infarction;

3) either peripheral or carotid arteriopathy;

4) sedentary life and age >35 years, who plan on commencing intensive physical exercise;

5) presence of 2 or more risk factors (i.e. hyperlipidemia, arterial hypertension, smoking, family history of a cardiovascular disease at an early age, either micro or macroalbuminuria).

ADA proposals basically agree with Italian guidelines in stressing that the usefulness of diagnostic investigations in high risk diabetic patients is based on the consensus of experts; in fact, few studies have evaluated the accuracy of criteria proposed by ADA guidelines in detecting subjects with silent ischemia. (26,27)

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B. DIABETIC NEPHROPATHY - SCREENING AND MANAGEMENT

RECOMMENDATIONS

General Recommendations

> Optimise glycemic control to reduce the risk and/or slow down the progress of nephropathy. (**I, A**)

> Optimise pressure control to reduce the risk and/or slow down the progress of nephropathy. (**I, A**)

> In patients with overt nephropathy, protein intake should be reduced to the recommended diet ration (0.8 /kg/day). A further reduction (0.6-0.8 g/kg/day) can be useful in slowing down the drop in GFR in patients presenting the disease progress, despite optimised glycemic and pressure control and the use of ACE-inhibitors and/or ARBs. (**III, B**)

> Correct any lipid profile alterations to both slow down the progress of nephropathy and reduce the associated cardiovascular risk. (**I, B**)

Screening and Stadiation

> Yearly test microalbuminuria in type 1 diabetics with a disease duration >5 years and in all type 2 diabetics, starting from the time of diagnosis and during pregnancy. (**VI, B**)

> Serum creatinine should be yearly tested to estimate glomerular filtration rate in all adult diabetics, irrespective of the level of albumin excretion with urine. Serum creatinine alone should not be deemed as a kidney function marker; it must rather be used to estimate the glomerular filtration rate. (**VI, B**)

Treatment

> ACE-inhibitors or ARBs should be recommended in the management of both microalbuminuria and macroalbuminuria, except during pregnancy. (**I, A**)

> Despite the lack of appropriate direct comparisons between ACE-inhibitors and ARBs, some trials support each of the following statements:

- ACE-inhibitors slow down the progress of nephropathy in patients with type 1, hypertension and any level of albuminuria. (**I, A**)
- ACE-inhibitors reduce the risk of microalbuminuria developing in patients with type 2, hypertension and normal albuminuria. (**I, A**)
- ACE-inhibitors reduce the cardiovascular risk in patients with type 2, normal blood pressure and microalbuminuria. (**I, A**)
- ACE-inhibitors and ARBs slow down the progress to macroalbuminuria in patients with type 2, hypertension and microalbuminuria. (**I, A**)
- ARBs slow down the progress of nephropathy in patients with type 2, hypertension, macroalbuminuria and renal failure (serum creatinine >1.5 mg/dl). (**I, A**)
- If one of the two drug categories is not tolerated, it should be replaced with the other. (**VI, B**)

> Dihydropiridine calcium channel blockers (DCCB) as frontline treatment are not more effective than the placebo in slowing down the progress of nephropathy. Their use in nephropathy should be limited to the role of additional therapy to further reduce blood pressure in patients already treated with ACE-inhibitors or ARBs. (**III, B**)

> The use of non-dihydropyridine calcium channel blockers (NDCCB), beta blockers and diuretics can be considered to control blood pressure in patients who do not tolerate ACE-inhibitors and/or ARBs. (**VI, B**)

> When ACE-inhibitors, ARBs and diuretics are administered to patients with impaired renal function, we recommend testing renal function and serum potassium either 1-2 weeks after the treatment's start or after an increase in dosage and then at yearly or shorter intervals. (**VI, B**)

> To evaluate both response to treatment and the progress of the disease, we recommend testing microalbuminuria/ proteinuria at six-monthly intervals. (**VI, B**)

> Consider a consultation with a doctor expert in diabetic nephropathy when GFR is <60 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ or if there is any difficulty in managing either hypertension or hyperkalemia. A nephrology consultation is required when GFR is <30 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$. (**III, B**)

COMMENT

Introduction

Diabetic nephropathy appears in 20-40% of diabetic patients and, it is the main single cause of end stage renal disease (ESRD).

Microalbuminuria (see Table 13) is deemed the earliest stage of diabetic nephropathy in type 1 and a marker for the development of nephropathy in type 2; moreover, microalbuminuria is a known marker of an increased risk of cardiovascular disease (1,2). Patients with microalbuminuria who progress towards macroalbuminuria (≥300 mg/24 hours) have a high probability of developing end stage chronic renal failure over the years (3,4). However, various therapeutic interventions have proved effective in both reducing and slowing down the progress of the renal disease. The leading Italian epidemiological studies (Casale Monferrato, DAI, QuED, UDNH: total number >26,000 patients) conducted on subjects with type 2 report a 20-32% prevalence of microalbuminuria and 7.4-17.6% of macroalbuminuria.

Diabetics undergoing dialysis are about 12% of those under treatment; the percentage is growing though it is clearly less than the one recorded in the United States. (5)

Table 13. Abnormal albumin excretion (ADA 2007)

CATEGORY	SPOT COLLECTION (µg/mg creatinine)	MINUTE COLLECTION µg/min	24-HOUR COLLECTION mg/24 hours
Normal albuminuria	<30	<20	<30
Microalbuminuria	30-299	20-199	30-299
Macroalbuminuria	≥300	≥200	≥300

Glycemic Control

All guidelines agree on optimising glycemic control. Extensive randomised prospective studies have, in fact, proved that intensive diabetes care focused on achieving glycemic values that are very close to normal blood glucose concentrations can delay the onset of microalbuminuria and progress from the condition of microalbuminuria to macroalbuminuria in patients with type 1 (6-8) and type 2 (9-11). Besides, SID guidelines stress that though the effect of metabolic control on the progress of end-stage nephropathy has been repeatedly described in type 1 (12), it is not documented by controlled prospective studies; in the same manner, only observational studies show the importance of metabolic control in reducing GFR in type 2. (13)

Pressure Control

The UKPDS has proved that blood pressure control can slow down the evolution of diabetic nephropathy (14). Most guidelines recommend pressure goals <130/80 mmHg. Moreover, both SID and Australian guidelines recommend a therapeutic target <125/75 mmHg for patients with proteinuria >1g/day, on the basis of MDRD study results *(Modification of Diet in Renal Disease)*. (15)

Extensive randomised prospective studies centred on type 1 diabetics have proved that reaching systolic pressure levels <140 mmHg by administering treatment with ACE-inhibitors provides a selective advantage, compared to other categories of antihypertensive drugs, delays progress from microalbuminuria to macroalbuminuria and, slows down the drop in the GFR in patients with macroalbuminuria (16-18). In patients with type 2, ARBs have also proved effective in reducing progress from microalbuminuria to macroalbuminuria and, finally, to end stage chronic renal failure (19-21). The use of these drugs is further backed by the fact that ACE-inhibitors have proved effective in reducing the incidence of major cardiovascular events (i.e. myocardial infarction, stroke, death) in patients with microalbuminuria (22). Moreover, the BENEDICT study recently proved that the ACE-inhibitor tralandopril reduces the incidence of microalbuminuria in hypertensive type 2 diabetics with normal albuminuria, while verapamil effect is comparable that of traditional antihypertensive treatment (23). This result is validated by the recent metanalysis conducted by Strippoli and coll. (24)

Canadian and SID guidelines recommend the need to monitor both K+ and creatinine either 1-2 weeks after the beginning of treatment or after an increase in dosage and, then at yearly intervals in patients treated with ACE-inhibitors or ARBs. Treatment must be commenced with caution if creatinine is >3 mg/dl and, discontinued if the increase in creatinine after the treatment's commencement is 30% higher. ACE-inhibitors and ARBs must be used at the highest dose tolerated by the patient.

The use of DCCB did not prove more effective than the placebo in slowing down the progress of nephropathy; hence, it should be limited to the role of additional therapy to reduce pressure in patients already treated with either ACE-inhibitors or ARBs. Patients with albuminuria/nephropathy and intolerance towards ACE-inhibitors/ARB can be treated with non-dihydropyridine calcium channel blockers (NDCCB), beta-blockers or diuretics to control blood pressure. (25-27)

The Italian EURODIAB study data reveals a clear rise in the number of subjects presenting macroalbuminuria and satisfactory pressure control during the follow-up period (44%) (1997-1999), compared to the basal study (12%) (1989-1990), thus indicating a quality improvement in care provided to

type 1 diabetics (28). However, screening for microalbuminuria was yearly performed only by 68% of diabetics interviewed during the Quadri study. Moreover, in a small study conducted on type 2 diabetics attending a Local Health Authority (ASL) in Turin, only 33% of subjects underwent screening and 73% of patients with microalbuminuria were treated with neither ACE-inhibitors nor ARB. (29)

Multifactor Treatment

The Steno-2 study has proved that intensive pharmacological and behavioural treatment administered to type 2 diabetics with microalbuminuria to optimise glycemic, pressure and lipid control effectively reduce cardiovascular events and the risk of early stage nephropathy progressing to full-blown nephropathy. (30)

Protein Limitation

Studies conducted on subjects with various stages of nephropathy have revealed that low protein intake can have beneficial effects in patients, whose nephropathy seems to progress despite optimal glycemic and pressure control, and the use of ACE-inhibitors and/or ARBs (31). SID guidelines, which focus especially on the national framework, stress that, considering our diet habits, a daily intake of 0.8 g/kg is in practice normal or only mildly reduced, though it is significantly less than the usual intake in Great Britain.

Screening

Screening recommendations, which issue from either clinical experience or the consensus of experts, are very similar in the various guidelines. Screening for microalbuminuria must first envisage a standard urine test; if protein is detected (positive dipstick), a quantitative evaluation of proteinuria and an estimate of glomerular filtration are required, while a negative dipstick requires a microalbuminuria assay.

Screening for microalbuminuria can be performed in three ways: 1) measurement of the albumin/creatinine ratio (A/C) in a random, spot collection (preferred method); 2) 24-hour urine collection for creatinine testing to also evaluate creatinine clearance; 3) timed urine collection (i.e. either in 4 hours or during the night).

Urinalysis (of either occasional or preferably morning urine) to test the A/C ratio is an appropriate screening mode that is recommended by most scientific authorities (32-33). Only albumin testing without the concurrent creatininuria test is, instead, less costly, but it can produce false positive and negative results due to possible variations in urine concentration; hence, it is not recommended. Though A/C ratio testing has been accepted both as a screening and confirmation tool, testing 24-hour timed urine is often deemed a more reliable confirmation.

Screening for microalbuminuria is yearly recommended in type 1 diabetics with disease duration >5 years and, in all type 2 diabetics from the time of diagnosis and during pregnancy. In fact, microalbuminuria without urinary infections is a strong predictive index of eclampsia in pregnancies complicated by diabetes. A subject can only be deemed microalbuminuric if high values are found in at least two of the three tests performed over a 6-month period. Moreover, Canadian guidelines list a set of conditions (Table 13) suggesting the presence of non-diabetic nephropathy and, recommending a nephrological consultation for further investigations.

Results published in *Quality Indicators of Diabetes Care in Italy* drafted by the AMD report that the percentage of diabetics, whose renal function is monitored, is 48.1% of type 2 diabetics and 58.6% of type 1 diabetics.

Staging / Monitoring

Most experts agree in recommending a six-monthly follow-up of micro/macroalbuminuria both to evaluate response to treatment and to monitor the progress of the disease. It is also deemed that restoring microalbuminuria levels to near normal values can improve renal and cardiovascular prognosis, though this theory has yet to be formally evaluated in prospective studies.

The variable albumin excretion rate (AER) requires two or three out of range test results over a 3-6 month period, before a patient can be deemed to have exceeded a certain diagnostic threshold (Table 13). The fact that extreme physical exercise during the 24 hours prior to the test, infections, fever, heart failure, acute hyperglycaemia and evident hypertension can falsely raise AER values above basal levels, must also be taken into account.

Both AER and renal function have been used to stage diabetic nephropathy. Mogensen's staging method is primarily based on the AER, while the National Kidney Foundation's recent method is mainly based on estimated GFR levels (34) (Table 15). The ADA document especially stresses the importance of estimating the glomerular filtration rate in all adults with diabetes, irrespective of the AER level.

Table 14. Alterations suggesting non diabetes-related renal disease in diabetic patients

Absence of retinopathy or neuropathy.
Persistent microscopic or macroscopic hematuria.
Signs and symptoms of a systemic disease.
Rapid increase in creatininemia.
High levels of creatininemia with either scarce or no proteinuria.
Family history of non diabetic renal disease (e.g. Alport syndrome, polycystic kidney).
Short duration of diabetes.

Table 15. The stages of chronic renal disease

STAGE	DESCRIPTION	GFR (ml/min in 1.73 m^2)
1	Renal damage* with normal or increased GFR	≥90
2	Renal damage* with slightly reduced GFR	60-89
3	Moderate GFR reduction	30-59
4	Severe GFR reduction	15-29
5	End stage renal failure	<15 or dialysis

* Renal damage is defined by the presence of abnormal features in urinary sediment, blood chemistry, anatomopathological or diagnostic investigations.

This recommendation is based on certain studies, which have proved that a considerable percentage of diabetic adults present a GFR reduction without an AER increase (35,36); it is designed to prevent screening only for AER from leading to the failure to detect a considerable number of CRF cases (34). However, the Casale Monferrato Study's prospective analysis conducted on a cohort population of type 2 diabetics highlighted the higher predictive importance of AER than of estimated GFR concerning mortality. (37)

Serum creatinine alone should not be used as a measure of renal function; it should rather be the reference

to estimate glomerular filtration volume with either Cockcroft-Gault's formula or the MDRD study's equation modified by Levey (38). The estimated GFR can be easily calculated by visiting the web page: www.kidney.org/professionals/KDOQI/gfr_calculator.cfm.

A consultation with an expert in diabetic nephropathy must be considered when GFR is <60 ml·min^{-1}·1.73 m^{-2} or in case of management issues for hypertension and hyperkalemia. A nephrological consultation is required when GFR is <30 ml·min^{-1}·1.73 m^{-2}; in these patients an early consultation has, in fact, proved effective in reducing costs, improving the quality of care and delaying the commencement of dialysis treatment. (39-40)

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C. DIABETIC RETINOPATHY - SCREENING AND MANAGEMENT

RECOMMENDATIONS

General Recommendations

> Optimising glycemic control reduces the risk and progress of retinopathy. (**I, A**)

> Optimising pressure control reduces the risk and progress of retinopathy. (**I, A**)

> Treatment with acetylsalicylic acid neither prevents diabetic retinopathy nor does it increase the risk of retinal bleeding. (**I, A**)

Screening

> Adults with type 1 should first have their fundus oculi examined with pupil dilation by either an ophthalmologist or a trained health-care professional within 3-5 years after the onset of diabetes. (**III, B**)

> Patients with type 2 should first have their fundus oculi examined with pupil dilation by either an ophthalmologist or a trained health-care professional soon after the diagnosis of diabetes. (**III, B**)

> Subsequent testing in both types of diabetes should be repeated at least every two years by either a specialised ophthalmologist or a trained health-care professional expert in diagnosing and managing diabetic retinopathy. Less frequent testing can be considered if the ophthalmologist recommends it. The examination must be performed more frequently, if retinopathy progresses. (**III, B**)

> Diabetic women who plan on starting a pregnancy should undergo a complete eye examination and be informed about the risk of diabetic retinopathy developing and progressing. (**III, B**)

> Pregnant diabetic women should undergo a complete examination when pregnancy is confirmed and be monitored throughout pregnancy (at least every 3 months until delivery, failing eye lesions; when the ophthalmologist diagnoses retinopathy of any level, according to ophthalmologist judgement) and during the first year after delivery. (**III, B**)

> Screening is not recommended in women with gestational diabetes mellitus because they do not have a high risk of developing diabetic retinopathy. (**III, D**)

> Diabetic retinopathy can be screened with one or more of the following methods: ophthalmoscopy (direct and/or indirect) with dilated pupils and either colour or black and white photographs of the fundus oculi. (**V, C**)

Diagnosis

> Retinal fluorangiography is not recommended as a diagnostic tool for diabetic retinopathy. (**VI, D**)

> Retinal fluorangiography must be performed in view of laser treatment in all cases, whose lesions require a pathogenetic interpretation that cannot be provided on the basis of the clinical examination. Specifically:

- pathogenetic interpretation of macular oedema;
- detection of suspicious neovascularisations;
- exact definition of ischemic retinal areas;
- study of the macula in cases of clinically unjustified impaired vision. (**VI, B**)

> Refer to the ophthalmologist in case of:

**** sudden loss of vision;

**** evidence of retinal detachment;

*** vessel neoformation;

*** preretinal or retinal bleeding;

*** presence of rubeosis iridis;

*** unexplained deterioration in visual acuity;

** hard exudate within one diameter of the foveal disk;

** macular edema;

** unexplained retinal findings;

** early stage proliferative or worsening retinopathy. (**VI, B**)

**** Refer immediately (within 1 day);

*** Refer urgently (1 week);

** Refer within 4 weeks.

Treatment

> Laser treatment reduces the risk of impaired vision in patients with high risk retinal lesions. (**I, A**)

> Promptly refer patients with any level of macular oedema, severe non proliferative diabetic retinopathy (NPDR) or any proliferative diabetic retinopathy (PDR) to an ophthalmologist who is knowledgeable and experienced in the management and treatment of diabetic retinopathy. (**I, A**)

> Patients with macular oedema, severe NPDR or PDR require a prompt consultation with an ophthalmologist who is knowledgeable and experienced in the management and treatment of diabetic retinopathy because laser treatment, especially at this stage, is associated with either a 50% reduction in the risk of acute loss of sight or the need for vitrectomy, especially in patients with type 2 mellitus and severe NPDR. (**VI, B**)

> Patients with serious sight impairment should be referred to rehabilitation. (**V, B**)

Follow-up

> Testing frequency must be: every two years, if there is no diabetic retinopathy; yearly, if there is mild to moderate background diabetic retinopathy (**VI, B**); earlier (3-6 months), if either new lesions are detected or if lesions have worsened, compared to the last follow up, if there is exudate within one diameter of the foveal disk, if the patient has a high risk of progress (rapid improvement in glycemic control, presence of arterial hypertension or renal complications). (**VI, B**)

COMMENT

Diabetic retinopathy is a highly specific vascular complication of both type 1 and type 2. Its prevalence is closely related to the duration of diabetes and can be deemed as the most frequent cause of new cases of blindness in adults aged 20-74 years, from an overall perspective (1-3). PDR has a 23% prevalence in patients with type 1, 14% in patients with type 2 treated with insulin and, 3% in patients with type 2 that is not treated with insulin (4), while macular oedema occurs in 11%, 15% and 4% of the above mentioned groups, respectively (5). The latest case studies conducted on cohorts of patients attending Italian Diabetes Units highlight a 42% prevalence of retinopathy with more than one third numbering either proliferating or laser treated forms. Blindness has about 0.5% prevalence. The incidence of retinopathy in the Italian diabetic population is 5-7/100 patients a year, with higher rates in type 1 and type 2 treated with insulin. To judge by the records of the *Unione Italiana Ciechi* [Italian Union of the Blind], diabetic retinopathy ranks as the first cause of either poor sight or legal blindness at working age in Italy. The incidence of diabetes-

related blindness is 2-3 cases/100,000 inhabitants/year aged <70 years, and 6-12 cases/100,000 inhabitants/year aged >70 years (6). It must be reported that the examination of the fundus oculi has yet to be added to the process indicators envisaged in the AMD's data file, due to the lack of standardisation in the various centres' mode of recording the related information.

Scientific evidence available today has proved that diabetic retinopathy screening and management programmes can drastically reduce diabetes-related blindness. Countries where these programmes have already been implemented have achieved a remarkable reduction in the incidence of diabetes-related blindness, besides a considerable drop in social and healthcare expenditure (7-10). In addition to glycaemia (11-12), many other factors seem to increase the risk of diabetic retinopathy. The presence of nephropathy is associated with retinopathy. Arterial hypertension is a well defined risk factor for the development of macular oedema and, it is associated with the presence of PDR (13-14). Many case-control studies and controlled prospective studies have reported that pregnancy in type 1 can worsen retinopathy. Retinopathy can worsen transiently during pregnancy and the first year after delivery; laser photocoagulation can minimise this risk. (15-16)

One of the main reasons for the need to subject patients to screening for diabetic retinopathy is the ascertained efficacy of laser photocoagulation in preventing blindness. Two extensive studies sponsored by the National Institute of Health – the Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS) – reveal the important therapeutic advantage of photocoagulation.

The DRS evaluated whether (panretinal) photocoagulation could reduce the risk of impaired sight in PDR. Acute sight impairment (e.g. visual whetting ≤ 5/200) could be noticed in 15.9% of untreated eyes, vs. the 6.4% of treated ones. Beneficial effects were more extensive among patients, whose basal evaluations detected certain characteristics (especially neovascularisation in the foveal disk or vitreous bleeding with retinal neovascularisation). 26% of eyes belonging to the control group and presenting high risk retinal lesions progressed towards a severe loss of sight, compared to the 11% of treated ones. Considering the risk of a moderate loss of visual whetting and of the visual field's contraction resulting from panretinal laser surgery, this therapy has been mainly recommended for eyes that either present or are near high risk features.

However, panretinal photocoagulation is not recommended in NPDR, if a thorough follow-up is performed. When, instead, retinopathy is more acute, systemic photocoagulation should be considered without delay if the eye has reached the high risk proliferation stage. In patients, whose retinopathy sets in at a later age and, who have acute NPDR or low risk PDR, the risk of vitrectomy and a serious loss of sight drops by about 50% when laser photocoagulation is practiced. The ETDRS has established the beneficial effect of focal laser photocoagulation in eyes with macular oedema, especially those with clinically important macular oedema. Two years after laser surgery, 20% of these patients' untreated eyes had doubled the visual angle (e.g. from 20/50 to 20/100), compared to the 8% of treated eyes. Laser photocoagulation effectively reduced the risk of a further loss of sight both in the DRS and the ETDRS studies, but it was generally ineffective in restoring lost visual whetting. This preventive effect, associated with the fact that patients with RDP or macular oedema can be asymptomatic, strongly backs the need for a diabetic retinopathy screening programme. NICE and SID guidelines on diabetic retinopathy also provide indications and recommended times for ophthalmology consultations. (17,18)

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D. DIABETIC NEUROPATHY - SCREENING AND MANAGEMENT

R E C O M M E N D A T I O N S

General recommendations

> Optimising glycemic control reduces the risk of the onset and progress of neuropathy. (**I, A**)

> Screening for neuropathy must be performed on all type 2 diabetics at the time of diagnosis and on type 1 diabetics after 5 years of disease duration. Subsequent testing must be performed at yearly intervals. (**VI, B**)

Distal Symmetrical Polyneuropathy

> Screening for chronic distal symmetrical sensitive and motor polyneuropathy must be implemented with simple clinical tests, such as pressure sensitivity testing with the 10 g single filament and vibratory sensibility testing on the big toe with a tuning fork, preferably performed within a structured score- based system. (**I, A**)

> Screening for distal symmetrical polyneuropathy does not require electrophysiological testing, which is instead useful towards a differential diagnosis, when clinical characteristics are atypical. (**VI, B**)

> If distal symmetrical polyneuropathy is diagnosed, the diabetic should be inserted in a specific educational programme to prevent ulceration and amputation of diabetic foot. (**III, B**)

Vegetative Neuropathy

> Screening for vegetative neuropathy must be performed with a detailed case history integrated by cardiovascular reflex testing, since symptoms are non specific and do not allow a diagnosis of vegetative dysfunction. (**VI, B**)

> Cardiovascular tests are very useful when symptoms suggest vegetative dysfunction, when there is a high cardiovascular risk or a risk of microangiopathic complications (diabetic retinopathy or nephropathy), before major surgery, when planning a physical exercise programme and, in diabetics with poor glycemic control. (**VI, B**)

Pharmacological Treatment

> Pain generated by peripheral neuropathy can be relieved by anticonvulsants and serotoninergic, noradrenergic and tricyclic antidepressants (first choice drugs) and opiates (second choice drugs). (**I, A**)

COMMENT

Distal Symmetrical Polyneuropathy (DPN)

DPN is a common disease that counts about 20-30% prevalence in diabetic adults. An Italian multicentre study conducted on a total of 8,757 type 2 diabetics and involving 109 Diabetes Units reported a 32.3% prevalence of peripheral neuropathy, explaining that the disease grows severe with age and the duration of diabetes (1). A study conducted in Piedmont in a cohort of type 1 diabetics found a 28.5% prevalence of polyneuropathy. (2)

Table 16. Diabetic Neuropathy Index (DNI) (4)

	SCORE (PER SIDE)
Inspection of the foot: • deformity • dry skin • callosity • infection • ulcers	Normal = 0 Altered = 1 (if ulcers are present: +1)
Achilles tendon reflex	Present = 0 Strengthened = 0.5 Absent = 1
Vibratory sensibility in the big toe	Present = 0 Reduced = 0.5 Absent = 1

Positive test: >2 points.

Risk factors number metabolic control, arterial pressure, plasma lipids, diabetes duration, BMI, cigarette smoking and alcohol consumption (3). Many classifications have been proposed for DPN in recent years; one of the most frequently adopted ones distinguishes generalised symmetrical polyneuropathy − divided

into acute sensitive, chronic sensitive, motor and vegetative − and focal and multifocal neuropathies (i.e. cranial, truncal, focal in the limbs and proximal motor neuropathy). (3)

DPN screening must be performed with simple clinical tests, such as pressure sensitivity testing with a 10 g single filament and vibratory sensibility testing on the big toe with a tuning fork, preferably within a structured score-based system like the Diabetic Neuropathy Index (Table 16) (4). The DPN diagnosis can be formulated with an accurate clinical test that must be yearly repeated to evaluate peripheral sensitivity (i.e. pain, heat, pressure, vibration), Achilles' bone-tendon reflexes and muscular strength. The combination of many tests ensures 87% sensitivity. Reduced perception of both tactile pressure (confirmed by a 10 g single filament) and of vibratory sensibility are the most sensitive and specific tests for the risk of foot ulcers. (5-7)

Other forms of neuropathy − such as chronic inflammatory demyelinising polyneuropathy (CIDP), the lack of vitamin B12, hypothyroidism and uraemia − must be ruled out before diagnosing DPN. The observation of clinical signs, vitamin B12, creatinine plasma assay and screening of the thyroid function are useful to this end. Distal sensitivity deficiency − either with or without typical neuropathic symptoms − are highly suggestive of DPN; a neurological consultation and the performance of electrophysiological tests are recommended in suspicious cases. (3)

DCCT and UKPDS trials have proved that the first step in DPN treatment must be achieving stable and optimal glycemic control.

Pharmacological treatment must be prescribed for painful neuropathy (3). Various drugs, whose efficacy has been confirmed by controlled randomised trials, are currently available; however, none of them is specifically authorised for DPN pain treatment, except for duloxetine and pregabalin (8-10). Management of painful neuropathy is often a problem due to both the irregular efficacy of available drugs and frequent adverse events; hence the need for drug titration and monitoring to ensure the treatment's efficacy and safety. A change from one drug category to another is required in case of either a lack of efficacy or adverse events.

Tricyclic antidepressants number among drugs that have been used the longest: the use of amitriptiline and imipramine has been validated by many controlled and randomised trials (8). Though they are inexpensive and generally effective in treating neuropathic pain, in many cases side effects – especially the anticholinergic ones (dry mouth, urine retention, etc.) – limit their use. Effects on the central nervous system (asthenia), cardiac effects (arrhythmias) and standing hypotension are also common. Hence, the recommendation to start treatment with low drug dosages and increase the dose gradually (mean dose= 75-100 mg/day).

Anticonvulsants are another important group of therapeutic drugs. Gabapentin, whose higher efficacy than the placebo and same or higher efficacy than amitriptiline in relieving neuropathic pain was proved by two controlled studies on DPN; it is one of the most frequently administered drugs in recent years (11). The efficacy of pregabalin for peripheral neuropathic pain has been evaluated by various randomised double blind studies in parallel groups compared against the placebo and, the drug has been recently marketed in our country to treat neuropathic pain. (10)

Opiates (tramadol, oxycodone) can be deemed as second choice drugs. (3,11)

Vegetative Neuropathy (DAN)

DAN is a frequent complication of diabetes mellitus and it is associated with an increased mortality rate (12). It is estimated that it concerns about 20% of patients, but its prevalence is 17-21% in type 1 and 16-22% in type 2, depending on the diagnostic methods used and population study characteristics. Age,

duration of the disease, type of diabetes, metabolic control and cardiovascular risk factors are associated with the onset of the complication. (12,13)

A clinical prospective cohort study conducted in 2000 evaluated the link between the prolonged QT interval and mortality in type 1 diabetics. A 5-year follow-up reported that patients presenting a major risk of death either had a prolonged QTc or suffered from vegetative neuropathy (14). These important observations stress the need for greater focus on screening for DAN as it could reduce the cardiovascular risk and the risk of mortality in diabetics presenting this complication.

The clinical signs of DAN are many and can concern all systems. Heart and circulation systems number tachycardia at rest, intolerance to physical exercise, standing hypotension, silent cardiac ischemia, cardiac denervation syndrome and sudden death. Gastrointestinal symptoms number dysphagia, gastroparesis, constipation, diarrhoea, faecal and urogenital incontinence, bladder dysfunction and erectile dysfunction. Moreover, both the function of sweat glands and the ability to recognise signs of hypoglycaemia can be compromised till the onset of an anaemic picture, subsequent to inappropriate erythropoietin secretion.

Screening can be performed with a simple reproducible panel of cardiovascular tests proposed by Ewing in the '70s. These tests are based on the change in either heart rate or arterial pressure; while the former mainly explore vagal cardiac function, the test of standing hypotension evaluates the sympathetic function (15). Heart rate tests that are most frequently administered number *deep breathing* (a series of deep expirations and inspirations), Valsalva's manoeuvre (forced expiration against resistance) and, *lying-to-standing* (rising and standing up after lying down on the bed). To be performed, these tests only require a sphygmomanometer and electrocardiograph; software has also been designed to perform and read the tests. The physician must keep in mind that cardiovascular tests are influenced by many confusing factors, especially adequate stimulus and age; hence, the need to refer all values to age, besides being cautious when interpreting results in conditions, such as respiratory failure, heart failure, drug abuse (i.e. alphalytics and psychoactive drugs).

Three tests, the so-called concise panel of Ewing's tests, can be used for outpatients' screening (Table 17) (15). The standing hypotension test, two heart rate tests (*deep breathing*, Valsalva's manoeuvre and *lying-to-standing*) are recommended.

Table 17. Test for vegetative neuropathy (15)

TEST	PERFORMANCE MODE	INTERPRETING THE TEST
Standing hypotension	With the patient supine, measure blood pressure in the left arm till it stabilises. Then invite the patient to stand up quickly (within 3 seconds) and measure blood pressure at 30-60-90-120 seconds.	There is standing hypotension, if a systolic pressure drop of at least 30 mmHg is recorded in two consecutive checks; borderline values are 20-29 mmHg.
Deep breathing	In a clinostatic position, the patient breaths 6 respiratory acts a minute, 5 seconds to inhale and 5 seconds to exhale. Calculate the mean differences between maximum inspiration frequency and minimum expiration frequency, or, calculate the ratio between the average of the longest RR intervals during expiration and the average of the shortest RR intervals during inspiration.	Normal: >15 beats/minute Borderline:11-15 beats/minute Pathological:10 beats/minute

Lying to standing	After 5 minutes of rest in a supine position, the patient stands up suddenly. Calculate the ratio between the longest RR interval around the 30th beat and the shortest RR interval around the 15th beat (30:15 ratio).	Normal: >1.03 Borderline: 1.01-1.03 Pathological: ≤1.0
Valsalva's manoeuvre	Invite the patient to blow into a manometer with the glottis open and, to maintain a pressure of 40 mmHg for 15 seconds. At the end of this time, he will return to normal breathing. The Valsalva ratio is calculated from the ratio between the longest RR interval after expiration and the shortest one during expiration.	Normal: >1.2 Borderline: 1.11-1,2 Pathological: ≤1.1

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E. ERECTILE DYSFUNCTION

RECOMMENDATIONS

> Erectile dysfunction (ED) is an endothelial dysfunction equivalent; hence, it implies a strong risk of atherosclerotic complications. This involves the need for cardiovascular diagnostic investigations. (**I, A**)

> The presence of ED in type 2 diabetics must be sought at the time of diagnosis and, evaluated again once a year. ED must be sought in type 1 diabetics with a long disease duration (>10 years) or with chronic complications, especially neuropathy and vasculopathy. (**VI, B**)

> Screening, which must be periodically performed, simply consists in asking: "Over the past six months have you noticed any significant changes during sexual intercourse?" (**VI, B**)

> The positive answer requires the implementation of a diagnostic pathway comprising:
– the International Index of Erectile Function (IIEF-15* o IIEF-5);
– case history;
– physical examination;
– laboratory tests (testosterone, prolactin, TSH, PSA);
– an evaluation of vegetative cardiovascular tests can be useful.
* Depending on the score obtained, the IIEF-15 classifies ED in: severe (<10), moderate (11-16), mild (17-26) and, absent (26-30). (**VI, B**)

> Other tests are not generally required unless surgery is recommended. (**VI, B**)

> Medical treatment recommends the use of PDE-5 inhibitors (sildenafil, vardenafil, tadalafil), taking into account the specific pharmacokinetic characteristics and, especially, the duration of their action (4 hours for sildenafil and vardenafil, over 17 hours for tadalafil). Weight loss, physical exercise and improved glycemic control can be useful. (**VI, B**)

COMMENT

Definition: as established at the NIH Consensus Conference on Impotence, ED is the *"inability of the male to obtain and maintain an adequate erection of the penis to enable satisfactory sexual intercourse."* This inability must be persistent.

ED has a 3-fold prevalence in diabetics, compared to non diabetics. It is often associated with the presence of peripheral neuropathy and/or vasculopathy.

Considering the strong risk of arteriosclerotic complications in subjects with ED, especially if they are under treatment with PDE inhibitors, the cardiovascular risk must be calculated using the algorithm proposed by the Second Princeton Consensus Conference, when required. (3)

The Italian situation has been described with population studies by Parazzini and coll. (4) in the population at large, and by Fedele and coll. (5-7) and De Berardis and coll. (8) in diabetics. In 2,010 men interviewed by 143 general practitioners, Parazzini reports a prevalence of ED in 12.8% of them; the incidence was closely related with age and the presence of risk factors, such as, especially, heart disease, diabetes, hypertension, neuropathy and smoking.

Fedele and coll. (5) found a mean 35.8% prevalence in 9,868 diabetics attending 178 Diabetes Clinics. An analysis based on the type of diabetes (6) highlights a higher prevalence (51%) in 1,383 type 1 diabetics, compared to the one found in the 8,373 type 2 diabetics (37%). Even in diabetics, prevalence closely depends on age, smoking, disease duration and the presence of other chronic complications.

The incidence of ED in diabetics – evaluated in 1,010 subjects with a 2.8-year follow-up (7) – was 68 cases/1000/year.

Hence, it was more than double the incidence reported by the Massachusetts Male Aging Study on the

general population in the United States (2.8%) (9). A multivariate analysis found that significant ED predictors are age, disease duration, nephropathy and hypertension. (9)

A subsequent study coordinated by the Istituto Mario Negri Sud (8) conducted on 1,460 type 2 diabetics confirmed a 34% prevalence of ED, which was more frequently associated with depression and a worse quality of life.

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F. FOOT CARE

RECOMMENDATIONS

Screening and Prevention

> All patients with diabetes mellitus must undergo a complete examination of the foot at least once a year.

> Feet must be examined in high risk patients on every visit. (**VI, B**)

> Risk factors for diabetic foot must be defined at the time of screening. The subsequent follow up can be scheduled to suit the risk and presence of lesions. (**VI, B**)

> All diabetics must be guaranteed an educational programme on the diabetic foot. (**I, A**)

> A diabetic foot care team should include doctors specialised in diabetic foot care, health-care professional qualified in the educational field and trained in diabetic foot care (podiatrist and/or nurses). (**VI, B**)

> The elderly (age >70 years) require special attention, especially if they live alone, if they have a long disease duration and if they have impaired vision and financial problems, since they have a higher risk of foot lesions. (**III, B**)

> Specific healthcare pathways must be organised for the management of diabetic foot in diabetics who are either warded in long stay wards or are following a homecare programme. (**VI, B**)

> Patients with feet at risk of lesions must be prescribed appropriate footwear and orthotic devices that reduce peak plantar pressure. (**II, B**)

Foot examination

> The foot examination should include the evaluation of the case history of past ulcers and amputations, examination, palpation, evaluation of the perception of pressure (with the 10g Semmes- Weinstein monofilament) and of vibration (with the tuning fork 128-Hz or with the biothesiometer). (**I, A**)

> Screening for peripheral arteriopathy should include a history for claudicatio, assessment of the pedal pulses and measurement of the ankle- brachial index (ABI). (**III, B**)

Treatment

> High risk diabetics, especially those with either past or present ulcers, require a multidisciplinary approach. (**I, A**)

> Healthcare for patients with a foot lesion should be organised in three levels: 1st level (screening and diagnosis); 2nd level (medication, minor surgery, off-load neuropathic plantar lesions); 3rd level (distal, surgical and intraluminal revascularization procedures, orthopaedic surgery, both urgent and elective). (**VI, B**)

> Urgent admission to hospital is recommended for patients presenting one of the following clinical pictures:
– critical ischemia;
– acute infection. (**VI, B**)

> Request the consultation of a multidisciplinary team expert in foot care within 24 hours of evidence of either ulcers or a foot infection, to implement the following actions:
– urgently treat acute infections (cellulitis, gangrene, necrotizing fasciitis);
– appropriately manage the wound with debridement, surgical treatment of osteomyelitis, dressing;
– start systemic antibiotic therapy (often long term) for cellulitis or bone infections;
– off-load lesions;
– study and manage arterial failure;
– request radiological investigations (both conventional and MRI imaging), bone biopsy in case of suspected osteomyelitis;
– optimise glycemic control. (**VI, B**)

> Patients with vascular disease and ulcers must be referred to distal, surgical and intraluminal revascularization procedures, both urgent and elective. (**III, B**)

> For adequate pressure relief the use of a plaster or fibreglass off- loading cast is recommended in the management of neuropathic plantar ulcers without ischemia (TcPO2 >30 mmHg). (**II, B**)

> During the acute phase of Charcot foot, apply a stiff orthotic device and off-load the foot for 3-6 months to avoid deformity while awaiting recovery. (**VI, B**)

> Do not resort to major amputation unless a detailed vascular evaluation has been performed and one or more of the following conditions is present:
– ischemic rest pain that cannot be managed with analgesics or revascularization;
– life-threatening infection that cannot be treated otherwise;
– a non-healing ulcer that does not heal and causes a higher burden than an amputation. (**VI, B**)

> Systemic hyperbaric oxygen therapy is recommended to save the limb in the management of acute infections. (**III, C**)

> VAC (vacuum-assisted closure) therapy is recommended in the management of non vascular diabetic ulcers. (**II, B**)

> Autologous cultured grafts reduce the healing time of neuropathic ulcers, especially when they are located on the dorsum of the foot. (**II, B**)

> The prescription of orthotic devices (i.e. appropriate footwear and custom- made insoles) is recommended to prevent relapses in patients when ulcer has healed. (**VI, B**)

Table 18. Risk levels for the onset of diabetic foot

Not at risk	Preserved sensitivity with no signs of either peripheral vasculopathy or other risk factors.
At risk	Presence of neuropathy or other individual risk factors.
High risk	Reduced foot sensitivity and deformity or evidence of peripheral vasculopathy. Past ulcers or amputations.
Ulcerated foot	Presence of foot ulcers.

Table 19. Risk-based management of patients with diabetic foot

Not at risk	Agree on a management programme that includes education on foot care with each patient.
At risk	Schedule regular visits, about every 6 months, with a team specialised in diabetic foot care. On each visit: – examine both feet; guarantee health aids for foot care; – examine footwear; provide appropriate recommendations; – strengthen education on foot care.
High risk	Organise frequent visits every 3-6 months with a team specialised in diabetic foot care. On each visit: – examine both feet; guarantee health aids for foot care; – examine footwear; provide appropriate recommendations, special insoles and orthopaedic footwear, if required; – consider the need to refer the patient to a vascular specialist for either evaluation or management; – check and strengthen education on foot care.

Table 20. Educational programme on diabetic foot care

1st level	Discuss with each diabetic patient the importance of periodical follow up for foot care, as part of an educational programme on diabetic foot care.
2nd level	Plan with each diabetic patient a foot care programme based on information recorded during yearly visits.
3rd level	Evaluate and provide appropriate education on foot care, taking into account individual requirements and the risk of ulcers and amputation.

COMMENT

Diabetic foot is characterised by the presence of ulceration or deep tissues destruction associated with neurological anomalies and various degrees of peripheral vasculopathy. It is the first cause of non traumatic limb amputation and, it is a frequent reason for diabetic patients' admission to hospital (1). Amputations of lower limbs are almost always preceded by an ulcer (85%), whose prevalence is 0.6-0.8%. It has been estimated that diabetics have a 15% probability of having a foot lesion during their lifetime (1,2). Scientific evidence has proved that screening for diabetic foot can reduce the risk of major amputations (1-3). Microangiopathic and macroangiopathic (peripheral vasculopathy) complications, foot deformations and past ulcers or amputations are risk factors for diabetic foot (1,3-5). The highest incidence has been found in men, in subjects with a longer disease duration and poor metabolic control and, in people with a low social and economical condition. (1)

In 2004 the AMD and the SID's intersociety study group for foot care organised an Italian Consensus, which approved the Italian version of the international consensus paper on diabetic foot, proposing, in many cases, significant changes and improvements to the original version (1). Moreover, to guarantee standardised capillary assistance to all patients with foot lesions, it proposes organising diabetes care facilities based on three levels of complexity (Table 21). The QUED study, which involved 3,564 patients

with type 2 diabetes enrolled by 125 Italian Diabetes Units and by 103 general practitioners, revealed that over 50% of patients had never undergone a foot examination, while 28% reported that they had never been educated to take care of their feet and, 6.8% of subjects had complications in the lower limbs. The study also noticed a strong tendency on the part of doctors to examine the feet of male patients under insulin treatment with foot complications, but not those with either diabetic neuropathy or peripheral vasculopathy (6). The *Annali AMD 2006* highlight that feet are yearly screened only in 46% of patients, though this percentage is partly distorted by incomplete data recordings (7). A case-controlled multicentre study conducted on 348 diabetics with complications in the lower limbs and on 1,050 controls enrolled by 35 Italian Diabetes Units and by 49 general practitioners proved that subjects who had received no educational intervention had a 3-fold risk of developing vasculopathic and neuropathic complications in the lower limbs, compared to those who regularly received information on the topic (8). Concerning amputations, a study conducted in the Campania Region to analyse diagnoses on discharge from hospital reported that diabetes was the cause of 47.1% of major amputations in the lower limbs. Even minor amputations were more frequent in diabetics than in the population at large (38.8% vs. 29.1%; $p<0.001$) and, so was the frequency of reamputations (7.2% vs. 2.9%; $p<0.01$) (9). The prevalence of peripheral vasculopathy is very frequent in diabetics, as found by a multicentre study involving 2,559 type 2 diabetics enrolled from 265 Italian Diabetes Units; it estimated a prevalence of ABI <0.9, which corresponds to 21.1% (10). Claudicatio was diagnosed in 7.3% of patients and cyanosis of the feet was observed in 3.4% of the studied population, while 33.5% had atrophied skin appendages.

This data proves the importance of screening for diabetic foot and peripheral vasculopathy in subjects with type 2 diabetes mellitus.

Table 21. Healthcare levels for diabetic foot

HEALTHCARE LEVEL	ACTIVITIES GUARANTEED BY THE CENTRE	OPERATING TEAM
Level 1	Prevention, educational therapy and diagnosis of diabetic foot.	Diabetologist, dedicated nurse, podiatrist and orthopaedic technician.
Level 2	Prevention, diagnosis and care of acute and chronic diabetic foot: medication, minor surgery and discharge of neuropathic plantar lesions.	Diabetologist, dedicated nurse, podiatrist, orthopaedic technician and, plastic, general or orthopaedic surgeon.
Level 3	Distal, intraluminal and surgical revascularisation procedures, surgery (both urgent and elective).	Diabetologist, dedicated nurse, podiatrist, orthopaedic technician, interventional radiologist, vascular surgeon, plastic surgeon, orthopaedic surgeon.

Neuropathy

Peripheral and vegetative neuropathy are the most frequent complications associated with diabetic foot, because they reduce sensitivity, thus exposing feet to repeated traumas, which are a frequent cause of skin

lesions (1-4,11). Neuropathy concerns about 20-40% of diabetics and, this prevalence increases both with the duration of the disease and when there is poor metabolic control (11). 12.3% of diabetics in the UKPDS study already presented this complication on diagnosis, which concerned one third of patients after a 12-year follow-up. (12)

Skin alterations (i.e. dryness and oedema) resulting from vegetative neuropathy and reduced sensitivity encourage ulceration. Moreover, neuropathy causes changes in plantar balance, with the formation of hyperkeratosis.

Much scientific evidence has revealed that regular inspections of the foot and sensitivity detection with the Semmes-Weinstein monofilament can prevent the onset of foot lesions. (1-5,11,13)

Vasculopathy

Peripheral vasculopathy predisposes patients to the onset of ulcers; it is associated with a 2-4-fold higher incidence of amputations (1,2,14-16). The examination of feet must, hence, also include screening for peripheral vasculopathy based on the patient's case history and on the clinical examination of foot pulses. Patients with neuropathy can present asymptomatic vasculopathy in the lower limbs with the subsequent need to resort to diagnostic investigations. The most frequently adopted method calculates the ankle-brachial pressure index (ABI), which can present a false increase in diabetics due to hardened arteries resulting from calcification of the intima (1,2,4,14). Other non invasive methods, such as colour Doppler ultrasound imaging of the lower limbs and transcutaneous oximetry, are more specific and can better define the extent of vasculopathy. (1,2,4,14)

Invasive techniques, like arteriography, are more precise, but they require special precautions for patients under treatment with metformin, which must be discontinued before the investigation.

Peripheral angioplasty has proved to be the first choice technique in the management of diabetic arteriopathy (17,18); this was confirmed by the BASIL trial that involved 452 patients with acute ischemia in the lower limbs (42% of them were diabetics); the study proved that both bypass surgery and angioplasty obtain the same amputation free survival during a 5.5-year follow-up. (19)

Foot Deformations

Many studies have proved the importance of plantar balance and biomechanics in forming ulcers (1,2,4,15, and 20). The onset of foot deformations, which change plantar pressure, depends on tissue structure alterations produced by various causes, numbering neuropathy and non enzymatic protein glycosilation. Specific clinical signs are listed below.

– An area of hyperkeratosis formed when foot bearing pressure increases is associated with a higher risk of ulceration. Moreover, hyperkeratosis itself behaves like a foreign body by further increasing plantar pressure in the same site, thus creating a further risk of forming ulcers. There is clear evidence that plantar pressure reduction is an essential aid in the prevention and management of ulcers. Many measures have proved effective in reducing callosity, especially plantar pressure relieving modes involving the use of appropriate soles and shoes and the removal of corns. The Italian NHS envisages a prescription for a pair of protective shoes every 12 months and a pair of custom-made insoles every 6 months, free of charge, for all individuals with recognised 34% civil disablement.

– Foot deformations caused by either neuropathy or past amputations are an important risk factor for both the formation of ulcers and a new amputation, especially if they are associated with peripheral vasculopathy. Past amputations cause the risk of mortality to rise by 68% in 5 years; they also increase the risk of new ulcerations 3-fold. (21)

Severe deformations of the neuropathic diabetic foot are often associated with severely unstable articulations; they create a condition that involves a high risk of recurrent ulcerations, which can lead to deep tissue infections and a high risk of major amputation. Corrective surgery of deformities and stabilisation of joints has proved useful in stopping the progress of the disease by enabling correct orthosis of the foot, thus reducing ulcerative relapses and major amputations. (22,23,24,25)

Ulcers

Foot ulceration is found in 85% of amputation cases and past amputation predisposes for further amputation (1,4,15, and 26). Local risk factors for ulceration are foot deformities and callosities, especially if they are associated with neuropathy or peripheral vasculopathy. (1-4,15)

In case of neuropathic plantar ulcers without ischemia, treatment with a plaster or fibreglass off-bearing cast is more effective than all other lesion discharge modes (i.e. footwear with a stiff sole, Barouk's shoe, removable orthortic device, like Aircast). (27,28)

Infected ulcers are a serious complication that considerably increases the risk of amputation (1,2,4,15, and 16). They can be clinically diagnosed, while microbiological testing can be useful to establish targeted treatment.

A lesion is infected when there are (1,2):

– clinical signs of an infection;

– purulent secretions;

– two or more local signs or symptoms of inflammation.

However, the possible reduction of signs of infection in diabetics must be taken into account.

Damp environments encourage healing of ulcers. The correct approach envisages coordinated global management of the skin lesion (Wound Bed Preparation: debridement, exudate and infection management, stimulation of the granulation and of epithelialisation processes) to remove local barriers to healing. Better knowledge of the pathogenic processes that delay healing and make lesions become chronic in diabetics will lead to advanced medications designed to improve treatment standards. (29)

A therapeutic tool we wish to mention is systemic hyperbaric oxygen therapy for ischemic ulcers (30). Cochrane's metanalysis highlights that when there are diabetic foot ulcers, hyperbaric oxygen therapy significantly reduces the risk of major amputations, improving the chances of healing the ulcers after 1 year; but the metanalysis does not justify the method's routine use. (31)

Systemic hyperbaric oxygen therapy is currently recommended to save limbs in the management of serious foot infections associated with medical and surgical treatment of the infection, either after revascularisation procedures or when revascularisation cannot be performed; it is not recommended for non ischemic ulcers. (32)

Innovative techniques number VAC *(vacuum-assisted closure)* therapy, which creates negative pressure on

the wound to speed up the healing process and reduce the need for reamputation; it has been proved safe and effective, compared to standard treatments (33). The use of cell culture implants can also increase the healing percentage and reduce the time required to heal dorsal ulcers. (34).

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VII. DIABETES CARE IN SPECIFIC POPULATIONS

A. DIABETES CARE IN CHILDREN AND ADOLESCENTS

R E C O M M E N D A T I O N S

1. Type 1 Diabetes

Glycemic Control

> All children and adolescents with diabetes mellitus must be followed by a multidisciplinary team of specialists from the time of diagnosis. (**VI, B**)

> The choice of glycemic goals must be personalized in the various age groups, balancing the beneficial effect of achieving low HbA_{1c} levels with the risk of hypoglycaemia. Recommended HbA_{1c} goals are 6.5-8.5% at 0-6 years; <7.5% at 6-12 years; and <7.5% in adolescents (age: 13-19 years), if it can be reached without too many hypoglycaemic episodes. (**III, B**)

Screening of associated autoimmune diseases (thyroid disorder and celiac disease)

> On diagnosis run the following tests: TSH, FT4; antithyroid antibodies, IgA, EMA or antitransglutaminase.

> Yearly check TSH, antithyroid antibodies, EMA or antitransglutaminase. If EMA or antitransglutaminase are positive on 2 occasions, perform an intestinal biopsy for histological evidence of celiac disease. (**VI, B**)

Screening and management of chronic complications

Nephropathy

> Yearly screening for microalbuminuria should be initiated at the age of 10 or after 5 years of disease duration. (**III, B**)

> Once confirmed, persistent high levels of microalbuminuria must be treated with a titrated ACE-inhibitor, if possible, till microalbuminuria is normalized. (**IV, B**)

Hypertension

> Management of normal-high pressure values (see below) must include, when appropriate, an intervention on diet and on physical exercise focused on weight control and on increased physical exercise. Pharmacological treatment should be started, if pressure goals are not achieved after 3-6 months of intervention on the lifestyle. (III**, B**)

> ACE- inhibitors must be taken into account as initial treatment of hypertension. (**III, B**)

Dyslipidaemia

> Prepubertal children: fasting lipid profile must be tested on all children aged >2 years on diagnosis of

diabetes (after appropriate glycemic control has been reached) with a family history of hypercholesterolemia (total cholesterol >240 mg/dl), positive family history of cardiovascular events before the age of 55 or unknown family history. If the family history is negative, the first lipid screening should be performed at puberty (>12 years). If values are within acceptable risk levels (LDL cholesterol <100 mg/dl), the test should be repeated every 5 years. (**III, B**)

> Pubertal children (>12 years): the fasting lipid profile must be tested on diagnosis of diabetes (after appropriate glycemic control is achieved). If values are within acceptable risk levels (LDL cholesterol <100 mg/dl), the test must be repeated every 5 years. (**III, B**)

> Treatment of dyslipidaemia must be based on the fasting lipid profile (especially on LDL cholesterol) evaluated after appropriate glycemic control is achieved: the goal of treatment is a LDL cholesterol value <100 mg/dl. (**III, B**)

> Initial treatment must envisage both optimizing glycemic control and medical nutrition therapy to reduce the diet's saturated fat content. (**VI, B**)

> The addition of pharmacological agents is recommended when LDL cholesterol is >160 mg/dl and in patients with LDL cholesterol 130-159 mg/dl, considering the cardiovascular risk profile, after nutrition therapy and lifestyle changes have failed. (**III, B**)

Retinopathy

> The first ophthalmological evaluation must be scheduled at the onset and, if it is normal, repeated when the child is 10 years old and has had diabetes for 3-5 years. (**III, B**)

> A yearly follow-up is generally recommended after the age of 10 years. Less frequent controls can be deemed acceptable, if proposed by the ophthalmologist. (**VI, B**)

COMMENT

Apply the same diagnostic criteria that are adopted in adults to paediatric patients; especially the diagnostic threshold of Impaired Fasting Glucose (IFG) is at 100 mg/dl. Hence, in non obese children (in conditions of wellness and when there are no hyperglycaemic agents treatment), whose fasting blood sugar is reconfirmed ≥100 mg/dl, seek the presence of beta-cell specific autoantibodies (GADA, IA2, anti- insulin). Positive test results, which indicate a condition of risk for type 1 diabetes, will require a careful follow-up and completion of the investigation with genetic data (HLA at risk) and metabolic data (OGTT and subsequent IVGTT to evaluate the first phase insulin response). This will avoid a late diagnosis of DMT1 with the possible onset of ketoacidosis. (1,2)

In Italy, all current cases of diabetes in subjects aged under 18 years comprise type 1 diabetes with a very low percentage of patients with neonatal monogenic diabetes, MODY *(*Maturity Onset Diabetes of the Young*)* or type 2 diabetes with either genetic or essential obesity.

The specific aspects of treatment and management of type 1 diabetes in paediatric patients must be taken into account, as diabetic children differ from diabetic adults under many perspectives, varying insulin sensitivity associated with sexual maturation, physical growth, the ability to implement self-management, special neurological vulnerability to hypoglycaemia, diet variability and physical exercise. The development and implementation of optimal diabetes management also requires special focus on family dynamics, development stages and psychological differences associated with sexual maturation.

Recommendations are rarely based on evidence derived from rigorous research, due to the limits placed on scientific research centred on paediatric issues. Data published in this paper summarizes recommendations and guidelines published in a recent ADA statement (3) and in the 2000 ISPAD guidelines and, specifically related to the care and management of children and adolescents. (4)

Management of children and adolescents must be guaranteed by a multidisciplinary team of specialists specifically trained in diabetes care in a paediatric framework. Education on diabetes must be promptly organized at the time of diagnosis and specifically designed for the moment, expecting the balance between the adult's supervision and self-management to gradually develop and be defined to suit the patient's physical, psychological and emotional maturity. In the Italian healthcare system's current organizational framework, the most suitable way of providing this education is to admit the patient to a paediatric ward specialized in diabetology. Nutrition therapy should be provided at the time of diagnosis by a healthcare professional with expert knowledge of the nutritional needs of growing children and their behavioural problems, which have a special impact on the adolescent's diet. Patients must be assessed at least on a yearly basis.

Glycemic Control

While current standards for diabetes care mirror the need to maintain glycemic control close to normal levels, risks related to hypoglycaemia in small children require special consideration. Glycemic goals must be adjusted, considering that most children aged less than 6 years are unaware of hypoglycaemia, due to the yet immature counter regulation processes; this makes them lack the cognitive capacity of recognizing and responding to hypoglycaemic treatment. They are subsequently exposed to a higher risk of hypoglycaemia and its consequences. Many studies have also reported that near normal glycemic control can rarely be achieved in children and adolescents following the remission of diabetes (5); HbA_{1c} levels obtained by the DCCT in a cohort of adolescents under "intensive" treatment were 1% higher than those obtained in older patients and corresponded to the current ADA recommendations for patients at large (6). However, the availability of new insulin analogues and continuous subcutaneous insulin infusion (CSII) systems can achieve better metabolic control. Concerning insulin treatment, refer to the chapter on Pharmacological Treatment of Diabetes. When establishing glycemic goals, the benefit of obtaining a lower level of HbA_{1c} must be balanced with the risk of hypoglycaemia. Glycemic and HbA_{1c} goals for these age groups are listed in Table 22.

In 2001 a national survey was conducted on metabolic control in 3,500 subjects with type 1 diabetes (about half the population with the disease) aged less than 18 years. The mean HbA_{1c} total was 8.9%: 32% of patients had HbA_{1c} <8%, while it was >10% in 24% of subjects. 54% of subjects were under treatment with 4 or more injections, 38% with 3 injections, 7% with 2 injections and, only 1% by continuous subcutaneous insulin infusion (CSII) systems. (5)

Screening for associated autoimmune diseases (thyroid disorders and celiac disease)

Screening for thyroid disorders and celiac disease is recommended on diagnosis and during the follow-up, considering their high frequency and possible effect on psychophysical development (7,8). In patients with a multiple autoimmune disease and/or a family history of multiple autoimmune endocrinopathies, the search for anti-adrenal gland antibodies and anti-gastric mucous antibodies (PCA) is recommended.

Table 22. Plasma Blood Glucose and HbA_{1c} Goals by Age Group in Type 1 Diabetes

GLYCEMIC GOAL (mg/dl)					
VALUES BY AGE (years)	**PREPRANDIAL**	**POSTPRANDIAL**	**BEDTIME/NIGHT**	**HbA_{1c}**	**INDICATION**
Infants and preschoolers (<6)	100-180	140-200	110-200	<8.5% but >6.5%	High risk and vulnerability to hypoglycaemia
Schooling age (6-12)	90-180	130-180	100-180	<7.5%	Risk of hypoglycaemia and relatively low risk of complications before puberty.
Adolescents and young adults (13-19)	90-130	120-160	90-150	<7.5%	Serious risk of hypoglycaemia. Development-related psychological problems. A lower goal can be reasonably proposed, if it can be reached without too many hypoglycaemic episodes.
Key concepts in defining glycemic goals: – goals must be personalized; glycemic goals that are outside the lower recommended limit must be based on the evaluation of the risk of hypoglycaemia and the expected advantage; – glycemic goals should be higher than those mentioned above for children with either frequent hypoglycaemic episodes or episodes of hypoglycaemia unawareness. (Postprandial blood sugar must be tested if there is dissociation between pre-prandial blood glucose levels and HbA_{1c}).					

Screening and Management of Chronic Complications

Microalbuminuria can be screened by analyzing either the microalbumin-to-creatinine ratio on a casual urine sample or urinary excretion of albumin in a timed night collection or the albumin concentration in the first morning urine.

Hypertension in children is defined as mean systolic or diastolic pressure ≥95th percentile for age, sex and height, tested at least in 3 different days. “Normal-high” blood pressure is mean systolic or diastolic pressure ≥90th percentile but <95th percentile for age, sex and height, tested on at least 3 different days.

Normal blood pressure levels for age, sex and height and, the appropriate testing mode can be found on the Web page: www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf.

Although retinopathy most commonly occurs after the onset of puberty and after 5-10 years of disease duration, some cases have been reported in prepubertal children after only 1-2 years of disease duration. A fundus picture after pupil dilatation is a safe, non invasive, sensitive and reproducible screening tool for retinopathy.

Disease Management

An important topic worthy of special focus in this age group is “adhesion”. Appropriate adhesion depends on the family and/or individual’s capacity to implement it, irrespective of the therapeutic regime. The family’s involvement in diabetes care remains an important factor in the optimal management of the disease from infancy to adolescence.

School personnel must be provided with specific information to make them aware of the diagnosis of diabetes in students and of the signs, symptoms and treatment of hypoglycaemia. Most cases require capillary blood glucose testing to be performed at school or in nurseries before meals and, when there are either signs or symptoms of altered blood glucose levels. Many children, either at school or in nurseries, may require assistance before lunch (and often even before breakfast) for insulin delivery with either an injection or CSII. For further details, refer to the ADA’s Position Statement (9) and to the National Diabetes Education Program. (10)

2. Type 2 Diabetes

It is known that the incidence of type 2 diabetes is increasing in children and adolescents in the USA, especially in ethnic minorities (11,12). This trend is also expected in Italy, considering the increased incidence of obesity, though to date the incidence of type 2 diabetes is very low. An Italian case study conducted on 710 obese paediatric subjects (13) made only one diagnosis of diabetes on the basis of OGTT, while 33 cases were diagnosed with impaired glucose tolerance. National case studies conducted by the *Società Italiana di Endocrinologia e Diabetologia Pediatrica* (SIEDP) report only a few dozens of cases of type 2 diabetes vs. about 8,000 typical type 1 diabetes cases. It can be hard to distinguish type 1 and type 2 diabetes in children because some subjects who otherwise clearly have type 2 diabetes (including obesity and *acanthosis nigricans*) can present beta-cell antibodies and ketosis.

It is extremely important to correctly recognize the two types of diabetes on diagnosis, especially considering the presence of beta-cell specific autoantibodies and insulin levels, because management, educational approach and diet prescriptions clearly differ in the two types of diabetes. The ADA’s Consensus statement (14) provides guidelines for the prevention, screening and management of type 2 diabetes and its comorbidities in youth.

Lifestyle corrections are the first therapeutic measure. If they fail, metformin is the first choice drug for type 2 diabetes without ketosis in diabetic adolescents (15,16). Insulin treatment must be started in case of very high blood sugar with ketosis. There are no indications concerning the use of sulfonylureas in paediatric patients. These drugs are, instead, the choice maintenance therapy for permanent neonatal diabetes caused by Kir 6.2 mutations. (17,18)

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B. DIABETES CARE BEFORE AND DURING PREGNANCY

RECOMMENDATIONS

> All diabetic women of childbearing age must be informed about the need to achieve good metabolic control before conception, the risk of unscheduled pregnancy and the need to schedule conception with effective contraception methods. (**VI, B**)

> Every diabetic woman who wishes to start a pregnancy must undergo screening and treatment for any complications (retinopathy, nephropathy, neuropathy, cardiovascular disease). (**VI, B**)

> Glycemic control must be optimized before the conception. The therapeutic goal is normal or near normal HbA_{1c} levels, allowing for at most a 1% deviation from the upper normal limit. (**III, B**)

> Insulin therapy must be readily established in all women who fail to achieve the glycemic goal with nutritional therapy. Oral hypoglycaemic agents must not be administered during pregnancy, due to the lack of enough data on the absence of teratogenous effects. (**VI, B**)

> Rapid acting insulin analogues – aspart and lys- pro – can be either maintained or added to treatment during pregnancy; but data on the use of the rapid acting analogue glulisine during pregnancy is scarce; lastly, the use of delayed action analogues, which lack adequate safety data, is not recommended. (**VI, B**)

> The use of ACE-inhibitors, ARBs and statins is not allowed during pregnancy: hence, these drugs must be discontinued before conception. (**VI, B**)

> The glycemic goals that women with either gestational diabetes or pregestational diabetes (type 1 or type 2) must achieve during pregnancy are listed below:

- ≤95 mg/dl fasting blood glucose;
- ≤140 mg/dl one hour after meals;
- ≤120 mg/dl two hours after meals. (**VI, B**)

> Insulin treatment must be readily started in women with gestational diabetes, if glycemic goals are not achieved after 2 weeks of nutritional treatment. (**VI, B**)

> Insulin patterns must be personalized in gestational diabetes: patterns envisaging either 1 or 2 injections can be implemented, but intensive insulin treatment can be necessary to reach optimal blood glucose levels. (**VI, B**)

> Women with type 1 pregestational diabetes require multiple insulin delivery either subcutaneously or by CSII. Intensive insulin treatment is usually required to reach glycemic targets, even in type 2 pregestational diabetes. (**I, A**)

> Women with diabetes during pregnancy must self-test blood glucose at home (4-8 tests/day) with preprandial, postprandial (1 hour after the meal) and night time tests. Simplified chessboard patterns can be used in gestational diabetes treated only with the nutritional therapy. (**V, B**)

> Ketosis must be avoided during pregnancy; hence, daily ketonuria testing on awakening is useful. (**V, B**)

> Nutrition treatment during pregnancy must be personalized, taking into account both the diet habit of diabetic women and the BMI before the pregnancy. The goals are appropriate maternal and foetal nutrition, appropriate calorie, vitamin and mineral intake and optimal glycemic control when there is no ketonuria. (**VI, B**)

COMMENT

This paper chiefly refers to the ADA's *2006 Standard of care*, concerning preconception care. Recommendations for management during pregnancy are based on positions taken by the SID study group *Diabete e Gravidanza* in recent years and, in the *2003 Clinical Practice Guidelines* issued by the Canadian Diabetes Association.

Epidemiology

It has been estimated that about 6-7% of pregnancies in European women are complicated by diabetes mellitus, including 97.5% of cases of gestational diabetes and only 2.5% of cases of pregestational diabetes (type 1 or type 2) (1). Estimates based on national prevalence data (2) say that there are about 40,000 pregnancies complicated by gestational diabetes and about 1,300 complicated by pregestational diabetes in Italy every year.

As with European data, the percentage of scheduled pregnancies is less than 50% in women with type 1 diabetes and 40% in those with type 2 diabetes in Italy too. This explains, at least partly, why the incidence of malformations in the diabetic population is 5-10-fold the one in the population at large; likewise, the incidence of preterm deliveries and caesarean sections is also high. The lack of pregnancy planning and dedicated clinics keeps the Italian situation far below the optimal standards specified in the St. Vincent Declaration focused on making diabetic pregnancies outcomes like that of physiological ones..

Preconception Program

Careful pregnancy planning considerably reduces the risk of congenital malformations and diabetes-related maternal-foetal morbidity. Diabetic women must never leave pregnancy to chance, but rather make it coincide with optimal metabolic control and stable chronic complications.

Many studies have showed that the risk of malformations increases with the degree of alterations in the glucose metabolism during the early post-conception phase (3). The main congenital malformations develop during the first 7-8 weeks of gestation (4). There is a similar association between periconceptional diabetic control and the rate of early abortions (5). An HbA_{1c} threshold above which the risk of malformations increases has yet to be defined; HbA_{1c} levels that are at least 1% higher than the reference range increase the incidence of major malformations. (6)

Non randomized studies have proved that preconception intervention programs can significantly reduce the incidence of malformations (3,7-10). The need to reach the time of conception with the best metabolic control requires special commitment during months preceding the event and this can only be achieved by planning a pregnancy. Currently only very few diabetic women plan a pregnancy: the percentage of planned pregnancies is below 50% even in Europe. (11)

An educational program based on reproduction and female sexuality must, hence, be part of the current educational approach for diabetic women of childbearing age attending Diabetes Clinics. Targeted counselling must lead to real pregnancy planning, which must begin before conception, even involving the partner and all professional figures that are in contact with the diabetic patient.

The program must comprise various aspects:

> ascertain the ability to deliver insulin treatment (adjusting it to blood glucose levels), to recognize and treat hypoglycaemic episodes and, to correctly monitor blood glucose at home;

> medical and laboratory evaluation of the health condition, screening of thyroid function and study of complications; contraindications to pregnancy must be considered: ischemic coronary heart disease, active non treated retinopathy, acute arterial hypertension, renal failure (blood creatinine >3 mg/dl, creatinine clearance <30 ml/min) and diabetic gastroparesis;
> psychosocial evaluation;
> discontinue potentially toxic drugs: ACE-inhibitors, sartans, statins; the toxicity of ACE-inhibitors already during the first weeks of gestation has been recently proved (12); hence, the recommendation to discontinue their use during the pregnancy planning phase;
> start insulin therapy in patients treated with oral hypoglycaemic agents. To date there is no undisputed evidence of the innocuousness of many of these drugs during the organogenesis phase; hence, their use is not indicated during the first weeks of gestation and their discontinuation is recommended during the pre-conception phase.

Optimal metabolic control achieved by pursuing near normal HbA_{1c} levels usually requires the establishment of intensive insulin therapy (always in type 1 pregestational diabetes, very often in type 2 pregestational diabetes) with multiple subcutaneous delivery or CSII. Rapid acting insulin analogues – aspart and lispro – can be either maintained or added to treatment; delayed action analogues are, instead, not recommended as they are still not deemed safe during pregnancy.
Follow up visits must be scheduled at monthly intervals by a multidisciplinary team comprising, besides the diabetologist, an expert nurse, a dietician and other professionals required by the specific situation. Effective contraception must also be guaranteed till glycemic control is optimised.
There is by now considerable evidence to unequivocally prove that maternal hyperglycaemia during pregnancy involves an increase in foetal morbidity and mortality (13); especially an increase in perinatal complications is associated with the blood glucose levels recorded during the final phases of pregnancy. Despite this awareness, diabetic pregnancy is still burdened by an excessive maternal-foetal morbidity. (14)

Glycemic Goals

Though recent reports, based on either intensive testing of capillary blood (15) or continuous blood glucose testing (16), have highlighted that blood glucose levels during physiological pregnancy are considerably lower than previously estimated, clinical management of pregnant diabetic women still refers to goals recommended by the ADA and applied by major international scientific societies. (Table 23)

Table 23. Glycemic Goals during Pregnancy (whole capillary blood)

Fasting	≤95 mg/dl
1 hour after meals	≤140 mg/dl
2 hours after meals	≤120 mg/dl

Nutrition Therapy

Nutrition therapy is designed to: ensure appropriate maternal and foetal nutrition, provide appropriate calorie, vitamin and mineral intake and, guarantee optimal glycemic control without causing the onset of ketonuria. (17-20)

The diet must be personalized to suit diet habits and prepregnancy BMI. (Table 24)

Table 24. Energy Requirement and Recommended Weight Increase

STRUCTURE	BMI (kg/m^2)	ENERGY REQUIREMENT (kcal/kg/day)	WEIGHT INCREASE (kg)
Underweight	<18.5	40	12.5-18
Normal weight	18.5-25	30	11.5-16
Overweight	>25	24	7-11.5

The use of drastic low calorie diets is contraindicated even in case of severe obesity: calorie intake need not be reduced below 1,500 kcal/day. The overall calorie intake must be divided in 3 main meals and 3 snacks (mid morning, mid afternoon and bed- time) according to the following pattern:

– 10-15% before breakfast;

– 20-30% lunch;

– 30-40% dinner;

– 5-10% 3 snacks.

The evening snack should contain 25 g carbohydrates and 10 g proteins.

The recommended macronutrient ratio is 50% carbohydrates (complex carbohydrates with low glycemic index), 20% proteins, 30% lipids (both mono and polyunsaturated fat) and, 28 g/day of fibre. Postprandial blood glucose variations can be limited by reducing the carbohydrates ration, which should not drop under 40%.

Concerning oligoelements, the calcium, iron and iodine demand doubles during pregnancy. Women who take neither milk nor its derivates are recommended to take either food fortified with calcium or pharmacological supplements. Pharmacological supplementation of iron and the use of iodized salt must also be considered.

The intake of alcohol and caffeine exceeding 300 mg/dl is not recommended as they can delay foetal growth. Moderate quantities of aspartame, saccharin, acesulfame and sucralose are allowed.

Insulin Therapy

Insulin Requirement

The daily insulin requirement varies considerably during pregnancy (21). Home blood glucose monitoring enables to rapidly implement appropriate insulin dose variations. A low insulin requirement during the first three months of pregnancy is common in women treated with insulin before the conception (10-20%); the glycemic profile is often unstable during this period, with frequent hypoglycaemic episodes at night. Then the need gradually increases, reaching a “plateau” around the 36^{th} week (the overall increase can be 100% or higher); the glycemic profile has a tendency to stabilize as pregnancy progresses.

Insulin Treatment Patterns

Women with type 1 pregestational diabetes must be treated with multiple insulin doses with basal/bolus type patterns. Individual therapeutic plans that do not depend on the insulin treatment before pregnancy

must be established; an approximate division of the total insulin requirement during pregnancy is:
– rapid acting insulin (about 50% of total units) at mealtime: 20% before breakfast, 40% before lunch, 40% before dinner;
– intermediate action insulin (preferably Isophane) to guarantee insulinisation at night and during pre-prandial hours, 1-3 administrations/ day.
In this case too, dose adjustment to ensure daily glycemic control is essential. (22)
In gestational diabetes, insulin therapy must begin if glycemic goals are not achieved after 2 weeks of a precisely followed diet. This decision can also consider ultrasound parameters of foetal growth and, indirect indexes of foetal insulinisation (23-25). Insulin patterns can be simplified with either 1 or 2 injections, depending on the glycemic progress, but an intensive approach as in pregestational diabetes may be required.

Use of Insulin Analogues
Rapid acting analogues have pharmacological features that make them ideal for pregnancy, considering the importance of controlling post-prandial glycemic variations. Concerning safety, most experience has so far concerned the analogue lispro, which numbers no evidence of either teratogenous or other negative effects (26,27); but entirely reassuring data has recently been obtained for aspart too; hence, to quote the indications of the European Agency for the Evaluation of Medical Products (EMEA), the product's "technical sheet" (Summary of Product Characteristics, SCP) now clearly says that the drug "can be used during pregnancy". It can thus be declared that these drugs can be safely used in pregnant women; instead, data on the use of the rapid acting analogue of glulisin during pregnancy is still scarce, though animal reproduction studies have found no difference between this drug and human insulin in terms of pregnancy, embryo-foetal development, delivery and post-natal development.
The position of delayed action analogues is not as clear. Due to the limits of clinical observations during pregnancy
(only case reports solely related to glargine, with nothing about detemir), these analogues cannot still be deemed safe; there use, if any, during pregnancy must only follow the explicit consent of women, who have been appropriately informed about the risk/ benefit ratio.

Insulin Pump Therapy (CSII)
The use of the insulin pumps during pregnancy has recorded a progressive increase in recent years, especially during pregnancy planning. Despite the lack of randomised clinical trials, some retrospective and case-control studies have reported better glycemic stability with fewer variations and rarer hypoglycaemic episodes, most likely due to a more physiological release of insulin (28). Patients' excellent acceptance has also been reported, with positive repercussions on their quality of life.

Insulin Therapy during Labour, Delivery and Postpartum.
Optimized glycemic control during labour and delivery is essential for the newborn's wellness. To this aim and, especially to prevent neonatal hypoglycaemia, glycemic levels must be maintained within a very narrow range (70-120 mg/dl according to some authors, 70-90 mg/dl according to the ADA). Achieving these goals requires frequent capillary blood glucose testing and insulin and glucose infusion, following

established algorithms. Insulin requirement undergoes an abrupt drop during the postpartum period; insulin therapy must not be repeated sooner than one hour after delivery and, only when blood glucose levels are steadily higher than 140 mg/dl.

Metabolic Monitoring

All women with diabetes during pregnancy must self-test blood glucose at home. Gestational diabetes requires self-testing soon after the diagnosis. Intensive self-testing patterns with pre-prandial, postprandial and night time testing (6-8 points/day) must be performed in all insulin-treated patients. Simplified chessboard patterns can be used in gestational diabetes treated only with nutritional therapy. Postprandial blood sugar is extremely important and must be preferably tested 1 hour after meals. (29)

Frequent prolonged ketosis can have negative effects on the fetus and, must thus be avoided during pregnancy; to this end, ketonuria must be daily tested on awakening.

Outpatients' follow up must be performed every 2 weeks or more often if the glycemic control is unstable; more frequent visits (weekly) are usually scheduled during the 3rd three month period. The HbA_{1c} assay must be performed monthly in all diabetes types during pregnancy, while the complete urinalysis must be run at every follow up visit. The presence of puree requires urine culture.

In pregestational diabetes additional surveys are needed:

> thyroid function control (free T4, TSH) at the start of pregnancy; it must be repeated, if necessary;

> screening for microangiopathic complications with three-monthly testing of creatinine clearance and 24-hour proteinuria; the retina must be examined during the first three months and, later, as required;

> cardiac function must be kept under close control.

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C. DIABETES CARE IN THE ELDERLY

RECOMMENDATIONS

Glycemic control

> Glycemic goals should be individualized in elderly diabetics. If general conditions are good, HbA_{1c} levels can be 6.5-7.5%. (**VI, B**)

> In the frail elderly (with complications, dementia, multiple diseases, a high risk of hypoglycaemia and, in whom the risk of intensive glycemic control exceeds expected benefits) a less restrictive goal is recommended with HbA_{1c} levels between 7.5-8.5%. (**VI, B**)

> In elderly diabetics the self-monitoring pattern should be designed to suit the degree of self-sufficiency; hence, individual functional, affective and cognitive capacities. The pattern must be based on planned glycemic and HbA_{1c} goals, on the real feasibility of changing treatment and on the risk of hypoglycaemia. (**VI, B**)

> If oral hypoglycaemic agents are prescribed in the elderly, chlorpropamide and glibenclamide are not recommended. (**V, B**)

> In elderly diabetics with serum creatinine ≥1.5 mg/dl (≥1.4 mg/dl in women) or creatinine clearance levels indicating impaired kidney function metformin is not recommended, due to the higher risk of lactic acidosis. (**IV, B**)

> In elderly diabetics treated with metformin, serum creatinine should be tested at least once a year and at every dosage increase. Creatinine clearance should be tested in subjects aged ≥80 years or presenting a reduced muscular mass. (**VI, C**)

Cardiovascular risk and pharmacological treatment

> The cardiovascular risk must be evaluated in all elderly diabetics. (**VI, B**)

> Dyslipidaemia in elderly diabetics must be corrected, compatibly with an overall evaluation of the patient's health condition. (**II, B**)

> If an elderly diabetic has LDL cholesterol ≥130 mg/dl, he needs both pharmacological therapy and lifestyle changes. The lipid profile must then be retested at least once a year. (**I, A**)

> In elderly diabetics requiring antihypertensive pharmacological therapy, the treatment goal must be blood pressure <140/80, if it is well tolerated. A further drop in blood pressure (<130/80) can involve an additional advantage. (**I, A**)

> Considering that elderly subjects may poorly tolerate a pressure reduction (especially in case of past episodes of syncope, falls and orthostatic hypotension), antihypertensive treatment should be gradually established and titrated. (**VI, B**)

> In elderly diabetics treated with ACE- inhibitors or sartans, kidney function and serum K should be tested within 1-2 weeks of the treatment start, whenever the dosage is increased and, anyhow, at least once a year. (**VI, B**)

> Elderly diabetics treated with thiazides or loop diuretics require blood sodium and potassium testing within 1-2 weeks after the start of treatment, whenever the dosage is increased and, anyhow, at least once a year. (**VI, B**)

Functional evaluation

> Elderly patients with type 2 diabetes require a geriatric multidimensional evaluation and an evaluation of geriatric syndromes. (**VI, B**)

> The evaluation must include global/physical, cognitive and affective tests. (**VI, B**)

> The functional evaluation must be completed with the assessment of comorbidities and nutritional status. (**VI, B**)

> The elderly diabetic possibility of performing physical exercise should be periodically evaluated; he must be informed about the beneficial effects of exercise and the resources available to increase the degree of exercise. (**VI, B**)

> Food intake, nutritional status and hydration should be periodically evaluated in elderly diabetics; they should be provided with nutrition therapy instructions that are appropriate for their social, economic and cultural condition, advice on diet contents and the potential advantages of body weight loss. The risk of calorie-protein malnutrition, which is rather frequent in the elderly, must always be evaluated. (**VI, B**)

> Elderly diabetics have a higher risk of depression; hence the need for special focus to recognize symptoms suggesting this diagnosis, both during an initial evaluation and in case of a worsened clinical condition that cannot otherwise be justified. (**III, C**)

> Elderly diabetics should be invited to keep an updated record of the drugs taken, which they must show their attending physician. (**VI, C**)

> An elderly diabetic attending physician should take into account the possible presence of cognitive decline, both during the initial evaluation and when there is an otherwise unjustified decline in the clinical condition with, for instance, an increased difficulty to ensure safe care. (**VI, C**)

> Yearly screening of the elderly diabetic should include the search for symptoms of incontinence. (**VI, C**)

> The elderly diabetic should be questioned about any episodes of falls. In this case, the causes (i.e. drugs, environmental factors, etc.) will be investigated. (**VI, C**)

> During the initial evaluation, the elderly diabetic should be questioned on the possible presence of chronic pain. (**VI, C**)

> Every long stay ward admitting diabetic patients should have an established diabetes care plan or protocol that is subject to regular reviews. (**VI, B**)

Treatment goals for patients in long stay wards

The basic treatment goals for elderly diabetic patients living in long stay wards should be to (2):

- maintain the highest standards of quality of life and wellness, without inappropriate and superfluous medical and therapeutic interventions;

- provide backing and opportunities to enable patients to manage their diabetic condition, when this is useful and can be implemented;
- reach satisfactory (or optimal) metabolic control, avoiding both hyperglycaemia and hypoglycaemia and allowing the highest degree of physical and cognitive function;
- optimise foot care and sight care, to encourage the best degree of mobility, reduce the risk of falls and avoid unnecessary admissions to hospital;
- ensure a balanced nutritional and diet plan to prevent malnutrition due to either overeating or poor eating;
- effectively screen diabetes complications at regular intervals with special focus on neuropathy and peripheral vasculopathy that predispose towards ulceration, foot infection and eye complications.

COMMENT

The *Guidelines for Improving the Care of the Older Person with Diabetes Mellitus* issued by the California Healthcare Foundation/American Geriatrics Society Panel on Improving Care for Elders with Diabetes (1), on which especially the ADA 2006 *Standard of Care* and the European guidelines issued by the European Diabetes Working Party for Older People are based, have been carefully considered. (2)

Defining the problem and its dimensions

The ADA's *Standard of Care* and guidelines issued by the American Geriatric Society define people aged over 65 years as elderly, while indications given by the European Union Geriatric Medicine Society concern the care of patients aged over 70 years. This paper has deemed people aged over 65 years as elderly.
Globally, over10% of people aged over 65 years has diabetes, but the group is extremely heterogeneous due to the duration of the disease, comorbidity and life expectancy. The prevalence of the disease is clearly increasing, especially in the older age groups: the *Casale Monferrato Study* (3) reports that the prevalence of known diabetes has increased from 6.52% (IC 95%, 6.18-6.86) in 1988 to 9.10% (IC 95%, 8.72-9.48) in 2000 in the population aged >65 years. The increased prevalence is evident especially in the group aged over 80 years, whose risk of diabetes has doubled from 1988 to 2000. More than two thirds of the cohort population is aged >65 years and this trend will most likely continue in the future, in parallel both with the increased survival rate of the population at large and of diabetics themselves. This data is confirmed by the *Annali AMD 2006* "Quality Indicators of Diabetes Care in Italy": it reports that on 123,863 patients seen in 2004 in the 86 Diabetes Clinics participating in the study, more than half were over 65 old. Especially 33.35% of the people belonged to the 65-75-year age group, while 22.26% was aged >75 years.

General Approach

The care of elderly diabetics is complicated by many heterogeneous clinical and functional characteristics and attending physicians must take them into account when therapeutic goals are defined. Multidimensional evaluation can provide basic information to frame the geriatric patient. Special training for personnel dedicated to the care of the elderly is of essential importance.

Therapeutic Goals

Glycemic Control

Personalized Goals

Controlled clinical studies on the advantages of close glycemic control in elderly diabetics are currently lacking.

The analysis of UKPDS study data on type 2 diabetics with minimum comorbidity in the oldest age group revealed that, in this age group too, a 1% drop in HbA_{1c} levels is associated with a 37% reduction in microvascular complications and a 21% drop in diabetes-related adverse events (4,5). On the basis of such data, active, cognitively alert elderly diabetics in good health with an adequate life expectancy to benefit by the advantages of intensive long term diabetes management (about 10 years) who feel they can practice self-management should be encouraged to do so, focusing treatment on the same goals as younger diabetics. The European guidelines propose HBA_{1c} levels between 6.5% and 7.5%.

In elderly diabetics belonging to the oldest age group – the frailest with comorbidities and a subsequent low life expectancy – a less restrictive glycemic goal should be defined − approximately and consistently with European guidelines − with HbA_{1c} levels between 7.5 and 8.5%, also considering the fact that HbA_{1c} levels can be underestimated in the elderly due to increased splenic hemocatheresis and frequent calorie-protein malnutrition.

Self Management

While experts agree on the importance of blood glucose self-testing in type 2 diabetics treated with insulin (6), there is no clinical evidence concerning its usefulness in subjects treated with only the diet or with oral hypoglycaemic agents (7). But it is common belief that the incidence of complications can be reduced by making use of blood glucose self testing to perform the necessary therapeutic adjustments. It is also deemed that self-testing can reduce the risk of acute hypoglycaemic episodes in the elderly under pharmacological treatment. However, the optimal testing frequency has yet to be defined; the ADA believes that it must be adjusted to suit each patient's requirements.

Lipid Control

Coronary heart disease is the leading cause of mortality in type 2 diabetics and it remains the main risk for diabetic patients belonging to the oldest age group. Very high lipid levels are an independent risk factor for coronary heart disease and, there is evidence that hypolipidemic treatment is beneficial to the cardiovascular system (2). Both randomized clinical trials and metanalyses have proved that a drop in LDL cholesterol reduces the risk of cardiovascular events even in the most elderly diabetic patients.

The European guidelines on diabetes in the elderly deem a lipid profile with total cholesterol levels ≥190 mg/dl, LDL cholesterol ≥115 mg/dl and, triglycerides ≥205 mg/ml as abnormal.

Pressure Control

Elderly diabetics, compared to non diabetics the same age, present a higher risk of premature death, functional disability and comorbidities, such as hypertensive heart disease and stroke.

Many randomized trials − many of which comprise diabetic patients (8-10) − have highlighted that

antihypertensive treatment reduces cardiovascular events and mortality both in middle aged subjects and in the elderly. Most of these studies defined pressure goals <140/90 mmHg, while some indicated lower goals (<130/80), to slow down the progress of microangiopathic complications. (11)
Though the optimal time interval for pressure goals to be achieved has yet to be defined, experts agree on a gradual reduction in the elderly to avoid the onset of complications.

Therapeutic Approach

There is considerable evidence that a multidisciplinary intervention − designed to educate patients on the correct use of drugs, on glycemic monitoring and on recognising hypoglycaemic and hyperglycaemic episodes – can significantly improve glycemic control both in middle aged diabetics and in the elderly (12). It is also essential to control comorbidity and all cardiovascular risk factors.

Physical exercise

Randomised clinical studies conducted on elderly diabetics have highlighted that an increase in physical exercise − associated with proper nutritional education − can significantly reduce body weight and improve blood pressure levels and lipid and glycemic control (13,14). There is, however, little data on the effect of weight loss on morbidity and mortality in this age group and reducing body weight may not be an appropriate goal in all cases. Moreover functional or cognitive impairment prevents some of these patients from sufficiently increasing the level of physical exercise.
Some trials have also evaluated the role of nutritional education and nutrition therapy in the clinical management of adult or elderly diabetics, thus revealing how this approach can be useful in improving blood pressure and lipid and glycemic levels. (15)

Choice of Pharmacological Treatment

Hypoglycaemic treatment

Elderly patients can be treated with the same therapeutic patterns as younger subjects, but special care is required when specifying and monitoring pharmacological treatment.
Due to the risk of lactic acidosis − a rare but potentially serious complication of metformin treatment (16) − the use of this drug is contraindicated when there is either renal failure or heart failure. Hence the need for at least yearly monitoring of renal function in all elderly diabetics treated with metformin: the drug must be discontinued when serum creatinine is high.
Sulfonylureas and other secretagogues can cause hypoglycaemia; hence the short-acting drugs should be preferred. Due to their long half life, chlorpropamide and − to a lesser degree − glibenclamide, involve a high risk of hypoglycaemia, which increases with age and should be avoided in the elderly.
Thiazolidinediones should not be administered to patients with congestive heart failure (NYHA Classes III and IV).
Starting insulin treatment requires either the patient or those delivering the treatment to have adequate visual whetting, the ability to perform fine movements and cognitive skills.
Moreover, all drugs should be initially administered in the lowest doses and, gradually titrated till either the goal is achieved or side effects set in.

Antihypertensive Treatment

Though no drug class is specifically recommended for blood pressure control in elderly diabetics, special focus must be given to some commonly used therapeutic categories.

ACE-inhibitors have been associated with reduced renal function and serum K raising(17,18); hence, testing of renal function indexes and serum K must be performed a few weeks after the treatment's start, whenever the dosage is increased and, periodically, at least once a year.

Low serum K and ventricular arrhythmias have been reported during treatment with diuretics; serum K should thus be monitored when treatment starts and, later, at regular intervals.

Treating dyslipidaemia

Experts suggest defining specific LDL cholesterol levels as a guide for therapeutic decisions: the guidelines of the American Geriatric Society (1) propose the following actions:

– LDL cholesterol ≤100 mg/dl: the lipid profile should be rechecked at least every 2 years;

– LDL cholesterol =100-129 mg/dl: nutrition therapy is recommended along with increased physical exercise; the lipid profile must be rechecked at least yearly and pharmacological treatment should be added if levels ≤100 mg/dl are not reached;

– LDL cholesterol ≥130 mg/dl: pharmacological treatment is required, in addition to lifestyle changes. The lipid profile must be yearly rechecked.

Pharmacological treatment with statins, nutrition therapy, physical exercise and weight loss has proved effective in positively influencing cardiovascular risk profiles in elderly diabetics. Evidence concerning drug-based primary prevention in subjects aged >80 years is still inadequate.

Elderly diabetics with normal or near normal LDL cholesterol, low HDL cholesterol and high triglycerides levels should be treated with fibrates, besides nutrition therapy; however, scientific evidence is still scarce in this regard.

Antiplatelet Treatment

Despite studies on the efficacy of antiplatelet treatment in diabetics have yet to produce univocal conclusions, many guidelines agree in suggesting that elderly diabetics must take 75-325 mg/day of aspirin, unless they are under anticoagulant treatment or present contraindications for its use.

Geriatric Syndromes

Elderly diabetics have a higher risk of comorbidity and, hence, of suffering from common geriatric syndromes, like adverse drug reactions due to multiple drug treatment, depression, cognitive decline and dementia, urinary and faecal incontinence, traumatic falls, syncope and chronic mixed pain. All these conditions should be initially considered during the multidimensional evaluation and, later, during periodical tests, even seeking potentially reversible causes through appropriate rehabilitation.

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VIII. DIABETES CARE IN SPECIFIC FRAMEWORKS

A. DIABETES CARE IN HOSPITAL

R E C O M M E N D A T I O N S

> The diagnosis of diabetes mellitus must be clearly entered in the case records of all diabetic patients who are admitted to hospital. (**VI, B**)

> If hyperglycaemia is occasionally found during hospitalization, HbA_{1c} testing should be performed to identify a condition of undiagnosed diabetes. (**V, B**)

> Capillary blood glucose must be monitored in all diabetics admitted to hospital and the results must be entered in the case records to ensure their access to all attending team members. (**VI, B**)

> A treatment plan for hypoglycaemia must be defined for every patient. Episodes occurring during hospitalization must be recorded in the case records. (**VI, B**)

> Admission is not the most appropriate time to establish an organic educational program centred on diabetes. However, the diabetic must be instructed on some basic aspects − such as insulin injection and self-testing of blood glucose − before discharge. (**VI, B**)

> Undiagnosed diabetics presenting hyperglycaemia on admission to hospital must be referred to the competent Diabetes Unit. (**VI, B**)

Glycemic Goals

> During hospitalization, glycemic goals can be differentiated to suit the various clinical conditions:

- critical patients: blood glucose levels near 110 mg/dl and in any case <180 mg/dl; (**II, B**)
- non critical patients: pre-prandial blood glucose levels near 90-130 mg/dl, postprandial <180 mg/dl. (**VI, B**)

> Glycemic goals should be gradually achieved in some clinical conditions presenting a high risk of hypoglycaemia. (**VI, B**)

Treatment

> The use of the main oral hypoglycaemic drugs (secretagogues, biguanides, and thiazolidinediones) has considerable limits in the hospital framework. Insulin delivery is, hence, the choice treatment for non stabilized hospitalized diabetic patients. (**VI, B**)

> Subcutaneous insulin treatment must preferably follow a scheduled scheme, which is frequently adapted

to suit recorded blood glucose levels. This pattern can be integrated with a correcting algorithm based on blood sugar testing at the time of the injection. Insulin delivery only "when required" (sliding scale) is not recommended due to its poor efficacy. (**IV, B**)

> In critical patients and/or those who are unable to take food by mouth, during the perioperative period and in conditions of acute metabolic instability, insulin therapy must be delivered as continuous venous infusion, applying algorithms based on frequent blood glucose testing. (**VI, B**)

> Non critical patients who are expert in both self-delivery of insulin and blood glucose self- testing can be authorised to continue self management even during hospitalization, agreeing on the specific modes with the attending healthcare team. (**VI, B**)

> In patients already under treatment with an insulin pump (CSII), it can be useful to maintain this method even during hospitalization, as long as it can be correctly managed in the specific clinical situation. (**VI, B**)

COMMENT

The paper refers especially to the ADA's 2006 *Standards of Care*. This paper was in turn mostly based on a technical review by Clement (1) and on the acts of a conference held by the American Association of Clinical Endocrinologists. (2,3)

The problem dimensions

The international prevalence of diabetes in hospitalized adults is not precisely known, though it is estimated being 12-25%. 12.4% of patients discharged from hospital in the USA were diabetics in 2000. Even the Italian situation is only partly and incompletely known (4). In 1999 the rate of hospital discharges/1000 inhabitants with the code DRG 250*, which could also be referred to diabetes as main diagnosis on discharge, was 2.5% throughout the national territory, with a considerable interregional variability, ranging from 1.30% in Friuli-Venezia Giulia to 2.30% in regions like Piedmont, Lombardy and Lazio and, 4.60% in Molise, Apulia and Basilicata. Considering the primary and secondary diagnosis on discharge has enabled to estimate a 6.0% prevalence of diabetes in Campania and Piedmont and, 21% in Emilia-Romagna.

Patient Types

Patients with blood glucose levels within a pathological range during hospitalization can be divided into at least three different categories:

a) known and existing diabetes mellitus on admission;

b) diabetes mellitus first diagnosed during hospitalization and persistent after discharge;

c) hyperglycaemia related with hospitalization: these are undiagnosed diabetics with the first onset of hyperglycaemia during admission to hospital and its regression on discharge.

These forms are not always immediately distinguished. HbA_{1c} testing at the time of admission to hospital is very useful in this regard. (5)

Glycemic control and outcome

Countless evidence has been collected on the association between blood glucose levels during hospitalization and the outcome of hospitalization itself; hence, the attempt to define glycemic goals that can be used in various clinical conditions.

General Medicine and Surgery (non critical patients)

Some studies have highlighted the association in non intensive care wards of blood glucose levels and in hospital- mortality, rate of transfers to the Intensive Care Unit, duration of hospitalization and incidence of hospital infections. This finding also applies to subjects with newly detected hyperglycaemia, whose clinical evolution – according to some – is less encouraging than the one found in known diabetics (6). Both the surgical and medical framework have reported an increase in infectious complications with blood glucose >220 mg/dl (7); a better outcome is, instead, found in patients with fasting blood glucose on admission <126 mg/dl and, anyhow <200 mg/dl when tested at random. (6)

Clinical trials that can define glycemic goals in non critical hospitalized patients are unfortunately lacking. Current ADA guidelines suggest fasting blood glucose =90-130 mg/dl and postprandial <180 mg/dl for hospitalized patients; other authors, instead, recommend a more permissive attitude − even in the light of the risk of hypoglycaemic events − by establishing a pre-prandial range between 90 and 150 mg/dl with no absolute indications for the post- prandial phase. (8)

Coronary Units and Intensive Medical Treatment

The close association between hyperglycaemia and the final outcome in patients admitted to Coronary Units had already surfaced in past observational studies (9): a metanalysis centred on 15 studies and published in 2000 reported that the risk of intra-hospital mortality had significantly increased in subjects with undiagnosed diabetes and blood glucose >110 mg/dl and in diabetics with blood glucose >180 mg/dl at the time of admission (10). A study conducted in 2001 also associated mortality one year after AMI with glycaemia on admission. (11)

In 1999 the DIGAMI study highlighted that a 48-hour insulin and glucose infusion followed by 3 months of intensive insulin treatment in diabetics with acute myocardial infarction was associated with lower short and long term mortality (-30% after 1 year and -11% after 3-4 years) and a lower risk of non fatal reinfarction and heart failure (12). However, the point whether the beneficial effect could be attributed to better glycemic control during the acute phase or to metabolic compensation maintained with subcutaneous insulin delivery even after discharge or both remained undefined. The DIGAMI-2 study, which was designed to answer this question, revealed no significant differences between traditional and intensive treatment, most likely due to methodological problems. (13)

Other studies were conducted on mixed case studies, especially respiratory ones, in medical Intensive Care Units. In this framework, proposed glycemic ranges were 100-139 (14) or 80-110 mg/dl (15); the latter target, identical to the one adopted years before by a randomized controlled study in a Surgical Intensive Care Unit (16), succeeded in significantly reducing morbidity, preventing renal damage, accelerating detachment from mechanical ventilation and shortening hospitalization times in the Intensive Care Unit.

Stroke Unit

Hyperglycaemia and diabetes are frequent in patients with stroke and, they influence both the short term outcome and the rehabilitation. A metanalysis of 26 studies revealed that levels =108-144 mg/dl on admission are associated with increased mortality rates both in hospital and after 30 days in ischemic and haemorrhagic strokes, compared to blood glucose <108 mg/dl. (17)

Labour

Maternal blood glucose testing is essential even in the final stages of pregnancy to avoid foetal hyperinsulinization and, subsequent neonatal hypoglycaemia. Recommended ranges are 70-120 and 70-90 mg/dl, but controlled studies are lacking in this regard.

Heart Surgery

In the framework of heart surgery, close control of blood glucose levels is associated with reduced mortality and a lower risk of deep sternal infections (18,19); this finding strengthens the belief that perioperative hyperglycaemia is an independent predictor of infection. The lowest mortality rates are observed in patients with blood sugar <150 mg/dl. (18)

Intensive Surgical Treatment

The first Van den Berghe trial randomized a group of patients hospitalized in the surgical ICU for either intensive insulin therapy (glycemic target: 80-110 mg/dl) or for traditional treatment (glycemic target: 180-200 mg/dl). Both mortality during hospitalization in the ICU and overall hospital mortality were reduced in the intensive treatment group. Intra-hospital and ICU survival rates directly depended on blood glucose levels, with the highest survival rate in patients achieving mean blood glucose <110 mg/dl. (16)

The potential negative effect of a hypoglycaemic crises during the critical phase must, however, be stressed. A Swedish observational study conducted on diabetic patients with AMI revealed that both hyperglycaemia at the time of admission and hypoglycaemia during hospitalization were independently associated with an increased risk of death in a two-year follow-up period (20). This aspect recalls recent editorials on the need to carefully evaluate the risk-benefit ratio of such urgent glycemic goals during admission to hospital. (8)

Therapeutic Management

An overall picture of the management of hyperglycaemia in non critical hospitalized patients was defined in a recent detailed update published in the New England Journal of Medicine (21). The summary pattern of this approach is proposed once again in Table 25 with minor changes.

Blood Glucose Testing

Capillary blood glucose testing at the point of care has by now become an irreplaceable clinical management factor that enables the speedy implementation of hypoglycaemic treatment patterns. To this end, results must be easy to trace in the patient's case records. In non critical conditions testing can be recommended approximately every 4-6 hours for patients who are unable to take food by mouth, while those with a normal food intake should test blood glucose before meals and when they go to bed, with the

option of adding postprandial and night time testing, when required. Intensive 1-2 hourly testing must be performed during continuous IV insulin infusion, to suit clinical needs.

Oral Hypoglycaemic Agents

There are no systematic studies on the role of the main categories of oral hypoglycaemic agents in the hospital framework. However, all these drugs have characteristics that could recommend against their use in non stabilized patients.

> *Secretagogues.* These long acting drugs and the predisposition towards hypoglycaemia in patients who lack regular food intake contraindicate the use of sulfonylureas in hospital (22). In practice, these drugs do not allow the rapid adjustments required by the changing needs of hospitalized patients. Even if meglitinides (only repaglinide is available in Italy) should theoretically cause fewer hypoglycaemic episodes than sulfonylureas, the lack of data produced by clinical trials should recommend against their use in hospital

> *Insulin-sensitizing agents*

Metformin. The main limitation to the use of metformin in hospital is the risk of lactic acidosis, which is a potentially lethal complication. This condition, which is rare outside hospitals (23,24), is more frequent when there is congestive heart failure, peripheral hypoperfusion, renal failure, elderly age and chronic pulmonary diseases (25), which are frequent conditions in hospitalized patients. Considering the link reported between lactic acidosis and treatment with metformin, caution requires its use to be limited during hospitalization.

Thiazolidinediones. Considering the latency period required to develop their clinical effect, treatment with these drugs should not start during hospitalization. Moreover, they increase intravascular volume, which is a problem, especially for patients who are predisposed towards congestive heart failure, for those with hemodynamic disorders (i.e. acute coronary ischemia) and for those who have undergone surgery.

Insulin

Considering the limits of oral hypoglycaemic agents, the choice treatment for non stabilized hospitalized patients must today be deemed insulin, whose positive effects on short term mortality have been proved by a recent metanalysis. (26)

Subcutaneous insulin administration

Insulin can be administered subcutaneously to most non critical hospitalized patients when continuous intravenous infusion is not indicated. Insulin delivery modes can differ:

As Required

The custom of delivering insulin therapy “as required” (*sliding scale*) with regular insulin injections at established intervals (every 4-6 hours) only if blood sugar exceeds an established threshold is still widespread in our country too, though it is currently deemed an inappropriate and ineffective method (14,27,28). In fact, this approach neither solves the issue of basal insulinisation nor does it prevent hyperglycaemic episodes, since it only intervenes after the episode; it also involves a subsequent risk of hypoglycaemia.

Scheduled multi-delivery patterns

In most diabetic patients, proper insulin treatment requires scheduled patterns that are frequently updated on the basis of blood glucose monitoring with both pre- and post-prandial tests. This basic program is often integrated with a corrective algorithm that considers measured blood glucose levels to avoid excessive glycemic variations and to guide delivery pattern changes over the following days. (27)

Delivery patterns can comprise both human regular insulin or rapid acting insulin analogues at meal times, and delayed action insulin (usually Isophane) or other slow acting analogues, with either one or more administrations a day. There are no studies on the use of insulin analogues in hospital; however, from a practical perspective, they can prove to be advantageous; specifically, the use of rapid acting analogues in correcting hyperglycaemic episodes should involve a lower risk of build up, compared to regular insulin.

Table 25. Schematic hyperglycaemia management model in non critical hospitalized patients (from 21, modified)

NON CRITICAL PATIENT ADMITTED WITH HYPERGLYCEMIA			
Test HbA_{1c}			
Patient with type 1 or type 2 insulin-treated diabetes or clinically significant and persistent newly diagnosed hypoglycaemia.		Patient with type 2 diabetes only treated with diet therapy or with oral hypoglycaemic agents.	
Non eating patient.	Eating patient.	Non eating patient.	Eating patient.
	If there is good glycemic control, continue current homecare (moderately reduce the dosage if a calorie intake reduction is envisaged during hospitalization).		If there is good glycemic control with no contraindications, continue treatment with oral hypoglycaemic agents.
Ensure appropriate sc basal insulinisation (either maintain the dosage administered at home or start with 0.2-0.3 U/kg/day): insulin Isophane every 12 h, insulin Detemir every 12-24 h or insulin Glargine every 24 h, plus corrective sc insulin boluses regular insulin every 6 h for blood	In case of uncontrolled glycaemia, ensure appropriate sc basal insulinisation (higher than the dosage administered at home or start with 0.2-0.3 U/kg/day): insulin Isophane every 12 h, insulin Detemir every 12-24 h or insulin Glargine every 24 h, plus pre-prandial sc insulin boluses (higher than the dosage administered at home or start with 0.05-0.1 U/kg/meal): insulin	Discontinue oral hypoglycaemic agents. Start regular insulin every 6 h: corrective sc insulin boluses >150 mg/dl (variable dose 1-4 U for every 50 mg/dl increase, depending on the envisaged insulin sensitivity level).	In case of uncontrolled glycemia, discontinue oral hypoglycaemic agents (cautious administration of insulin-sensitizing agents can be continued) and start sc basal insulinisation (start with 0.2-0.3 U/kg/day): insulin Isophane every 12 h, insulin Detemir every 12-24 h or insulin Glargine every 24 h, plus sc prandial insulin

sugar >150 mg/dl (variable dose 1-4 U for every 50 mg/dl increase, depending on the envisaged insulin sensitivity level).	lispro, aspart, glulisin or regular, plus corrective sc insulin boluses for glycemia >150 mg/dl (variable dose 1-4 U for every 50 mg increase, depending on the envisaged insulin sensitivity level): same type of insulin used for prandial boluses (to which it must be added).		boluses (start with 0.5-0.1 U/kg/meal): insulin lispro, aspart, glulisin or regular, plus corrective sc insulin boluses for glycemia >150 mg/dl (variable dose 1-4 U for every 50 mg/dl increase, depending on the envisaged insulin sensitivity level): same type of insulin used for prandial boluses (to which it must be added).
If glycemic control is unsatisfactory, make the following corrections, considering other potential causes of hyperglycaemia.			
Change the dose of basal sc insulin by 10-20% every 1-2 days to reach the glycemic target. If the response is inadequate, change the dose of corrective sc insulin boluses by 1-2 U/bolus every 1-2 days.	Change the basal sc insulin dose by about 10-20% every 1-2 days to achieve the glycemic target. If the response is inadequate, change the dose of prandial sc insulin boluses by 1-2 U/bolus every 1-2 days. If the response is inadequate, change the dose of corrective sc insulin boluses by 1-2 U/bolus every 1-2 days.	Add basal insulin (start with 0.2-0.3 U/kg/day); adjust by about 10-20% every 1-2 days to achieve the glycemic target): insulin Isophane every 12 h, insulin Detemir every 12-24 h or insulin Glargine every 24 h. If the response is inadequate, change the dose of corrective sc insulin boluses by 1-2 U/bolus every 1-2 days.	Change the basal sc insulin dose by about 10-20% every 1-2 days to achieve the glycemic target. If the response is inadequate, change the dose of sc prandial insulin boluses by 1-2 U/bolus every 1-2 days. If the response is inadequate, change the dose of corrective sc insulin bolus by 1-2 U/bolus every 1-2 days.
Evaluate IV infusion of insulin.			

Using the insulin pump

Despite the increasingly widespread use of insulin pumps (CSII) for type 1 diabetics (29), there are no studies on their use in hospital. Patients treated with insulin pumps usually have a high capacity of self management of the disease and, if their condition is not critical, they usually need to keep the device operating even during hospitalization. Recommendations on the topic have been recently published (30); however, this choice must be evaluated in various situations, while awaiting the problem to be better defined, taking into account:

- patient's clinical condition;
- experience of the medical staff, nursing staff and dieticians;
- possibility of an immediate consultation with a specialist expert in the management of insulin pumps;
- availability of material required and technical assistance for the specific pump.

Intravenous infusion of insulin: algorithms

Continuous IV insulin infusions always deliver regular insulin. IV infusion therapy is specifically recommended for Intensive Care Units, but also ordinary wards − medical and surgical − often prefer this therapeutic approach, which is necessary to patients who are unable to eat by mouth and to critical patients in a broad sense. Besides diabetic ketoacidosis and non ketotic hyperosmolar coma, the main indications comprise hyperglycaemia associated with the following conditions:

a) perioperative period;

b) heart surgery;

c) organ transplantation;

d) cardiogenic shock;

e) high dosage steroid treatment;

f) need to define total insulin dosage before starting sc insulin therapy.

Recent years have witnessed the proposal of various algorithms that can be directly handled by nursing staff; they envisage adjusting infused insulin doses to suit blood glucose levels tested every 1-2 hours. But, to date, there are no comparative studies between the various algorithms; hence, a specific protocol cannot be recommended. The latest dynamic algorithms that envisage defining the insulin dose both on the basis of absolute glycemic values and of glycemic progress, specifically of the direction and speed of glycemic changes, seem to be especially interesting. Worth mentioning is the one proposed by the Yale University (31), which is illustrated as an example in Table 26. The possibility of managing insulin algorithms with continuous sc glucose monitoring systems also seems to be very promising. (32,33)

Restoring subcutaneous therapy during the post-critical phase

Once the critical phase is overcome, the transition from IV to sc insulin therapy requires the delivery of either intermediate or delayed action insulin 2-3 hours before discontinuing IV infusion and of regular insulin and rapid acting analogues 1-2 hours before discontinuing the IV infusion.

Therapeutic Self-Management

Self-management can be allowed even during hospitalization to diabetic adults who have already achieved an appropriate competence in self-management at home with a known and relatively stable insulin demand and, who can self-administer insulin injection and eat by mouth. The diabetic patient, the attending physician and nursing staff must, however, agree on this procedure.

Nutrition

A personalized nutritional program should be defined to suit therapeutic goals, physiological parameters and concomitant pharmacological therapy. Hence, the diet prescription must be issued by a dietician who belongs to the diabetes team and is expert in medical nutrition therapy. (34)

Preventing hypoglycaemia

Hypoglycaemia, especially in patients under insulin treatment, is the main limiting factor in the management of glycemic control in diabetes. (35)

Even non diabetic patients can suffer from hypoglycaemia during their stay in hospital, in case of malnutrition, heart failure, renal or liver failure, tumours, infections or sepsis (36). The same conditions can worsen the risk of hypoglycaemia in diabetics (37), along with the usual causes of iatrogenic hypoglycaemia; hence, the need for caution when rapidly reducing the dose of corticosteroids and calorie intake and, when there are episodes of emesis. The ability to correctly refer premonitory symptoms must be taken into account; moreover, anaesthesia-related impaired consciousness can conceal the typical symptoms of hypoglycaemia.

Professional figures involved: the diabetologist

Diabetic patients can be effectively managed in hospital by the ward doctor; but, the involvement of either a specialist or a specialist team can shorten hospitalization times and improve blood glucose control and the final outcome (38-40). A team approach is required to define care pathways in hospital.

Educating the patient

Educating patients to self-manage diabetes in hospital is a hard demanding task. Hospitalized patients experience suffering and stress; besides, they are often in environments that do not encourage learning. Basic education however should be provided during the stay in hospital with adequate information to ensure that the patient runs no risks on his return home. Newly diagnosed diabetics and those who have started either insulin treatment or blood glucose self-testing must be trained to guarantee safe management outside the hospital and referred to the competent Diabetes Clinic on discharge from hospital.

Table 26. Dynamic algorithm for IV infusion of insulin, derived from the one adopted by Yale University, New Haven, CT (31)

YALE INSULIN INFUSION PROTOCOL (amended by: A Goldberg PA et al. Diabetes Spectrum 2005;18:188-191)
This infusion protocol is designed for use in hyperglycaemic adults warded in the Intensive Care Unit, but it is not specifically targeted at subjects with metabolic emergencies, like diabetic ketoacidosis (DKA) or hyperglycaemic hyperosmolar conditions. Such diagnoses and blood glucose (BG) ≥500 mg/dl require a medical consultation for specific therapeutic measures. Immediately contact the attending doctor if the response to insulin infusion is either unusual or unexpected or if a condition in which these indications cannot be appropriately applied sets in. Every patient under insulin infusion should have serum electrolytes frequently tested, especially potassium.
STARTING INSULIN INFUSION
1) INSULIN INFUSION: mix 1 unit of regular human insulin with 1 ml 0.9% NaCl normal saline (i.e. 50 U insulin in 50 ml normal saline). Deliver with infusion pump (increasing 0.5 U/h). 2) PRIMING: before starting the infusion, inject 50 ml of the solution in the infusion tubes (to saturate insulin-binding sites in the tubes). 3) THRESHOLD: IV insulin delivery is recommended for patients in critical conditions with persistent blood glucose ≥140 mg/dl; its use must be considered in case of BG >120 mg/dl.

4) GLYCEMIC TARGET: **90-120 mg/dl**.

5) BOLUS and INITIAL INSULIN INFUSION VELOCITY: if initial blood sugar is ≥150 mg/dl, divide by 70, then round off with the closest 0.5 U for the bolus and for the initial infusion velocity. If initial GM is <150 mg/dl, divide by 70 only the basal infusion velocity (NOT the bolus).

Examples: 1) initial GM = 335 mg/dl: 335:70=4.78, round off to 5: deliver an IV bolus of 5 U and start infusion at 5 U/h.

2) Initial BG = 148 mg/dl: 148:70=2.11, round off to 2: start infusion with 2 U/h (**DO NOT administer the bolus**).

MONITORING BLOOD SUGAR)

1) Hourly test BG till it stabilizes (3 consecutive tests within the target). In patients with low blood pressure, capillary blood glucose testing (i.e. tested on the thumb) may not be accurate; hence, it is better to sample blood from a fixed vascular catheter.

2) Then test BG every 2 h; once levels have stabilized for 12-24 h, BG testing can be performed every 3-4 h, if:

a) there are no significant changes in clinical conditions, and b) there are no significant changes in nutritional intake.

3) Evaluate a temporary return to hourly BG testing till new stabilization is achieved or if one of the following conditions occur:

a) any change in infusion velocity (hence, BG outside the reference range);

b) significant change in clinical conditions;

c) either start or discontinue pressure or steroid treatment;

d) either start or discontinue haemodialysis or continuous veno- venous hemofiltration (CVVH);

e) start, discontinue or change nutritional intake velocity (NPT, NPP, enteral tube nutrition, etc.).

CHANGES IN THE INSULIN INFUSION VELOCITY

If BG <50 mg/dl: STOP INSULIN INFUSION **If BG=50-69 mg/dl: STOP INSULIN INFUSION**	- Inject 25 g of glucose IV (50 ml of 50% glucose solution or 75 ml of 33% glucose solution); retest BM every 10-15 minutes. - With BG ≥90 mg/dl, wait 1 h and, retest BG. If it is still ≥90 mg/dl, resume infusion at half the last velocity. **if the patient is symptomatic (or unable to evaluate symptoms)**: inject 25 g of glucose IV (50 ml of 50% glucose solution or 75 ml of 33% glucose solution); retest GM every 15 minutes. **If the patient is asymptomatic**: evaluate the injection of 10-15 g of glucose IV (20-25 ml of 50% glucose solution, or 30-45 ml of 33% glucose solution) or the oral administration of 200 ml of fruit juice. - With BG ≥90 mg/dl, wait 1 h, retest BG. If BG is still ≥90 mg/dl, recommence infusion at 75% the last velocity.

If GM ≥70 mg/dl:

STEP 1: Define the CURRENT GM LEVEL – this identifies a COLUMN in the table:

GM =70-89 mg/dl

GM =90-119 mg/dl

GM =120-179 mg/dl

GM ≥180 mg/d

STEP 2: Define CHANGING VELOCITY, compared to the previous GM level – this identifies a CELL in the table – From there, move to the right for INSTRUCTIONS. [Warning: if BG was last tested 2-4 h before the current BG, calculate the hourly velocity change. Example: if BG was 150 mg/dl at 2.00 pm, and now at 4.00 pm it is 120 mg/dl, the overall change in the 2 hours is -30 mg/dl; however, the hourly change is thus calculated: -30 mg/dl: 2 hours = -15 mg/dl/h.]

GM =70-89 mg/dl	GM =90-119 mg/dl	GM =120-179 mg/dl	GM ≥180 mg/d	INSTRUCTIONS*
		GM ↑ >40 mg/dl/h	GM ↑	↑ **INFUSION by "2Δ"**
	GM↑ di >20 mg/dl/h	GM ↑ 1-40 mg/dl/h, or **GM UNVARIED**	**GM UNVARIED**, or GM ↓ 1-40 mg/dl/h	↑ **INFUSION by "Δ"**
GM↑	GM ↑ 1-20 mg/dl/h, or **GM UNVARIED**, or GM ↓ 1-20 mg/dl/h	GM ↓ di 1-40 mg/dl/h	GM ↓ di 41-80 mg/dl/h	**DO NOT CHANGE THE INFUSION**
GM UNCHANGED or GM ↓ 1-20 mg/dl/h	GM ↓ 21-40 mg/dl/h	GM ↓ 41-80 mg/dl/h	GM ↓ 81-120 mg/dl/h	↓ **INFUSION by "Δ"**
GM ↓ >20 mg/dl/h See below^	GM ↓ > 40 mg/dl/h	GM ↓ >80 mg/dl/h	GM ↓ >120 mg/dl/h	**DISCONTINUE x30' then ↓ INFUSION by "2Δ"**

^ DISCONTINUE INSULIN INFUSION; test BG every 15-30 min; when it is ≥90 mg/dl, recommence

infusion at 75% of the previous velocity.		
***INFUSION VELOCITY CHANGES ("delta" or "Δ") are defined on the basis of the current infusion velocity.**		
Current velocity (U/h)	D = velocity change (U/h)	2 D = 2 xvelocity change (U/h)
<3	0.5	1
3-6	1	2
6.5-9.5	1.5	3
10-14.5	2	4
15-19.5	3	6
20-24.5**	4**	8**
≥25**	5**	10**

** Depending on the clinical condition, infusion velocity is generally 2-10 U/h.
Doses higher than 20 U/h are unusual and, if they are required, the doctor in charge should be informed in order to consider other potential concurrent factors (including technical problems, like dilution errors, etc.).

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B. DIABETES CARE AT SCHOOL AND IN DAY CARE CENTRES

R E C O M M E N D A T I O N S

> The diabetes team must draft a personalized care plan for the diabetic student with parents/guardians. (**VI, B**)

> An appropriate number of school teachers or other employees should be trained in procedures to be implemented for hypoglycaemic episodes. These people must not necessarily be healthcare professionals. (**VI, B**)

> Diabetic students must have instant access to whatever they need for diabetes treatment at all times and under supervision if it is necessary. (**VI, B**)

> The student must be able to test blood glucose in the classroom and to treat hypoglycaemia either in the classroom or wherever he is for schooling activities, as envisaged by his care plan. (**VI, B**)

COMMENT

Italy counts about 8,000-10,000 individuals aged under 18 years with diabetes (1); most of them attend school, hence the need to guarantee a safe environment through appropriate personnel training. Often diabetics attending school still face discrimination. Parents and the diabetes team should develop a "personalized care pathway" with school personnel to provide the information required to enable the diabetic child to fully and safely participate in the schooling experience. Appropriate diabetes care at school is necessary for the child's immediate safety, long term wellness and better performance at school. (2)

An appropriate number of either school teachers or other employees should be trained in some necessary diabetes care procedures (i.e. blood glucose monitoring) and measures to be implemented in case of either hypoglycaemia or hyperglycaemia. This will ensure that at least one adult is present and speedily takes part in the necessary measures when the student is at school, on a school trip or participates in other school events. These people need not be healthcare professionals.

The diabetic student must have immediate access to what he needs for diabetes care at all times, under supervision, if necessary; he must be able to test blood glucose and to implement the necessary measures in the fastest and most appropriate way, minimizing the loss of classroom lessons. Subsequently, a student who can do so must be able to test his blood glucose in class and treat it wherever he is for school-related activities. Even the student's need for privacy to perform the test and apply the necessary measures must be guaranteed.

Other countries deem that school staff must be trained to administer insulin and glucagon: this recommendation is, for instance, inserted in the ADA's *Standards of Care* (2). In Italy, however, legal provisions and school regulations do not oblige healthcare professionals to perform these tasks; they are often forbidden to either perform blood glucose testing or to administer insulin and glucagon. Protocols drafted by the Regional Administration on agreements between healthcare facilities and schools should be referred to, whenever they are available.

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C. DIABETES CARE IN DIABETES EDUCATIONAL CAMPS

RECOMMENDATIONS

> Every participant in an educational camp must have a standardized case record filled out by both the family and the attending diabetologist. (**VI, B**)

> Medical healthcare staff must be guided by an expert in the management of type 1 and type 2 diabetes and must comprise educators and nurses specialized in diabetes, besides dieticians skilled in diabetes. (**VI, B**)

> All camp personnel − doctors, nurses, nutritionists and voluntary workers − must undergo a basic training test to ensure the appropriate working mode with children. (**VI, B**)

COMMENT

The concept of residential or day-care camps for diabetic children has spread extensively in various parts of the world (1).

These camps especially focus on guaranteeing a holiday experience in a safe environment where education and practical training will be provided on diabetes management, also enabling young diabetics to be autonomous from the family to build responsible disease management.

Children should be involved under supervision in interesting and exciting sports activities to show the compatibility of such activities with diabetes.

Another equally important goal is to enable diabetic children to meet and share their experiences. This requires the attendance of qualified personnel, both medical and for camp organization, to ensure the safety of diabetics.

The camp experience is brief and, is generally associated with a greater degree of physical exercise than what is practiced at home. Hence, blood glucose control must focus on avoiding extreme blood glucose fluctuations rather than optimize glycemic control.

All participants in the camp must have a standardized case record filled out by both the family and the diabetologist with a detailed explanation of the case history, vaccinations administered and habitual diet. The case record must also report the dose and type of insulin, besides the time the injection is administered at home.

The participant's glycemic progress must be daily recorded during the camp. All blood glucose levels and insulin doses must be recorded. To guarantee patient safety and optimal diabetes management, blood glucose must be repeatedly tested during the 24 hours: before meals, when going to bed, after or during intensive prolonged physical exercise, half way through the night when recommended due to a past hypoglycaemic episode.

If important diet changes are recommended, they should be discussed with the patient, his family and his attending diabetologist.

Documentation of camp events must be discussed with the family when they come for the child.

Every camp must ensure formal relations with a medical facility nearby, so that the camp's medical staff can refer to this facility for immediate treatment for medical emergencies.

Medical staff must be guided by a person who is experienced in the management of type 1 and type 2 diabetes.

Healthcare staff must comprise educators and nurses specialized in diabetes. Dieticians experienced in diabetology must contribute towards the draft of both the menu and the educational program. The entire camp staff − doctors, nurses, nutritionists and voluntary workers − must undergo a basic training test to ensure their fitness to work with children.

Italy counts many educational and holiday experiences organized by both medical and lay institutions.

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D. DIABETES IN HOUSES OF CORRECTION

RECOMMENDATIONS

> At the time of access to the house of correction, diabetics should promptly have a complete case history taken and undergo a complete examination on the part of healthcare personnel. (**VI, B**)

> Patients with type 1 diabetes must be identified due to their high risk of diabetic ketoacidosis. Insulin treated patients should have capillary blood glucose tested within 1-2 hours after arrival. (**VI, B**)

> Pharmacological treatment must be continued without interruption. (**VI, B**)

> The penitentiary doctor should establish every patient's calorie requirement and diet composition. (**VI, B**)

> Menus served must be balanced and based on healthy Italian diet recommendations. (**VI, B**)

> Capillary blood glucose testing must be organized following formal protocols well defined to suit the type of diabetes, treatment and diet. (**VI, B**)

> If the patient is imprisoned in a penitentiary institute that lacks continuous nursing service, he should be moved to a second level penitentiary institute to appropriately face diabetes-related clinical needs and insulin delivery, if required. (**VI, B**)

> Prisoners under treatment with oral hypoglycaemic agents and/or insulin with a tendency to self harm and those who have psychiatric disorders must be ensured special attention. (**VI, B**)

> The patient must be provided with a source of rapid absorption sugars to be taken at the first signs of a hypoglycaemic crisis. (**VI, B**)

> Regular continuous physical exercise must be encouraged (at least 30 min.) 3-4 days a week; a daily activity plan to be performed during airing time can be agreed with the patient when there are no appropriate facilities. (**VI, B**)

> Procedural protocols must be processed and spread to ensure the entire healthcare staff appropriate knowledge on the management of metabolic emergencies (i.e. hypoglycaemia and hyperglycaemia); moreover, the diabetic patient must be provided with appropriate education. (**VI, B**)

> Reference facilities must be found either inside or outside the main clinical centres of penitentiaries for diagnosis and periodical staging of chronic complications and for the management of diabetic emergencies. (**VI, B**)

> If a diabetic is transferred from one house of correction to another, a summary medical report must be filled out to accompany the patient on the journey. (**VI, B**)

> Medications and drugs required to treat diabetes must accompany the patient on the journey. (**VI, B**)

> The discharge plan must be established in appropriate advance to ensure care continuity and, in case of release from prison, to facilitate the patient's admission to external healthcare facilities. (**VI, B**)

COMMENT

The *Associazione Medici Amministrazione Penitenziaria Italiana* (Italian Association of Penitentiary Administration Doctors -AMAPI) and the *Società Italiana di Medicina Penitenziaria* (Italian Society of Penitentiary Medicine - SIMPe) published a paper on *La Gestione del diabete in carcere* (Diabetes Management in Prison) in 2005. (1)

The problem's dimensions

According to recent data published following a survey promoted by penitentiary administration doctors, 4.5% of prisoners in Italy suffered from diabetes mellitus in a prison population of about 60,000 units (numbering over 95% of men) on 31 December 2005; of these, 30% were treated with insulin. The percentage was the same as the one in the USA, where about 80,000 of the over 2 million prisoners were diabetics. (2-3)

Considerations on healthcare

Access to prison and the stay in a "hostile" environment − with the subsequent loss of personal freedom and repercussions both on the emotional condition and on self esteem − involve prolonged stress that can potentially interfere with the metabolic balance of people who either have or are at risk of diabetes. Moreover, the lack of even the lightest physical exercise program (especially where there are no appropriate facilities) and an often unbalanced diet are obstacles to achieving good glycemic control in patients living in seclusion. Concerning the diet, it must be stressed that Ministerial diet tables do not envisage personalized diets − as would be hoped for diabetes care − assigning every diabetic prisoner an intake of 1,800 kcal/day, often with a high content of fat and proteins and a low intake of fiber. The same tables envisage a calorie intake of about 3,500 kcal for healthy adults. These conditions, along with those resulting from the management of hypoglycaemic treatment, from the difficulty to treat metabolic emergencies and the impossibility to perform periodical screening for complications, must be carefully considered on access to the house of correction, so that national diabetes care standards are met by these facilities too.

Evaluation at the time of access to prison should guarantee the patient's utmost safety. Specifically, it is essential to immediately identify all insulin-treated patients to recognize those with the highest risk of acute metabolic complications (i.e. hypoglycaemia, hyperglycaemia and ketoacidosis). Pharmacological treatment must be continued without interruption

and diet characteristics (calorie content and composition) should be established in a personalized manner. When it is deemed necessary, capillary blood glucose testing must be performed according to well defined protocols related to the type of diabetes, treatment and diet.

The therapeutic approach must be personalized: in type 1 diabetics insulin treatment must be optimized

with 4 daily administrations; a simplified insulin pattern with 3 daily administrations can be envisaged for special cases. In type 2 diabetics oral hypoglycaemic agents (not those with a long half life) must be correctly administered to suit meals; special attention must be given to prisoners under treatment with oral hypoglycaemic agents with a tendency to self harm or with psychiatric disorders.

Special attention must be dedicated to the educational and training aspects both of the patient and of facility personnel. To this end, it is important to establish from the very first days relations based on cooperation between healthcare personnel (both medical and non medical) and the diabetic patient. Structured educational activity must be scheduled when possible with training and educational courses targeted at diabetics. Periodical refresher courses about diabetes are recommended for medical and healthcare staff within prison walls.

A precise definition of procedures for the treatment of metabolic emergencies must envisage processing protocols that are easily accessible to all healthcare staff and to personnel in contact with the diabetic patient.

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IX. DIABETES MELLITUS AND REGULATIONS

A. DRIVING LICENCE MEDICAL REPORT

Ministerial guidelines (1)

- The evaluation of the clinical symptoms of diabetes performed by diabetes specialists employed by NHS facilities must necessarily integrate the evaluation of personnel authorised to issue medical reports concerning fitness to drive, especially for advanced expiry dates.

- The final judgment of fitness for higher category licenses (C, D, CE, and DE) is the competence of the Local Medical Commission.

- For A, B and BE category licenses, the presence of diabetic complications that can cause a high risk for safe circulation and doubts concerning fitness to drive requires the opinion of a Local Medical Commission.

- In case of doubt, the specialist can always refer the opinion on fitness to the Local Medical Commission.

> The opinion on fitness issued by the specialist must be based on the degree of metabolic control, on the frequency and characteristics of hypoglycaemic reactions and, on the presence and gravity of chronic complications.

- Glycemic control is evaluated on the basis of HbA_{1c} levels, as appropriate (HbA_{1c} <9.0%) or inappropriate (HbA_{1c} >9.0%).

- In the final evaluation, the subject with diabetes mellitus can be identified with a low, medium or high risk profile.

- In subjects with a low risk profile, no limitations may be envisaged concerning the expiry date of the licence.

- In situations characterized by a higher risk profile (excluding “high” risk conditions, which are the competence of the Local Medical Commission), a shorter validity period will be established by the specialist, depending on the degree of calculated risk directly related with the presumed future development times of complications.

R E C O M M E N D A T I O N S

> The state of chronic complications must be ascertained within the past 12 months. (2)

> The HbA_{1c} assay used to classify the degree of glycemic compensation must be performed within the past 3 months. (2)

COMMENT

Law number 85 dated 22.03.2001 published in the *Gazzetta Ufficiale della Repubblica Italiana* number 76 dated 31.03.2001 (3) amended article number 119 of the new Road Code (4), specifying that "the ascertainment of psychic and physical requisites in subjects with diabetes mellitus to attain, review or confirm A, B, BE category and subcategory licenses is performed by NHS specialists in diabetology and metabolic diseases." Higher category licenses (C, D, DE and subcategories), instead, remain the competence of the Local Medical Commission integrated with a diabetologist, in compliance with Law number 472 dated 7 December 1999. The diabetologist is thus deemed a forensic expert.

The practical application of these legal regulations has been very heterogeneous throughout the national territory, with regional differences.

In 2002 the Tuscan Regional Administration drafted exhaustive and organic guidelines on attaining, reviewing and confirming licenses belonging to A, B, BE categories and subcategories for subjects with diabetes mellitus. These guidelines are contained in Deliberation number 490 dated 20 May 2002. (3,5)

But there remained the need for a national univocal application of the regulation and, this led to the formation of a Technical Group comprising experts of the Ministry of Health and Ministry of Transport and experts appointed by the scientific diabetes associations (AMD and SID), in the General Administration for Preventive Healthcare, in collaboration with the General Administration for Motorisation, over the past months.

This group's work was completed on 04.05.2006 with the publication of a well known Circular Letter of the Ministry of Health *Linee-guida per l'accertamento e la valutazione della capacità alla guida di soggetti affetti da diabete per il conseguimento, la revisione, o la conferma delle patenti di categoria A, B, BE* [Guidelines on ascertaining and evaluating driving skills in diabetic subjects who wish to attain, review or confirm an A, B or BE category licence]. (1)

Stressing "the need for standardized consistent evaluation criteria throughout the national territory to guide decisions concerning advanced driving license expiry to ensure safe driving for diabetics presenting complications (if the extent of the latter does not involve unfitness to drive)", this paper has highlighted the central role played by NHS diabetes, concurrently providing general indications that must be followed when issuing the opinion on fitness to drive and when establishing an advanced expiry, if required.

The evaluation, which must be recorded in a special form, must take into account certain clinical criteria that are deemed essential to discriminate the driving risk profile.

Glycemic control, which is classified to suit HbA_{1c} levels (the test is "appropriate" <9.0%, "not appropriate" >9.0%), must first be considered.

Even the frequency and characteristics of hypoglycaemic episodes are very important: the opinion "good", "acceptable"

and "poor" may depend on the number of episodes in a month (i.e. <2, 2-4 or >4); this opinion must also envisage evaluating the ability to both recognize and manage hypoglycaemia.

The above parameters are completed with a precise consideration of the status of microangiopathic and macroangiopathic complications, finally specifying the overall risk profile that will be defined "low", "medium" or "high", according to the pattern described below:

1. LOW risk profile:
   – no retinopathy;
   – no neuropathy;
   – no nephropathy or microalbuminuria;
   – well controlled hypertension;
   – ADEQUATE glycemic control;
   – GOOD overall opinion on hypoglycaemic episodes;

2. MEDIUM risk profile:
   – background or proliferating retinopathy, if sight preservation is good;
   – mild vegetative or sensitive-motor neuropathy, if the preservation of sensitive perception and motor capacity is good;
   – nephropathy, if there is only macroalbuminuria;
   – hypertension, if well controlled;
   – ischemic heart disease, if well controlled;
   – INADEQUATE glycemic control;
   – ACCEPTABLE overall opinion on hypoglycaemic episodes;

3. HIGH risk profile:
   – proliferating retinopathy with impaired sight;
   – severe autonomous or sensitive-motor neuropathy, with loss of sensitive perception and motor capacity;
   – nephropathy with chronic renal failure;
   – uncontrolled hypertension;
   – recent (<1 year) or uncontrolled coronary heart disease;
   – INADEQUATE glycemic control;
   – POOR overall opinion of hypoglycaemic episodes.

The Circular Letter issued by the work group provides neither precise indications concerning certain investigational methods that must be applied when evaluating chronic complications nor a validity period for the clinical and investigational tests on which the opinion of fitness must be based: in this regard, it seems realistic to refer to recommendations published in the previously mentioned regulation issued by the Tuscan Regional Administration (it is basically equivalent to other regional regulations):

– diabetic retinopathy: complete ophthalmological examination including *fundus oculi* performed within 12 months;
– diabetic neuropathy: case history with targeted questionnaire, neurological examination (even by biothesiometer) performed within 12 months;
– diabetic nephropathy: renal function indexes performed within 12 months;
– diabetic macroangiopathy: electrocardiogram performed within 12 months;
– metabolic control: HbA1c assay performed within 3 months.

The established advanced expiry of the license must be based on the risk evaluation that fitness can be lost due to the predictable evolution of the disease in later years.

No validity limitations concerning normal expiry may be envisaged for "low" risk subjects, while "medium" risk subjects will have duration limitations that directly depend on the predictable evolution period of detected impairments. A date for another assessment will be fixed, if an opinion of temporary unfitness is given.

The opinion on the fitness of "high" risk subjects must, instead, be referred to the Local Medical Commission.

The 2006 Circular Letter provides no indications whatsoever even concerning the possible degree of limited validity; once again we can approximately consider specifications issued by the Tuscan Regional Administration:

– no complications, with good glycemic control (category: "low" risk profile): no limitations;

– no complications with unacceptable glycemic control (category: "medium" risk profile): limited to 1-3 years;

– presence of mild complications with good glycemic control and no significant hypoglycaemic episodes (category: "low"-"medium" risk profile): limited to 5 years;

– presence of medium complications and/or unacceptable glycemic control (category: "medium" risk profile): limited to 1-3 years;

– presence of medium-serious complications, irrespective of glycemic control (category: "medium"-"high" risk profile): limited to 1 year or, in special cases, to 6 months;

– presence of serious complications, serious or unaware hypoglycaemic episodes or other situations that can compromise safe driving (category: "high" risk profile): the patient is referred to the Local Medical Commission.

A patient can however be referred to the Commission, if the specialist deems it necessary for doubtful cases.

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B. CIVIL DISABLEMENT

Diabetes mellitus is a disease that is deemed as disabling; hence, the access to all facilitations envisaged by current regulations, proportionately with the degree of disablement (1). But associations of patients and healthcare professionals have long fought against the idea of diabetes as a disabling disease (see, for instance, the latest achievements concerning driving licenses).

Reasons can lead to the presentation of an application for civil disablement and, the diabetic will be subsequently acknowledged:
– the right to be listed for compulsory employment;
– higher age limits for public competitions;
– the right to obtain duties that are compatible with the disabling infirmity;
– better guarantees for the preservation of the work place;
– a possible right to certain forms of subsidizations.

The application for civil disablement is evaluated by a medical commission comprising a specialist in forensic medicine, who acts as president, and two doctors, one of whom is chosen – as a priority – from specialists in occupational medicine (Law number 295 dated 15.10.1990). (2)
Ministerial Decree dated 05.02.92 (3) distinguishes 4 categories (I-IV) that consider:
– the type of diabetes;
– metabolic control;
– presence/absence of complications and, the degree of damage.

Then the various disablement percentages are defined, depending on the category the subject belongs to (see table). People with type 2 diabetes mellitus with good metabolic control (category I) or type 1 diabetes mellitus with good metabolic control or type 1 and 2 diabetes mellitus with initial microangiopathic and macroangiopathic signs that can only be detected with diagnostic investigations (category II) must not be deemed as disabled because they do not reach the minimum disablement percentage, unlike the categories mentioned herein.
Unfortunately the interpretation of these regulations is left to the common sense of forensic commissions, since the definition is rather general, and this generates processing disparities between commissions.
The medical commission must fix an ascertaining examination within three months after the application is presented; in case of non compliance with the said deadline, the party concerned can present a notice to the competent regional office, which will fix the visit within the maximum deadline of 270 days from the date the application is presented; failing a response (rejecting silence), the party can resort to the ordinary judge.
The person who has been acknowledged civil disablement can apply for recognition of increased damage.
The application is presented along with a form that can be found at the related NHS clinics and an annexed medical certificate precisely specifying and documenting that the disablement has either worsened or that there are new handicaps.

CATEGORY	DISABLEMENT %	
	MINIMUM	AXIMUM
Type 1 or 2 diabetes mellitus with microangiopathic and macroangiopathic complications and medium clinical expression. (Class III)	41	50
Insulin-treated diabetes mellitus with either poor metabolic control and dyslipidaemia or frequent hypoglycaemic crises, despite treatment. (Class III)	51	60
Diabetes mellitus complicated by acute nephropathy and/or proliferating retinopathy, maculopathy, vitreous bleeding and/or obstructive arteriopathy. (Class IV)	91	100

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C. MEDICATION, EQUIPMENTS AND SUPPLIES FOR PATIENTS WITH DIABETES MELLITUS

RECOMMENDATIONS

> Patients and professionals should have access to all categories of devices and medication required to treat diabetes with no unjustified limitations. (**VI, B**)

COMMENT

To facilitate achieving glycemic goals and to reduce the risk of complications, it is essential for diabetics to have access to the various medications that are currently deemed an integral part of the management of this disease. To this end, healthcare devices like syringes, needles, glucometers and reactive strips must be provided in an adequate quantity for the type of diabetes and clinical situation, with no unjustified limitations that could hinder treatment efficacy.

In compliance with Ministerial Decree dated 8 February 1982 (1) and Law number 115/87, art.3 (2), medications supplied to subjects with diabetes mellitus are defined by type, as specified below. This general regulation may be adjusted by Regional Laws and/or local regulations or agreements with individual Local Healthcare Administrations (LHA). (3)

1. Insulin injection syringes: they can be given to patients under insulin treatment in the same number as the daily injections for a one-month period. These syringes must have no dead space; they must be sterile and disposable with a welded needle and 28G-30G needle diameter. Syringes must have a U100 scale with 0.5 or 1.0 ml capacity. Paediatric patients will also be given 0.3 ml U100 syringes on request. Patients using

the pen injection system, instead of traditional syringes, can be supplied at most two cartridge pens, always with the diabetologist prescription. Needles compatible with the pen will be supplied in the number required for monthly injections. These insulin injection systems too require a prescription from the diabetologist.

2. Lancets for finger prick devices: it is deemed useful to supply them in the same number as the reactive strips for blood glucose testing, considering the marketed disposable products and the wording printed on them: “sterile, disposable”.

3. Reactive strips for blood glucose testing: the patient has the right to receive the reactive strips he normally uses for capillary blood glucose testing with the glucometer in his possession. The number of reactive strips that can be prescribed varies by region and type of diabetes, treatment, glucose metabolism compensation and the presence of intercurrent diseases. However, the diabetologist will always be the one to define and quantify the requirements of patients for the various medical devices. Scientific diabetes societies have recently published recommendations in this regard. (4)

4. Portable glucometers with optical blood glucose level readers with therapeutic indication for self-testing and self-management of the disease can only be supplied with a diabetologist prescription.

5. Insulin pumps: they can only be supplied to highly screened patients, who are motivated and appropriately instructed and only following the specific opinion of a diabetologist employed by a 2nd level Diabetes Unit or 1st Level Units that are already experienced in this field. Of the various infusion systems, the most modern and reliable models should be privileged. In this case too, the Local Health Administration will purchase the devices, which will be provided to patients free of charge on gratuitous loan for use by Diabetes Units. When the Diabetes Clinic is in hospital, the LHA must obviously agree with the Hospital Administration concerning the most appropriate mode of facilitating citizen access to these devices. Material required by the device, which can be supplied in the quantity required to ensure its correct function, can only be the one that best suits the device.

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D. THERAPEUTIC PLAN - RELATED PRESCRIPTION DRUGS

Till recent years, diabetics were supplied commonly used drugs (insulin and oral hypoglycaemic drugs, all preparations belonging to refundable drug category A) prescribed by either the NHS specialist or the general practitioner. Recently marketed new drugs have introduced various prescription modes.

The problem initially concerned the delayed action insulin analogue glargine and Thiazolidinediones (glytazones), whose distribution was limited to the hospital framework for some years due to their classification in category H. The situation has partly changed since 2005, when the Italian Drug Agency (AIFA) decided to reposition glargine, pioglitazone and rosiglitazone in the refundable category A with a prescription that required both the diagnosis and a therapeutic plan drafted by a specialist centre (1). The same methods were then applied following the AIFA’s decree dated 27.02.2006 to detemir, another long

acting analogue that has only shortly been marketed in our country. (2)

Since May 2006 the therapeutic plan is not required for Thiazolidinediones (glytazones).

Even some hypolipidemic drugs are listed in this prescription category, but only for high dosages (40 mg) of Rosuvastatin and Atorvastatin.

Considering the single national reference scene, the current regulation leaves room for some applicative differences in the local framework with methods that vary by region and, at times, even by LHA, depending on the organizational decisions and healthcare strategy adopted in each framework.

The AIFA's 2004 decision (3) concerning the *Prontuario della Distribuzione Diretta − PHT* [Handbook for Direct Distribution], which lists drugs required to ensure that patients are both accepted by Hospital (H) and Territory (T) and guaranteed ongoing healthcare, also envisages the "mixed" distribution of the said drugs. They can be supplied either through NHS hospital frameworks (hospitals and LHA) or through territorial channels (pharmacies outside hospitals).

Considering this dual possibility, the decision to prefer hospital distribution – some local administrations are thus inclined for reasons that mostly depend on financial management – should be re-evaluated case by case, since this method could make the patient's access to drugs less easy and rapid in certain local situations.

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X. IMPROVEMENT STRATEGIES FOR DIABETES CARE

The systematic implementation of diabetes care standards has proved to be inadequate in various clinical contexts. Data published in the *Annali AMD 2006* (1) prove, for instance, that the lipid profile was only evaluated in about 63% of subjects in 86 Diabetes Clinics in 2004, that blood pressure is only evaluated in 70% of subjects, that nephropathy is monitored only in about 50% and that the feet are examined only in 50% of subjects at risk. Intermediate outcome indicators highlight that 25.5% of type 1 and 43.1% of type 2 diabetics achieved the HbA_{1c} goal, that 32.2% of type 1 and 29.8% of type 2 diabetics achieved the LDL cholesterol goal and the blood pressure target was achieved by 65.5% of type 1 and 36.6% of type 2 diabetics.

Most likely the main cause of inadequate treatment levels must be sought in the service supply system, which is only too often fragmentary, lacks clinical information skills, often fails to coordinate services and, lastly, is not designed to provide treatment for chronic diseases. The Italian *Piano nazionale per le linee-guida* [National Plan for Guidelines] (2) and the *Piano nazionale per la prevenzione* [National Plan for Prevention] (3) are active in view of intervening on these issues. In this framework Project IGEA (Integration, Management, Healthcare) (4) focuses on organizing a collaborative network for diabetes healthcare between General Medicine and Diabetes Clinics, also by applying evidence-based targeted organizational guidelines.

Collaboration within the multidisciplinary team should be appropriately organized and sustained with targeted interventions to guarantee this type of treatment in patients with chronic diseases, like diabetes, and to improve the performance of patients concerning appropriate self-management. In recent years, many healthcare organizations have developed strategies to improve diabetes care. Effective interventions have focused on healthcare professionals, supply systems and patients. The features of some of these successful interventions published in literature comprise:

– improving the education of healthcare professionals concerning treatment standards through formal and informal educational programs;

– promoting education towards diabetes self-management, which has proved effective in increasing adherence to treatment standards;

– adopting guidelines that witness participation in the definition process of all healthcare professionals; guidelines should be easily accessible in work places, on the patient's case record, in visiting rooms, in handouts, on hand-held PCs and on computer networks in medical facilities; guidelines should be introduced by a summary of the main recommendations that inform the healthcare professional on "what to do" and "how to do it";

– using check-lists that mirror guidelines; the method has proved effective in improving adherence to treatment standards;

– changing process recording and documentation systems and the availability of automatic memos for > healthcare professionals and patients and of result indicators for operators, especially to identify subjects at risk due to the failure to achieve treatment goals or the lack of recorded data;

– adopting quality improvement programs that combine analysis cycles and quality checks with interventions based on the performance data of operators;

– changing certain aspects of clinical practice, like, for instance, grouping visits dedicated to diabetics in specific moments of a general medicine program and/or organizing visits with different healthcare professionals on the same day and in groups;

– adopting systems to define people who need evaluations and/or treatment changes − both with electronic case records and patient records − has proved to be useful in increasing adherence to treatment standards; these systems could most likely be more effective if they also suggested specific therapeutic interventions; (5)

– both doctors and patients have found the use of various non automatic systems, like a mailed memo to patients, stickers on case records and treatment flow charts encouraging;

– the availability of treatment programs dedicated to a specific case or (preferably) to a specific treatment that is normally administered by a nurse. The contributions of nurses, pharmacists and other non medical healthcare professionals skilled in using detailed algorithms under the supervision of a doctor and/or a nurse-educator have proved to be useful. Likewise, the interventions of dieticians − who can use guidelines on medical nutrition therapy – have proved effective in improving glycemic control;

– the helpfulness and involvement of expert consultants, like consultant diabetologists and educators, in general medical care.

Evidence reveals that these single initiatives yield their best when they are provided as individual components of a multifactor intervention. It is, hence, hard to evaluate the contribution of every individual component; in any case, it is clear that optimal management of diabetes requires an organized and systematic approach, besides the involvement of a coordinated team of healthcare professionals.

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APPENDIX: DIABETES INDICATORS

INTRODUCTION

Measurement, analysis and improvement

The measurement of professional performance and the subsequent feedback of information are essential in facilitating knowledge building and ongoing improvements in healthcare.

The growing worldwide interest in indicators mirrors the need to measure processes and healthcare outcomes. Hence, diabetic unit must plan and implement monitoring, measurement and analysis actions required to prove product compliance with the standards of the best current scientific knowledge and, to steadily improve the efficacy of healthcare activities.

The diabetic unit should overcome the concept of one-to-one duties, of attention focused on the single patient and, hence, on measurement of the efficacy of personal actions on individual parameters to build an information system designed to systematically collect individual data with the aim to measure the success of global performance. The goal is to highlight problems in an attempt to change the clinical, therapeutic, management and economic outcome (see Table 27).

Table 27

ISO 9001:2000
8.2.3 Monitoring and measurement of processes Monitor and measure the performance of the processes that make up the QMS. Compare these actual results to the planned results. Take corrective action to make sure the product or service meets requirements
ISO 9001:2000
8.2.4 Monitoring and measurement of products During the production process, monitor and measure the product to assess if requirements are met. Keep records showing: • The product meets acceptance criteria. • The name of the person who authorized release of the product. • The product has proceeded through all of the planned process steps, including all planned verifications.

Indicators are variables that describe the complex phenomena of healthcare to facilitate decisions concerning either implementing or maintaining changes.

An indicator requires quality attributes, in fact, it must:

- measure important aspects of healthcare quality;
- measure in a valid, precise, accurate, reproducible manner;
- be speedily measurable in the framework of available resources;
- be able to direct decisions;
- be able to differentiate the various conditions;
- obtain consensus regarding its meaning and mode of use.

From: *Joint Commission on Accreditation of Healthcare Organizations. Characteristics of indicators in primer on indicator development and applications. Oakbrook Terrace (IL) 1990.*

Hence, the choice of indicators that can meet all quality requirements, either entirely or almost entirely.

Type of indicators used:

1 – process

2 – intermediate result

3 – final result.

Note: measurement methods must ensure that products comply with the current standards and expectations of reference subjects' privileged indicators obtained from data collected during daily activity management. The AMD data file, a tool currently accessible in Italy to those who either use compatible electronic case records (most of them) or wish to do so, was referred in this perspective.

DIABETES CARE

EVALUATING GLYCEMIC CONTROL

Process indicators:

PERCENTAGE OF DIABETIC SUBJECTS PERFORMING BLOOD-GLUCOSE SELF-MONITORING PER YEAR	
Indicator code	08 - AMD 2006 indicators
Numerator	Number of diabetic subjects performing blood glucose self-testing.
Denominator	Number of diabetic subjects cared for in the in the last 12 months.

PERCENTAGE OF DIABETIC SUBJECTS WITH AT LEAST ONE HbA_{1c} TEST PER YEAR	
Indicator code	10 - AMD 2006 indicators
Numerator	Number of diabetic subjects receiving at least one or more HbA_{1c} tests annually
Denominator	Number of diabetic subjects cared for in the last 12 months.

Intermediate result indicators:

MEAN VALUES (S.D.) OF THE MORE RECENT HbA_{1c} VALUE	
Indicator code	18 - AMD 2006 indicators
Numerator	Sum of HbA_{1c} values (normalized at 6%) – measured in the more recent test over a time period of 12 months–
Denominator	Diabetic subjects with at least one HbA_{1c} measurement in the last 12 months.

MEAN HbA_{1c} AND S.D. (LAST VALUE) BY TYPE OF DIABETES	
Indicator code	19 - AMD 2006 indicators
Numerator	Sum of HbA_{1c} values (normalized at 6%) of the last assay performed in the examined period, by type of diabetes, in all subjects cared for in the examined period.
Denominator	Diabetic subjects cared for in the examined period with at least one HbA_{1c} test, by type of diabetes.

MEAN HbA_{1c} AND S.D. (LAST VALUE) BY ANTIDIABETIC TREATMENT IN TYPE 2 DM	
Indicator code	20 - AMD 2006 indicators
Numerator	Sum of HbA_{1c} values (normalized at 6%) of the last assay performed in the examined period, for each treatment type group, in all subjects with type 2 DM cared for in the examined period.
Denominator	Subjects with type 2 DM cared for in the examined period, with at least one HbA_{1c} test, by antidiabetic treatment.

DISTRIBUTION OF HbA_{1c}	
Indicator code	21 - AMD 2006 indicators
Numerator	Sum of HbA_{1c} values (normalized at 6%) of the last assay performed in the examined period, for each HbA_{1c} group, in all active subjects in the examined period.
Denominator	Total subjects for each HbA_{1c} class, with at least one HbA_{1c} value, among those cared for in the examined period.

*As defined in the AMD data file.

MEAN HbA_{1c} (LAST VALUE) OF 9 AGE GROUPS*	
Indicator code	22 - AMD 2006 indicators
Numerator	Sum of HbA_{1c} values (normalized at 6%) of the last assay performed in the examined period, for each age group, in all active subjects in the examined period.
Denominator	Total subjects for each age group, with at least one HbA_{1c} value, among those cared for in the examined period.

*As defined in the AMD data file.

GLYCEMIC GOALS

Intermediate result indicator:

PERCENTAGE OF DIABETIC SUBJECTS WITH HbA_{1c} ≤7.0%	
Indicator code	23 - AMD 2006 indicators
Numerator	Number of subjects with last HbA_{1c} ≤7.0% (normalized at 6%) in the examined period
Denominator	Diabetic subjects with at least one HbA_{1c} value, among subjects cared for in the examined period

MEDICAL NUTRITION THERAPY

Intermediate result indicator:

DISTRIBUTION OF BMI	
Indicator code	34 - AMD 2006 indicators
Numerator	Sum of BMI values for each BMI group in all subjects cared for in the examined period.
Denominator	Total subjects, for each BMI group, cared for in the examined period.

*As defined in the AMD data file.

PHARMACOLOGICAL TREATMENT FOR HYPERGLYCEMIA

Process indicators:

PERCENTAGE OF DIABETIC SUBJECTS BY ANTIDIABETIC DRUG	
Indicator code	09bis - AMD 2006 indicators

Numerator	Absolute number of subjects following the various diabetes treatment types.
Denominator	Total subjects with known diabetes treatment among subjects cared for in the examined period.

PREVENTION AND MANAGEMENT OF DIABETIC COMPLICATIONS

CARDIOVASCULAR DISEASES

Hypertension and its treatment

Process indicator:

PERCENTAGE OF DIABETIC SUBJECTS WITH AT LEAST ONE BLOOD PRESSURE MEASUREMENT	
Indicator code	12 - AMD 2006 indicators
Numerator	Absolute number of subjects who have had at least one blood pressure check in the examined period.
Denominator	Total subjects cared for in the examined period.

Intermediate result indicator:

PERCENTAGE OF DIABETIC SUBJECTS WITH BP ≤130/85 mmHg	
Indicator code	28 - AMD 2006 indicators
Numerator	Absolute number of subjects with last BP ≤130/85 mmHg in the examined period.
Denominator	Total subjects with at least one BP value among subjects cared for in the examined period.

PERCENTAGE OF DIABETIC HYPERTENSIVE SUBJECTS WITH BP ≤130/85 mmHg	
Indicator code	29 - AMD 2006 indicators
Numerator	Absolute number of subjects diagnosed with hypertension and/or treated with antihypertensive drugs, with last BP ≤130/85 mmHg in the examined period.
Denominator	Total subjects diagnosed with hypertension and/or treated with antihypertensive drugs, among subjects cared for in the examined period.

PERCENTAGE OF DIABETIC SUBJECTS TREATED WITH ANTIHYPERTENSIVES DRUGS HAVING BP ≥140/90 mmHg.	
Indicator code	30 - AMD 2006 indicators
Numerator	Absolute number of subjects treated with antihypertensive drugs, with last BP **≥1**40/90 mmHg in the examined period.
Denominator	Total subjects treated with antihypertensive drugs among subjects cared for in the examined period.

PERCENTAGE OF DIABETIC HYPERTENSIVE SUBJECTS WITH BP ≥140/90 mmHg NOT TREATED WITH ANTIHYPERTENSIVES DRUGS	
Indicator code	31 - AMD 2006 indicators
Numerator	Absolute number of subjects not treated with antihypertensive drugs with last BP ≥140/90 mmHg in the examined period.
Denominator	Total subjects not treated with antihypertensive drugs among subjects cared for in the examined period.

DISTRIBUTION OF SYSTOLIC BP *	
Indicator code	32 - AMD 2006 indicators
Numerator	Sum of systolic BP values last tested in the examined period, by systolic BP strata, in all active subjects in the examined period.
Denominator	Total subjects by systolic BP strata, cared for in the examined period.

*As defined in the AMD data file.

DISTRIBUTION OF DIASTOLIC BP *	
Indicator code	33 - AMD 2006 indicators
Numerator	Sum of diastolic BP values last tested in the examined period, by diastolic BP strata, in all active subjects in the examined period.
Denominator	Total subjects by diastolic BP strata, cared for in the examined period.

*As defined in the AMD data file.

Dyslipidaemia and its management

Process indicator:

PERCENTAGE OF DIABETIC SUBJECTS WITH AT LEAST ONE LIPID PROFILE TEST/YEAR	
Indicator code	11 - AMD 2006 indicators
Numerator	Absolute number of subjects who have undergone at least one LDL cholesterol test (or TC, HDL and TG) in the examined period.
Denominator	Total subjects cared for in the examined period.

Intermediate result indicators:

PERCENTAGE OF DIABETIC SUBJECTS WITH LDL CHOLESTEROL <100 mg/dl	
Indicator code	24 - AMD 2006 indicators
Numerator	Absolute number of subjects with last LDL cholesterol <100 mg/dl in the examined period.
Denominator	Total subjects with at least one LDL cholesterol value, among patients cared for in the examined period.

PERCENTAGE OF DIABETIC SUBJECTS WITH LDL CHOLESTEROL ≥130 mg/dl TREATED WITH HYPOLIPIDEMIC DRUGS	
Indicator code	25 - AMD 2006 indicators
Numerator	Absolute number of subjects treated with hypolipidemic drugs with last LDL cholesterol ≥130 mg/dl in the examined period.
Denominator	Total subjects treated with hypolipidemic treatment, among subjects cared for in the examined period.

PERCENTAGE OF DIABETIC SUBJECTS WITH LDL CHOLESTEROL ≥130 mg/dl NOT RECEIVING HYPOLIPIDEMIC DRUGS	
Indicator code	26 - AMD 2006 indicators
Numerator	Absolute number of subjects with LDL cholesterol ≥130 mg/dl not treated with hypolipidemic drugs in the examined period.

Denominator	Total subjects not treated with hypolipidemic treatment, among subjects cared for in the examined period.

DISTRIBUTION OF LDL CHOLESTEROL VALUES *	
Indicator code	27 - AMD 2006 indicators
Numerator	Sum of LDL cholesterol values obtained with the last assay performed during the period considered, by LDL cholesterol strata, in all subjects cared for in the examined period.
Denominator	Total number of subjectsby LDL cholesterol strata, cared for in the examined period.

*As defined in the AMD data file.

Antiplatelet Drugs

Intermediate result indicators:

PERCENTAGE OF DIABETIC SUBJECTS IN PRIMARY PREVENTION TREATED WITH ANTIPLATELET DRUGS	
Indicator code	00 - AMD 2007 indicators
Numerator	Absolute number of subjects with no cardiovascular events treated with antiplatelet drugs.
Denominator	Total subjects with no cardiovascular events among subjects cared for in the examined period.
REMARKS	It could be measured starting from 2007 data files (to be published).

PERCENTAGE OF DIABETIC SUBJECTS IN SECONDARY PREVENTION TREATED WITH ANTIPLATELET DRUGS	
Indicator code	01 – AMD 2007 indicators
Numerator	Absolute number of subjects with past cardiovascular events, treated with antiplatelet drugs.
Denominator	Total subjects with past cardiovascular events among subjects cared for in the examined period.
REMARKS	It could be measured starting from 2007 data files (to be published).

Discontinuing the Smoking Habit

Intermediate result indicators:

PERCENTAGE OF DIABETIC SUBJECTS WHO GAVE UP SMOKING/YEAR	
Indicator code	37 – AMD 2006 indicators
Numerator	Absolute number of subjects who gave up smoking during the period considered.
Denominator	Total smokers at the start of the period considered among subjects cared for in the examined period.
REMARKS	The indicator can be used as an approximate measure (proxy variable) of counselling activities on smoking. According to the experience of *Annali AMD 2006*, the quality of this indicator is poor. Data recorded on the habit of cigarette smoking in patients is scarce.

PERCENTAGE OF DIABETIC SMOKERS	
Indicator code	37 – AMD 2006 indicators
Numerator	Absolute number of smokers
Denominator	Absolute number of subjects cared for in the examined period.
REMARKS	According to the experience of *Annali AMD 2006*, the quality of this indicator is poor. Data recorded on the habit of cigarette smoking in patients is scarce.

PERCENTAGE OF STRONG SMOKERS (>20 CIGARETTES/DAY)	
Indicator code	36 - AMD 2006 indicators
Numerator	Absolute number of strong smokers.
Denominator	Absolute number of smokers amongsubjects cared for in the examined period.
REMARKS	According to the experience of *Annali AMD 2006*, the quality of this indicator is poor. Data recorded on the habit of cigarette smoking in patients is scarce.

DIABETIC NEPHROPATHY - SCREENING AND MANAGEMENT

Process indicator:

PERCENTAGE OF DIABETIC SUBJECTS MONITORED FOR DIABETIC NEPHROPATHY	
Indicator code	13 - AMD 2006 indicators
Numerator	Absolute number of subjects monitored for diabetic nephropathy.*
Denominator	Total subjects cared for in the examined period.
REMARKS	* Element distinguishing the monitoring process: microalbuminuria, AER, A/C ratio or proteinuria.

Final result indicator:

PERCENTAGE OF DIABETIC SUBJECTS WITH DIABETIC NEPHROPATHY	
Indicator code	39 - AMD 2006 indicators
Numerator	Absolute number of subjects with diabetic nephropathy.**
Denominator	Total subjects monitored for nephropathy among subjects cared for in the examined period.*
REMARKS	** Numerator: is required a definite diagnosis of diabetic nephropathy. * Denominator: subjects monitored for diabetic nephropathy by means of microalbuminuria or AER or A/C ratio or proteinuria.

DIABETIC RETINOPATHY - SCREENING AND MANAGEMENT

Process indicator:

PERCENTAGE OF DIABETIC SUBJECTS MONITORED FOR DIABETIC RETINOPATHY	
Indicator code	14 - AMD 2006 indicators
Numerator	Absolute number of subjects monitored for diabetic retinopathy.
Denominator	Total subjects cared for in the examined period.

Final result indicator:

PERCENTAGE OF DIABETIC SUBJECTS WITH DIABETIC RETINOPATHY	
Indicator code	38 – AMD 2006 indicators
Numerator	Absolute number of subjects with diabetic retinopathy.
Denominator	Total subjects monitored for retinopathy among those cared for in the examined period.

DIABETIC NEUROPATHY - SCREENING AND MANAGEMENT

Process indicator:

PERCENTAGE OF DIABETIC SUBJECTS MONITORED FOR DIABETIC NEUROPATHY	
Indicator code	15 - AMD 2006 indicators
Numerator	Absolute number of subjects monitored for diabetic neuropathy.
Denominator	Total subjects cared for in the examined period.

Final result indicator:

PERCENTAGE OF DIABETIC SUBJECTS WITH SOMATIC NEUROPATHY	
Indicator code	01 - Italian standards
Numerator	Absolute number of subjects with somatic neuropathy.
Denominator	Total subjects monitored for diabetic neuropathy among those cared for in the examined period.
REMARKS	This indicator is not present in the AMD 2006 Indicators List. It can be measured from the 2004 data file (by using the codes AMD037 and AMD038).

FOOTCARE

Process indicators:

PERCENTAGE OF DIABETIC SUBJECTS RECEIVING FOOT EXAMINATION	
Indicator code	17 - AMD 2006 indicators
Numerator	Absolute number of subjects whose feet were examined at least once.
Denominator	Total subjects cared for in the examined period.
Patient inclusion criteria	Peripheral sensitivity test (tuning fork, biothesiometer or single filament), EMG, foot examination, current or past trophic lesion, major non traumatic amputation, minor non traumatic amputation, osteomyelitis or soft tissue infection.

PERCENTAGE OF DIABETIC SUBJECTS WITH FOOT AT RISK	
Indicator code	16 - AMD 2006 indicators
Numerator	Absolute number of subjects whose feet were examined at least once.
Denominator	Total subjects at risk of foot lesions among those cared for in the examined period.
Patient inclusion criteria	A subject at risk is one who has peripheral diabetic neuropathy, vegetative neuropathy, peripheral arteriopathy, past trophic lesion, major non traumatic amputation or minor non traumatic amputation. One or more of these factors must be present prior to the period considered.

DIABETES CARE IN SPECIFIC POPULATION GROUPS

The same process and result indicators identified for the adult population can be applied for both the paediatric and elderly population, identifying the cohorts to be analyzed by introducing specific age limits and goals.

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