

# I Brazilian Guidelines for Diabetes

## PART I

### Presentation

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For many years, the Brazilian Society of Diabetes (SBD) has been publishing medical consensus-essays, which emerged from discussions among the most renowned specialists in diabetes and endocrinology in the Country. Such consensus-essays were meant to establish treatment standards in order that not only specialists but also clinicians of diabetic patients could develop their work with increasing safety.

These consensus-essays were published in the *Arquivos Brasileiros de Endocrinologia e Metabologia*, official journal of SBD, and were made available at the site of SBD ([www.diabetes.org.br](http://www.diabetes.org.br)). Only in the last two years nearly 220 thousand downloads were done, confirming the contribution brought by the journal.

However, the so-called guidelines will be published in 2006, reflecting the SBD's official viewpoint and having an evidence-based structure as a differential feature. Evidence-based medicine helps the physician in decision-making.

Diagnosing the disease, programming the treatment, knowing the prognosis, and making decisions are important stages in clinical practice. In order to attain them, access to information and to the literature, knowledge about the advantages and disadvantages of each study, and understanding both the statistical methods and the research process is needed. Information should be processed and synthesized to be transformed into recommendations, i.e., into practical guidelines that should serve as orientation for management. It is important that these guidelines be updated, diffused, and, above all, implemented; if they are not, there is the risk of waste in time, energy, and money.

Regarding the process of decision-making, the preferences of the patient – who should always be informed – the circumstances of medical assistance, the stage of the disease, and the availability of resources should be considered. Professional experience is fundamental; it is essential and molds the final decision, ensuring a greater benefit to the patient.

Since SBD has published its first consensus, a considerable progress in the way of evaluating scientific evidence has occurred. A system with both a ranking of recommendations and power of evidence was established in order that guidelines could

be classified and elaborated. Thus, different degrees are ascribed to experimental or observational studies with higher or lower consistency, case reports (non-controlled studies), and opinion without critical evaluation (either based on consensus, physiological studies, or animal models). Even recommendations with a lower level of evidence can be equally important provided they are well founded.

It is essential to understand that evidence is only one more component of decision-making. Since physicians care for patients, not populations, guidelines should be interpreted according to the needs of people with diabetes. Individual circumstances, co-morbidities, age, education, inability and above all the patients' individual values and preferences should be considered.

If patients understand how information is generated, interpreted, and applied, they will tend to be more participative and active in the process.

The final decision should be the consequence of integration among evidence, experience, competence, and ethics.

The text was organized by an editorial committee consisting of Dr. Leão Zagury, Dr. Marília Brito Gomes, and Dr. Sergio Dib, respectively the president, vice-president, and first secretary of SBD. Specialists of recognized knowledge were invited by the committee to write on the proposed themes that were then submitted to the SBD Directing Board.

The guidelines are organized in a way that annual update is possible, with inclusion of new themes or modifications based on progress of knowledge.

As the president of SBD, I thank the colleagues who generously lent their knowledge to produce this important and useful work, demonstrating once more their public spirit and social responsibility.

Health for all!

**Dr. Leão Zagury**

President of SBD - Administration 2004/2005

**Dr. Marcos Tambascia**

President of SBD - Administration 2006/2007

## BRAZILIAN SOCIETY OF DIABETES

This document, the first guidelines of the Brazilian Society of Diabetes (SBD), was initiated during the administration of Dr. Leão Zagury as the president of SBD (2004-2005) and concluded in the following administration of Dr. Marcos Tambascia (2006-2007).

These guidelines were elaborated by adopting the concept of evidence-based medicine following the international model recognized by the American Diabetes Association (ADA), and will be updated yearly with the inclusion of new themes and/or practices based on knowledge progress.

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## RECOMMENDATION DEGREES AND POWER OF EVIDENCE

<b>A</b>	Observational or experimental studies of best consistency
<b>B</b>	Experimental or observational studies of least consistency
<b>C</b>	Case reports (non-controlled studies)
<b>D</b>	Opinion without critical evaluation, based on consensus, physiologic studies or animal models

**LEVELS OF SCIENTIFIC EVIDENCE BY TYPE OF STUDY**  
**Oxford Centre for Evidence-Based Medicine (May 2001)**  
**Guidelines Project AMB-CFM**

<b>Recommendation degrees</b>	<b>Evidence levels</b>	<b>Treatments/ prevention - etiology</b>	<b>Prognosis</b>	<b>Diagnosis</b>	<b>Differential diagnosis / Prevalence of symptoms</b>
<b>A</b>	1A	Systematic (homogeneous) revision of controlled and randomized clinical trials	Systematic (homogeneous) revision of cohort studies since the beginning of the disease; Prognostic criterion validated in several populations	Systematic (homogeneous) revision of level 1 diagnostic studies Diagnostic criterion of level 1B studies in different clinical centers	Systematic (homogeneous) revision of (contemporary or retrospective) cohort studies
	1B	Controlled and randomized clinical trial, with a narrow confidence interval	Cohort study, since the beginning of the disease, with < 20% loss; Prognostic criterion validated in only one population	Validated cohort study, with a good reference standard; Diagnostic criterion tested in only one clinical center	Cohort (contemporary or retrospective) study with few losses
	1C	Therapeutic results of the "all-or-none" type	Series of "all-or-none" type cases	Sensitivity and specificity close to 100%	Series of "all-or-none" type cases
<b>B</b>	2A	Systematic (homogeneous) revision of cohort studies	Systematic (homogeneous) revision of historical (retrospective) cohort studies or follow-up of non-treated patients of a control group in a randomized clinical trial	Systematic (homogeneous) revision of level > 2 diagnostic studies	Systematic (homogeneous) revision of studies on level $\geq 2B$ differential diagnosis
	2B	Cohort study (including clinical randomized trial of less quality)	Historical cohort study; Follow-up of non-treated patients of a control group of a randomized clinical trial; Prognostic criterion derived or validated only in fragmented samples	Exploratory cohort study with a good reference standard; Diagnostic criterion derived or validated in fragmented samples or a database	Historical cohort study (retrospective cohort) or with follow-up of compromised cases (great number of losses)
	2C	Observation of therapeutic results (outcomes research); Ecological study	Observation of clinical evolution (outcomes research)		Ecological study
	3A	Systematic (homogeneous) revision of case-control studies		Systematic (homogeneous) revision of level $\geq 3B$ diagnostic studies	Systematic (homogeneous) revision of level $\geq 3B$ studies
	3B	Case-control study		Non-consecutive selection of cases, or reference standard applied in poorly consistent form	Cohort study with non-consecutive selection of cases or very limited study population
<b>C</b>	4	Case reports (including cohort or case-control studies of lower quality)	Series of cases (and prognostic cohort with less quality)	Case-control study; either poor or non-independent reference standard	Series of cases, or outdated reference standard
<b>D</b>	5	Opinion of a specialist without critical evaluation or based on basic subjects (physiologic study or study using animals)			

# Epidemiology of diabetes mellitus

## 1. The magnitude of the problem

A diabetes mellitus epidemic (DM) is in course. In 1985, 30 million adults were estimated to have DM worldwide; this figure grew to 135 millions (in 1995), has reached 173 millions (in 2002), and is projected to reach 300 millions in 2030. About two thirds of the individuals with DM live in developing countries where the epidemic has a higher intensity, and the proportion of affected people is increasing in groups of younger age range<sup>1</sup> (B, 3).

The number of diabetic individuals is increasing due to factors such as population growth and aging, greater urbanization, increasing prevalence of obesity and sedentarism, as well as longer survival of patients with DM. Current and future quantification of DM prevalence and the number of diabetic people is important to allow a rational way of planning and resource allocation.

At the end of the eighties, DM prevalence in the Brazilian adult population was estimated to be 7.6%<sup>2</sup>; recent data point to rates as high as 12.1% in the study of Ribeirão Preto, SP<sup>3</sup>. It is estimated that in 2005 there will be nearly 8 million individuals with DM in Brazil (B, 3).

The influence of age on both DM prevalence and decreased tolerance to glucose was well evidenced in the Multicenter Study on Diabetes Prevalence in Brazil<sup>2</sup>, where increases of 2.7% and 17.4% were observed for the 30-59- and 60-69-year age ranges, respectively, i.e., an increase of 6.4 times.

Striking differences in DM prevalence exist between countries and ethnic groups. The highest rates were described for inhabitants of Nauru (Oceania) and Pima Indians (Arizona, USA), where nearly half the adult population presents DM.

Other aspects such as repercussion of lifestyle changes within a short time, as observed in migrant groups should be highlighted. In Brazil, a study performed on the Nippo-Japanese community has shown a vertiginous increase in DM prevalence, whose rate changed from 18.3% (1993) to 34.9% (2000), evidencing the impact of lifestyle alteration, particularly in the feeding pattern, interacting with a probable genetic susceptibility<sup>4</sup> (B, 3).

The incidence of type 2 DM (DM2) is difficult to be determined in great populations since this involves a follow-up with periodical blood glucose measurements for some years. The studies on incidence are usually restricted to type 1 DM (DM1) since its initial manifestations are very characteristic. DM1 incidence presents a marked geographical variation, e.g., in Finland, Brazil, and Korea

the rates (per 100 thousand individuals) for ages <15 years are 38.4, 7.6 and 0.5, respectively. It is presently known that DM1 incidence is increasing, mostly in the infantile population with ages <5 years<sup>5</sup>.

The number of deaths ascribed to DM worldwide is nearly 800 thousand; however, it is a well-established fact that this number is considerably underestimated. Frequently, DM is not mentioned in death certificates since its complications, particularly those cardiovascular and cerebrovascular, are the causes of the death. These are the causes found in the mortality statistics. A more realistic figure suggests that nearly 4 million deaths per year are related to the presence of this disease, with an important contribution of cardiovascular complications. This value corresponds to nearly 9% of the total deaths in the world. Most of these deaths are premature, occurring while these individuals are still economically active in the society.

Brazilian data show that the rates (per 100 thousand inhabitants) of mortality due to DM present a marked increase with age, ranging from 0.58% to 181.1% for the ages of 0-29 and ≥60 years respectively, i.e. a gradient of more than 300 times. When analyzing only the basic cause of death, it is observed that in most developed countries DM is between the fourth and eighth positions in the ranking of main causes. Brazilian studies on mortality analyzed multiple causes of death and showed that, if DM is mentioned in the death certificate, the mortality rate due to DM increases up to 6.4 times<sup>6</sup>. The importance of DM as disease burden, i.e., the impact of both mortality and health problems that affect the quality of life of the diseased was analyzed through the Disability Adjusted Life of Years (DALY) in terms of years of life lost due to inability. It was observed that DM presented a rate of 12 per 1000 inhabitants in 1999 (eighth position), being surpassed by the groups of infectious and parasitic, neuropsychiatric, cardiovascular, chronic respiratory, of the digestive system, malignant neoplasms, and skeletal muscle diseases<sup>7</sup>. It must be reminded that DM, considered as a single entity is compared with groups of diseases and even so its importance can be noticed (B, 4).

Its chronic nature, and both the severity of its complications and the means required to control them make DM a very expensive disease not only for the affected individuals and their families but also for the health system. The health care costs in the USA were estimated to be two to three times higher for individuals with than those without DM.

Although DM costs affect everybody, this is not only an

economic problem. The intangible costs, such as pain, anxiety, inconvenience, and loss in quality of life also have a considerable impact on the life of people with DM and their families, and are difficult to be quantified.

The direct costs due to DM range from 2.5 to 15% of the annual Brazilian health budget, depending on its prevalence and degree of sophistication of the available treatment. The estimated value of direct costs with DM in Brazil is nearly 3.9 billion American dollars, as compared with 0.8 and 2.0 billion for Argentina and Mexico, respectively<sup>8</sup>.

Innumerable individuals with DM are unable to continue to work due to chronic complications or remain with some limitations regarding professional performance. To estimate the social costs of this loss in productivity is not easy. However, for some situations the estimated costs are equivalent or even higher than the direct costs with health. For instance, the values estimated for the treatment of patients with DM in the USA (1997) were US\$ 44 as compared to 54 billion in direct and indirect costs, respectively. Combining estimates for 25 Latin-American countries it can be inferred that costs due to productivity loss because of DM may be five times higher than the direct costs<sup>8</sup>. This would be due to a limited access to good health assistance with consequent high incidence of complications, inability and premature death (B, 4).

## 2. Prevention

Effective prevention also means more attention to health in an efficient way. This may be done by prevention at the beginning of DM (primary prevention) or of its acute or chronic complications (secondary prevention).

Primary prevention protects susceptible individuals from developing DM. It has an impact because it reduces or delays the need for giving attention to health and for treating DM complications.

Presently primary DM1 prevention lacks a rational basis that could be applied to the whole population. The proposed interventions for populations are still theoretical and further studies are required to confirm them. The most acceptable proposals are based on stimulation of breastfeeding and avoiding introduction of cow milk in the first three months of life. However recruitment of individuals at higher risk to participate in clinical trials is justified. The proposed interventions are based on immunomodulation or immunosuppression.

Regarding DM1, most individuals present obesity, arterial hypertension and dyslipidemia, and hyperinsulinemia would be a link between these metabolic disorders, there is a need of interventions involving these multiple metabolic abnormalities.

There is evidence that changes in lifestyle, with emphasis on feeding and reduction in physical activity, are associated with the marked increase in DM2 prevalence. The programs for primary prevention of DM2 are being based on intervention in diet and practice of physical activity aiming at reduction of excess weight. The results of the Diabetes Prevention Program (DPP)<sup>9</sup> demonstrated a 58% decrease in DM incidence by stimulating a healthy diet and the practice of physical activities, and this intervention is more effective than the use of metformin. The Finnish Diabetes Prevention Study (DPS)<sup>10</sup> has shown that a reduction in body weight ranging from 3 to 4 kg in four years caused a 58% reduction of DM incidence. A longitudinal study with 84,941 nurses and a 16-year follow-up has shown that the control of modifiable risk factors, such as habitual diet, physical activity, smoking, and weight excess were associated with a 91% reduction of DM incidence and 88% reduction of cases with familial history of DM<sup>11</sup> (B, 1).

Regarding secondary prevention, there is evidence that strict metabolic control plays an important role in preventing the appearance or progression of chronic complications, as shown for DM1 and DM2 by the Diabetes Control and Complications Trial (DCCT)<sup>12</sup> and the United Kingdom Prospective Diabetes Study (UKPDS)<sup>13</sup>, respectively (B, 1).

Other important measures in secondary prevention<sup>14</sup> include:

- treatment of arterial hypertension and dyslipidemia, which substantially the risk for DM complications (B, 1);
- specific care to prevent foot ulceration and amputation of lower limbs, that can decrease both frequency and duration of hospitalizations, as is the case of 50% for amputation incidence (B, 2);
- screening for diagnosis and early treatment of retinopathy, which is highly advantageous from the effective cost viewpoint, due to important consequences in direct, indirect, and intangible costs of blindness (B, 2);
- screening for microalbuminuria is recommended for preventing or delaying the progression of renal insufficiency, allowing early intervention in the natural course of kidney disease (B, 3);
- measures to reduce cigarette consumption also help DM control since smoking is associated with poor DM control, being strongly and causally associated with hypertension and cardiovascular disease<sup>15</sup> (A, 1).

## References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes. Estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004; 27(5): 1047-53.

2. Malerbi D, Franco LJ; the Brazilian Cooperative Group on the Study of Diabetes Prevalence. Multicenter Study of the Prevalence of Diabetes Mellitus and Impaired Glucose Tolerance in the urban Brazilian population aged 30-69 years. *Diabetes Care*. 15(11): 1509-16, 1992.
3. Torquato MTCG, Montenegro Jr RN, Viana LAL, Souza RAHG, Ianna CMM, Lucas JCB, et al. Prevalence of diabetes mellitus and impaired glucose tolerance in the urban population aged 30-69 years in Ribeirão Preto (São Paulo), Brazil. *Sao Paulo Med J*. 2003; 121(6): 224-30.
4. Gimeno SGA, Ferreira SRG, Cardoso MA, Franco LJ, Iunes M; the Japanese-Brazilian Diabetes Study Group. Weight gain in adulthood and risk of developing glucose disturbance – a study of a Japanese-Brazilian population. *J Epidemiol*. 2000; 10(2 ): 103-10.
5. Onkamo P, Väänänen S, Karvonen M, Tuomilehto J. Worldwide increase in incidence of type 1 diabetes: the analysis of the data on published incidence trends. *Diabetologia*. 1999; 42(12): 1395-403.
6. Franco LJ. Um problema de saúde pública. *Epidemiologia*. In: Oliveira JEP, Milech A, editors. *Diabetes mellitus: clínica, diagnóstico, tratamento multidisciplinar*. São Paulo: Editora Atheneu; 2004. cap. 4, p. 19-32.
7. Schramm JMA, Oliveira AF, Leite IC, Valente JG, Gadelha AMJ, Portela MC, Campos MR. Transição epidemiológica e o estudo de carga de doença no Brasil. *Ciência & Saúde Coletiva*. 2004; 9(4): 897-908.
8. Barceló A, Aedo C, Rajpathak S, Robles S. The cost of diabetes in Latin America and the Caribbean. *Bull World Health Organ* 2003; 81(1): 19-27.
9. Diabetes Prevention Program Research Group. Reduction of the incidence of type 2 diabetes with life style intervention or metformin. *N Engl J Med*. 2002; 346(6): 393-403.
10. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Hanne-Parikka P, Keinanen-Kiukaanniemi S; for the Finnish Diabetes Prevention Program. Prevention of type 2 diabetes mellitus by changes in life style among subjects with impaired glucose tolerance. *N Engl J Med*. 2001; 344(18): 1343-50.
11. Hu EB, Manson JE, Stamper MJ, Colditz G, Liu S, Solomon CG, Willett WC. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med*. 2001; 345(11): 790-7.
12. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993; 329(14): 977-86.
13. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet*. 1998; 352(9131): 837-53.
14. World Health Organization. *Diabetes: the cost of diabetes*. WHO fact sheet. September 2002. n. 236.
15. World Health Organization. *The World Health Organization Report 2002: Reducing Risks, Promoting Healthy Life*. Geneva, WHO, 2002.

# Etiologic classification of diabetes mellitus

## 1. Introduction

Diabetes *mellitus* is not a single disease, but a heterogeneous group of metabolic disorders presenting hyperglycemia as common feature. This hyperglycemia is a result of defects in insulin action or insulin secretion or both.

Current classification of DM is based on the etiology and not on the type of treatment, therefore the terms insulin-dependent and -independent DM should be eliminated. The classification proposed by the World Health Organization (WHO)<sup>1</sup> and American Diabetes Association (ADA)<sup>2</sup> is recommended and includes four clinical classes: DM1, DM2, other specific types of DM, and gestational DM (Table 1). There are also two categories, *altered fasting glycemia* and *decreased glucose tolerance*, called pre-diabetes. These categories are not clinical entities, but risk factors for developing DM and cardiovascular disease (CVD).

## 2. Type 1 diabetes mellitus

DM1 is present in 5-10% of the cases being the result of destruction of pancreatic beta cells with a consequent insulin deficiency. Although in most cases this destruction of beta cells is mediated by an autoimmune process, there are cases of DM1 in which there is no evidence of participation of such a process; these are called the idiopathic form of DM1. Autoimmunity markers are: anti-insulin, glutamic acid antidecarboxylase (GAD 65), and anti tyrosine phosphatases (IA2 and IA2B) autoantibodies<sup>3-5</sup>. These antibodies can be present for months or years before the clinical diagnosis is known, i.e., in the preclinical phase of the disease, and in up to 90% of the individuals (when hyperglycemia is detected). Besides the participation of the autoimmune component, DM1 presents a strong association with certain human leukocyte-antigen system genes (HLA) whose alleles may predispose to or protect against the development of the disease<sup>6</sup>.

The destruction rate of beta cells is variable, generally being faster in children. The slowly progressive form in general occurs in adults, being called *latent autoimmune diabetes in adults* (LADA).

Cases of idiopathic DM1 are a minority. They are characterized by a lack of autoimmunity markers both against beta cells and non-association with haplotypes of the HLA system. Individuals with this form of DM may develop

**Table 1. Etiologic classification of DM.**

DM1
• Auto-immune
• $\beta$ Idiopathic
DM2
Other specific DM types
Gestational DM

ketoacidosis and present insulin deficiency at variable degrees.

Since evaluation of autoantibodies is not available in all centers, etiologic classification of DM1 in autoimmune and idiopathic subcategories may be impossible.

## 3. Type 2 diabetes mellitus

The type 2 diabetes *mellitus* (DM2) form is present in 90-95% of the cases, being characterized by defects of insulin action and secretion. Both defects are usually present when hyperglycemia occurs, but one of them may prevail. Most patients with DM2 present overweight or obesity. Ketoacidosis rarely occurs spontaneously, only when associated with other conditions such as infection. DM2 may occur at any age, but it is generally diagnosed after the 40 years. Although these patients do not depend on exogenous insulin for their survival, they may require insulin treatment to obtain an adequate metabolic control.

Differently from autoimmune DM1, there are no specific indicators for DM2. It is likely that different mechanisms exist, resulting in the DM2 form and in the future, when identification of specific pathogenic processes or genetic defects is available, the number of individuals with DM2 will decrease at the expense of a change to another more specific and definitive DM classification.

## 4. Other specific types of DM

Less common forms of DM belong to this class, and their causing defects or processes can be identified. The clinical presentation of this group is quite varied, depending on basic alteration. Genetic defects in beta-cell function and insulin action, diseases of the exocrine pancreas, and other conditions listed in Table 2 are included in this class.

**Table 2. Other specific DM types.****Genetic defects in beta-cell function**

- MODY 1 (defects in HNF-4 alpha gene)
- MODY 2 (defects in glycolysis gene)
- MODY 3 (defects in HNF-1 alpha gene)
- MODY 4 (defects in IPF-1 gene)
- MODY 5 (defects in HNF-1 beta gene)
- MODY 6 (defects in Neuro D1 gene)
- Mitochondrial DM
- Others

**Genetic defects in insulin action**

- Type A insulin resistance
- Rabson-Mendenhall syndrome
- Others
- Leprechaunism
- Lipotrophic DM

**Diseases of exocrine pancreas**

- Pancreatitis
- Neoplasm
- Fibrocalculous pancreatopathy
- Pancreatectomia or trauma
- Cystic fibrosis
- Others

**Endocrinopathies**

- Acromegaly
- Glucagonoma
- Somatostinoma
- Others
- Cushing syndrome
- Pheochromocytoma
- Aldosteronoma

**Induced by medication or chemical agents**

- Certain toxins
- Nicotinic acid
- Thyroid hormone
- Beta-adrenergic agonists
- Interferon alpha
- Pentamidine
- Glycocorticoids
- Diazoxide
- Thiazide compounds
- Others

**Infections**

- Congenital rubella
- Others
- Cytomegalovirus

**Uncommon forms of autoimmune DM**

- Stiff man syndrome
- Others
- Anti-insulin receptor antibodies

**Other genetic syndromes sometimes associated with DM**

- Down syndrome
- Turner syndrome
- Friedreich's ataxia
- Laurence-Moon-Biedl syndrome
- Prader Willi syndrome
- Klinefelter syndrome
- Wolfram syndrome
- Huntington's chorea
- Myotonic dystrophy
- Others

MODY, maturity onset diabetes of the young.

## 5. Gestational diabetes mellitus

Is any glucose intolerance, of variable magnitude, beginning or being diagnosed during gestation. The possibility that this condition was already present before pregnancy, although not diagnosed, is not excluded. Similarly to DM2, gestational DM is associated with both resistance to insulin and decrease in beta-cell function<sup>7</sup>. Gestational DM occurs in 1-14% of all gestations, depending on the studied population, and is also associated with an increase in perinatal morbidity and mortality<sup>8</sup>. Patients with gestational DM must be reevaluated four to six weeks after delivery and reclassified as presenting

DM, altered fasting blood glucose, decreased glucose tolerance, or normoglycemia. In most cases reversion to normal tolerance occurs after pregnancy, but there is a risk (17-63%) for developing DM2 within 5-16 years after delivery<sup>9</sup>.

## 6. Pré-diabetes

Is considered an intermediate state between normal glucose homeostasis and DM. The category *altered fasting blood glucose* refers to fasting glucose concentrations that are lower than those for the diagnostic DM criterion,

but higher than the normal reference value. *Decreased glucose tolerance* represents an abnormality in the regulation of blood glucose levels in the post-overload state, being diagnosed by the oral glucose tolerance test (OGTT). This test includes determination of fasting blood glucose and 2 h after overload with 75 g glucose.

## References

1. Alberti KGMM, Zimmet PZ, for the World Health Organization Consultation. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Report of a WHO Consultation. Geneva: WHO; 1999.
2. American Diabetes Association. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*. 1998; 21 Suppl 1: S5.
3. Palmer JP, Asplin CM, Clemons P, et al. Insulin antibodies in insulin-dependent diabetics before insulin treatment. *Science*. 1983; 222: 1337.
4. Baekkeskov S, Aanstoof H, Christgau S, et al. Identification of the 64K autoantigen in insulin-dependent diabetes as the GABA-synthesizing enzyme glutamic acid decarboxylase. *Nature*. 1990; 347: 151.
5. Rabin DU, Pleasic SM, Shapiro JA, et al. Islet cell antigen 512 is a diabetes-specific islet autoantigen related to protein tyrosine phosphatases. *J Immunol*. 1994; 152: 3183.
6. Todd JA, Bell JI, McDevlin HO. HLA-DQB gene contributes to susceptibility and resistance to insulin-dependent diabetes mellitus. *Nature*. 1987; 329: 599.
7. Kuhl C. Insulin secretion and insulin resistance in pregnancy and GDM: implications for diagnosis and management. *Diabetes*. 1991; 40: 18.
8. Coustan DR. Gestational diabetes. *Diabetes in America*. In: National Institutes of Diabetes and Digestive and Kidney Diseases. 2 ed. NIH Publication n° 95-1468. Bethesda: NIDDK; 1995. p. 703-17.
9. Hanna FWF, Peters JR. Screening for gestational diabetes: past, present and future. *Diabet Med*. 2002; 19: 351.

# Methods and criteria for diagnosing diabetes mellitus

## 1. Introduction

The evolution to type 2 diabetes *mellitus* (DM2) occurs along a variable time interval, passing through intermediate stages named altered fasting glycemia and decreased glucose tolerance. These stages would be due to a combination of resistance to insulin action and beta-cell dysfunction. As for type 1 diabetes *mellitus* (DM1), its beginning is generally abrupt, and the symptoms clearly indicate the presence of the illness<sup>1,2</sup>.

In 1997, the diagnostic criterion was modified by the American Diabetes Association (ADA), then being accepted by the World Health Organization (WHO) and *Sociedade Brasileira de Diabetes* (SBD)<sup>1,2</sup>.

The modifications were introduced with the purpose to effectively prevent the micro and macrovascular complications of DM<sup>3-5</sup>.

At present, there are three accepted criteria for diagnosing DM:

- symptoms of polyuria, polydipsia, weight loss, and casual glycemia >200 mg/dL. Casual glycemia is understood as that determined at any time of the day, regardless of the meal schedule (A, 1)<sup>1,2</sup>;
- fasting glycemia  $\geq 126$  mg/dL (7 millimols). Should small increases in glycemia occur, the diagnosis should be confirmed by repeating the test on another day (A, 1)<sup>1,2</sup>;
- 2-h glycemia after overload with 75 g glucose >200 mg/dL (A, 1)<sup>1,2</sup>.

The glucose tolerance test should be performed with the care procedures recommended by WHO, with specific collection in order to differentiate from fasting glycemia and glycemia 120 minutes after glucose intake.

An intermediate group of individuals is recognized, whose glycemic levels do not fulfill the criteria for diagnosis

of DM. However, their levels are very high to be considered normal<sup>7</sup>. In such cases, the categories of altered fasting glycemia and decreased glucose tolerance were considered, according to the following criteria shown in the Table.

## 2. Altered fasting glycemia

- Fasting glycemia above 100 mg/dL and below 126 mg/dL. This criterion has not accepted by the WHO yet, however the *International Diabetes Federation* (IDF) recommends 100 mg/dL as a cut-off value.
- Decreased glucose tolerance – when, after a 75 g glucose overload, glycemia value after 2 hours is between 140 and 199 mg/dL (B, 2)<sup>2-6</sup>.

The preferred method for glycemia determination is its measurement in plasma. The blood should be collected in a tube containing sodium fluoride and centrifuged for separation of plasma, which must be frozen for later use. If fluoride is not available, glycemia determination should be performed immediately or the tube should be kept at 4°C for a maximum of 2 hours<sup>8</sup>.

To perform the oral glucose tolerance test, some considerations should be taken into account:

- fasting period between 10 and 16 hours;
- intake of at least 150 g carbohydrates in the three days before the test; performance
- normal physical activity;
- to inform the presence of infection, use of medication or inactivity;
- use of 1.75 g glucose per kg body weigh up to a maximum of 75 g<sup>8</sup>.

Glycated hemoglobin has shown to be inferior to fasting and postprandial glycemia for the diagnosis of diabetes

**Table. Plasma glucose values (mg/dL) for DM diagnosis and its preclinical stages.**

Category	Fasting*	2-h after 75 g glucose	Casual**
Normal glycemia	<100	<140	
Decreased glucose tolerance	>100 a <126	$\geq 140$ a < 200	
DM	$\geq 126$	$\geq 200$	$\geq 200$ (with classical symptoms)***

\*Fasting is defined as a lack of caloric ingestion for at least 8 hours; \*\*casual plasma glycemia is that determined at any time of the day, disregarding time since last meal; \*\*\* classical symptoms of DM include polyuria, polydipsia and non-explained weight loss.

Note: DM Diagnosis should always be confirmed by test repetition on another day, unless there is unequivocal hyperglycemia with acute metabolic decompensation or obvious DM symptoms.

*mellitus*<sup>2</sup>. Strips with reagents are not as precise as plasma determinations and should not be used for diagnosis.

## References

1. Report of Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 1997; 20: 1183-97.
2. Engelgau MM, Thompson TJ, Herman WH, et al. Comparison of fasting and 2 hours glucose and HbA1c levels for diagnosing diabetes. Diagnostic criteria and performance revisited. *Diabetes Care*. 1997; 20: 785-91.
3. Fuller JM, Shipley MJ, Rose G, et al. Coronary heart disease risk and impaired glucose: the Whitehall study. *Lancet*. 1980; 1: 1373-6.
4. Charles MA, Shipley MJ, Rose G, et al. Risk factors for NIDDM in white population. Paris Prospective Study. *Diabetes*. 1991; 40: 796-9.
5. Decode Study Group. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet*. 1999; 354: 617-21.
6. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care*. 2003; 26: 3160-7.
7. American Diabetes Association. Guide to diagnosis and classification of diabetes mellitus and other categories of glucose intolerance. *Diabetes Care*. 1997; 20 Suppl: 215-25.
8. Bennet PH. Definition, diagnosis and classification of diabetes mellitus and impaired glucose tolerance. In: Kahn CR, Weir GC, editors. *Joslin's Diabetes Mellitus*. 13 ed. EEUU: Editora Lea e Febiger Philadelphia, 1994. p. 193-215.

# Clinical and laboratory aspects of glycated hemoglobin

## 1. Concept of glycated hemoglobin

The generic term *glycated hemoglobin* refers to a set of substances formed by a reaction between hemoglobin A (HbA), the adult's normal hemoglobin, and some sugars. Regarding the control of diabetes *mellitus* (DM), fraction A1c is the most important and the most studied, having been endorsed by the two most important studies at present: Diabetes Control and Complications Trial (DCCT) and UK Prospective Diabetes Study (UKPDS). Depending on the analytical laboratory method, fraction A1c ranges from 3 to 6% of total HbA in normal people, reaching 20% or more in very poorly controlled diabetic individuals. In the normal individual, fraction HbA1C represents nearly 80% of the total hemoglobin A1 (HbA1). The remaining 20% correspond to the fractions HbA1a1, HbA1a2 and HbA1b. Glycated hemoglobin (which is the biochemically correct term) is also known as glycohemoglobin or simply as A1C.

## 2. Clinical usefulness of tests for glycated hemoglobin

The level of glycated hemoglobin of an individual reflects his/her average glycemia in the two to three months preceding the test, being thus very useful to evaluate the glycemic control level and efficacy of the ongoing treatment. On the other hand, the glycemia tests reflects the glucose blood level at the exact moment when the test was performed. In order to have a more global and clinically-based evaluation of the glycemic control, both methods are important since the information they give complement each other.

The level of glycated hemoglobin should routinely be evaluated in all patients with DM in order to document their degree of glycemic control. The treatment goals should be based on results of prospective clinical and randomized studies, as DCCT and UKPDS. These studies have shown a relationship between glycemic control, as

quantified by serial determinations of glycated hemoglobin, and the risks for development and progression of chronic DM complications (A, 1).

## 3. Correlation between the levels of glycated hemoglobin and glycemia

Glycemic control is better evaluated by combining the results of glycemia home monitoring and the levels of glycated hemoglobin. Table 1 shows the correlation between the level of glycated hemoglobin and the average levels of glycemia in the two to three months before the test.

## 4. Recommended frequency for glycated hemoglobin tests

Tests for glycated hemoglobin should be performed at least twice a year by all diabetic individuals and four times per year (every three months) by patients who underwent changes in their therapeutic schemes or are not attaining the recommended goals with the current treatment (A, 4).

## 5. Recommended levels for glycated hemoglobin

Levels of glycated hemoglobin above 7% are associated with a progressively increasing risk for chronic complications. Thus, the present concept of treatment for DM by objectives is associated with an recommended upper limit of 7%, above which a revision of the current therapeutic scheme is indicated, mainly considering that the risk for retinopathy, nephropathy, neuropathy, and microalbuminuria starts to effectively present a significant progression from the level of 7% onwards. Table 2 shows the recommendations published by the American Diabetes Association (ADA) in January 2005.

**Table 1. Correlation between glycated hemoglobin levels and average levels of glycemia in the last two to three months before the test.**

Glycated hemoglobin level (%)	Corresponding average glycemia (mg/dL)	Glycated hemoglobin level (%)	Corresponding average glycemia (mg/dL)
5	100	9	240
6	135	10	275
7	170	11	310
8	205	12	345

**Table 2. Recommendations and evidence levels regarding glyated hemoglobin control in diabetic patients.**

Recommendation of the American Diabetes Association (2005)	Evidence levels	
	ADA	SBD
Decrease in glyated hemoglobin levels is associated with a decrease in the amount of microvascular and neuropathic DM complications	A	1
Develop or adjust the strategy for glycemia control in order to attain the goal of < 7% glyated hemoglobin	B	2
More rigid goals (e.g., < 6% glyated hemoglobin) may be considered for individual patients and during pregnancy	B	2
A lower level of glyated hemoglobin is associated with a lower risk for myocardial infarct and cardiovascular death	B	2
A rigid control of glycemia with insulin can reduce morbidity in patients with severe acute disease in the perioperative period after myocardial infarct and during pregnancy	B	2
Less rigid treatment goals may be defined for patients with intense hypoglycemia, limited life expectancy, very young children or older adults, and in individuals with co-morbid conditions	B	2
Observation: ADA criteria for evidence levels (A, B, C and E) correspond to the SBD evidence levels (1, 2, 3 and 4) respectively.	E	4

## 6. Recommended levels of glyated hemoglobin for special populations

The levels of glyated hemoglobin recommended may be different from the 7% indicated for diabetic adults. For instance, the levels of glyated hemoglobin recommended for children and adolescents are a) up to 8% for children of prepuberal age; b) <8.5% in the puberal age range; and c) <7% in the final phase of puberty and in adults. For the elderly, the level of glyated hemoglobin should be individualized according to the clinical condition of each patient. A level of glyated hemoglobin of 8% or even above can be advised for already fragilized elderly individuals, those with limited life expectancy, and patients for whom the risk of an intensive glycemic control is higher than the potential benefits of the strict control. Pregnant women with DM present increased risk for both spontaneous abortion and congenital fetal malformation. The magnitude of these risks depends mainly on the DM control degree in the preconception period and in the first trimester of ges-

tation. Thus, levels of glyated hemoglobin that are more rigid (<6%) may be perfectly adequate for pregnant diabetic women. It is important to emphasize that glyated hemoglobin should not be used as a parameter for evaluation of glycemic control during gestation, since a change in the levels of glyated hemoglobin may take two months or more to reflect an inadequacy in the glycemic control.

## 7. Impact of the laboratory method on the interpretation of results for the glyated hemoglobin test

The objective of attaining a <7% level for glyated hemoglobin was validated by high performance liquid chromatography (HPLC), the method used in the DCCT and UKPDS studies. HPLC measures exactly the amount of glyated hemoglobin, differently from other methods that measure total hemoglobin A1 and/or fractions other than the glyated hemoglobin. Actually, among several

**Table 3. Analytical interfering conditions that can change the real results of a glyated hemoglobin test.**

Interfering clinical condition	Impact on glyated hemoglobin level
Hemolytic anemia or hemorrhagic state	↓
Anemia due to iron, vitamin B <sub>12</sub> or folic acid lack	↑
Presence of large amounts of vitamin C and E in the blood	↓
Increase in triglycerides, bilirubins and urea	↑
Presence of abnormal or variant hemoglobins (hemoglobin S, C, etc.)	↑ or ↓

available laboratory methods for the glycosylated hemoglobin test, some are specific enough to be classified as screening test or comparable to the original method (HPLC) endorsed by the above mentioned studies. The clinical laboratories should inform the used method and also if it can be used for screening as the method used as reference by DCCT. In practice, however, this does not happen, since many laboratories that use non-screening methods do not inform the patients and physicians. The goal of values <7% that are recommended for glycosylated hemoglobin does not apply to techniques which can not be screened by DCCT, and should be replaced by a recommendation of a maximum 1% limit above the normal maximum value for each method. The National Glycohemoglobin Standardization Program (NGSP) maintains a continuously updated listing of laboratory techniques with screened analytic performance relative to the reference method used in DCCT. People who are interested in knowing whether a method used by a given laboratory is certified or not by NGSP as a screening method by DCCT can consult its site in the web (<http://www.missouri.edu/~diabetes/ngsp.html>).

### **8. Method restrictions and analytical interferences**

Since a value for glycosylated hemoglobin reflects the average value for blood glucose in a given time period, sit-

uations may occur in which a patient presents systematically continuous periods of normal glycemia values alternating with significant hyper- and hypoglycemia conditions, in such a way that mean blood glucose values will remain within the normal limits during this period, i.e., in spite of predominance of periods with hyper- or hypoglycemia, glycosylated hemoglobin levels will remain within acceptable limits. Therefore, a systematic evaluation of glycemia at different times of the day is important to verify the validity of a correlation between the level of glycosylated hemoglobin and the patient's actual clinical situation. Table 3 shows a list of analytic interfering situations that may have an impact on the validity of results of glycosylated hemoglobin test.

### **References**

1. Grupo Interdisciplinar de Padronização da Hemoglobina Glicada; Sociedade Brasileira de Diabetes (SBD); Sociedade Brasileira de Endocrinologia e Metabologia (SBEM); Sociedade Brasileira de Patologia Clínica/Medicina Laboratorial (SBPC/ML); Associação Latino-Americana de Diabetes (ALAD); Federação Nacional das Associações e Entidades de Diabetes (FENAD). A importância da hemoglobina glicada para a avaliação do controle glicêmico em pacientes com diabetes mellitus: aspectos clínicos e laboratoriais. Posicionamento Oficial 2004.
2. American Diabetes Association. Standards of Medical Care in Diabetes. Position Statement. Diabetes Care. 2005; 28(suppl. 1): S4-S36.
3. Camargo JL, Gross JL. Conditions associated with very low values of glycohemoglobin measured by an HPLC method. J Clin Pathol. 2004; 57: 346-9.

# Analysis of markers for insulin resistance in everyday practice

## 1. Introduction

Insulin resistance is defined as a subnormal biological response to a given blood level for this hormone, being a pathophysiologic condition with a great clinical repercussion. Epidemiologic studies show that individuals who present insulin resistance have a higher probability to develop type 2 diabetes *mellitus* (DM2), some types of dyslipidemia, arterial hypertension, non-alcoholic steatohepatitis, neurodegenerative diseases, some neoplasms, as those of the breast, pancreas, and colon; and an increased (from two to four times) cardiovascular risk. Thus, it has become important in clinical practice to establish whether a patient presents insulin resistance or not.

The good methods used to evaluate insulin resistance are:

- four-fold infusion test;
- intravenous glucose tolerance test (Bergman's minimum model);
- oral glucose tolerance test (OGTT);
- insulin tolerance test (KITT);
- glucose clamp (euglycemic-hyperinsulinemic clamp)

There are simpler methods, in which only the basal dose of insulin and/or glucose is used, and the *homeostasis model assessment – insulin resistance* index (HOMA-IR) is the most widely used method. This index is calculated through the equation 'fasting glycemia (mmol/L = mg/dL:18) x fasting insulinemia ( $\mu$ U/mL)/22.5'.

## 2. Criteria for definition of insulin resistance

In a recent study performed by Stern et al.<sup>1</sup> the biggest collection of euglycemic clamp results was used, associating data of distinct populations. It allowed the development of clinically feasible and routine criteria, based on the definition for insulin resistance by using the euglycemic clamp method (gold standard). 2,321 clamp results were evaluated with 2,138 of them from non-diabetic individuals. The practical summarized results of this study define insulin resistance in clinical practice through three models:

### Model 1

Uses body mass index (BMI) and/or HOMA-IR

- a) BMI > 28.9 kg/m<sup>2</sup> or
- b) HOMA-IR > 4.65 or
- c) BMI > 27.5 kg/m<sup>2</sup> and HOMA-IR > 3.6.

These criteria of model 1 have 84.9% sensitivity and 78.7% specificity.

### Model 2

Uses only clinical criteria

- a) BMI > 28.7 kg/m<sup>2</sup> or
- b) BMI > 27.0 kg/m<sup>2</sup> and a familial history of DM.

The criteria of model 2 have 78.7% sensitivity and 79.6% specificity.

### Model 3

Uses clinical variables and determination of lipids

- a) BMI > 28.7 kg/m<sup>2</sup> or
- b) BMI > 27.0 kg/m<sup>2</sup> and a familial history of DM or
- c) negative familial history of DM, but triglycerides (TG) > 2.44 mmol/L.

Criteria of model 3 have 81.3% sensitivity and 76.3% specificity.

This study surely will be a landmark in the transition between research on insulin resistance and clinical practice because it evaluated distinct populations, analyzed a great number of individuals, and principally, used as definition parameter for comparison the euglycemic clamp. The three models derived from this study should be diffused as criteria to define insulin resistance in clinical studies or in medical practice (B, 1), but, model 1 presents better sensitivity and should be used whenever possible.

## 3. Insulin resistance and cardiovascular risk

In the last years, several epidemiologic and pathophysiologic studies showed that individuals with insulin resistance present elevated values of inflammatory markers, C-reactive protein (PCR) being the most used. There still is no consensus regarding the use of this marker as an additional measure for diagnosis of insulin resistance, and most studies point to advantages, although reduced, in associating this determination with other criteria. For clinical practice, PCR use should follow the recommendations of the Seminar on Inflammatory Markers of the Centers for Disease Prevention and Control, the American Heart Association (AHA)<sup>2</sup>, which however, are not specific for situations of insulin resistance. The recommendations for clinical practice are the following:

1. high-sensitivity PCR (hsPCR) is an independent risk marker, which can be used in the evaluation of patients with intermediate risk (10-20% risk for coronary disease in ten years) for cardiovascular disease (CVD). HsPCR may be helpful in sequential evaluation and treatment in CVD primary prevention. However, the benefits of the therapy based on this strategy remain uncertain (B, 2);
2. hsPCR is an independent risk marker and can be used as a part of the global coronary risk evaluation of adults without CVD. The benefits of this strategy remain uncertain (C, 2);
3. hsPCR may be used to motivate the patients to improve their behavior and lifestyle. The benefits of this strategy remain uncertain (C, 2);
4. in patients with persistently very high hsPCR levels (>10 mg/L) after repeated tests, evaluation of non-cardiovascular causes is required (B, 2);
5. inflammatory markers other than hs-PCR (cytokines and other acute phase markers) should not be used to determine the coronary risk (C, 3).

Finally, metabolic syndrome (MS); whose pathophysiologic basis is insulin resistance, but is not necessarily as a synonym for this hormonal resistance, should be emphasized. The presence of MS can predict the future development of DM2 and CD. There are three definitions for MS exist, but two of them are the most used in clinical studies: those of the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) and of WHO.

Based on NCEP-ATP III criteria, those who present three of the five risk factors have MS:

- a) abdominal circumference >102 cm in men and >88 cm in women;
- b) hypertriglyceridemia  $\geq$ 150 mg/dL;
- c) high-density lipoprotein (HDL) <40 mg/dL for men and <50 mg/dL for women;
- d) blood pressure (BP) >130/85 mmHg or use of anti-hypertensive medication;
- e) fasting plasma glucose > 110 mg/dL.

Recent studies suggest that the use of insulin resistance markers (HOMA-IR) in addition to the NCEP criteria

for MS to evaluate CVD risk is advantageous. However, these results must be confirmed by several studies involving a high number of individuals.

Diagnosis of MS based on WHO criteria includes:

1. presence of two or more of the following risk factors in individuals with glucose intolerance (OGTT or fasting);
  - a) hypertriglyceridemia  $\geq$ 150 mg/dL;
  - b) HDL <35 mg/dL for men and <39 mg/dL for women;
  - c) BP >140/90 mmHg or use of antihypertensive medication;
  - d) waist/hip ratio (WHR) >0.9 (men) or >0.85 (women) or BMI >30 kg/m<sup>2</sup>;
  - e) microalbuminuria  $\geq$ 20  $\mu$ g/min or albumin/creatinine ratio >30 mg/g;
2. presence of two of the above risk factors, associated with insulin resistance (as determined by fasting insulin or HOMA-IR) in individuals without glucose intolerance.

Since the OMS criterion uses glucose intolerance and/or insulin resistance, in some population studies this criterion seems to better predict the development of DM2 or CD than that of NCEP.

#### 4. Conclusion

Summarizing, we may define in clinical practice that a patient is insulin resistant, when his/her laboratory data meet the criteria of models 1, 2 or 3 as proposed by Stern et al.<sup>1</sup>.

MS as defined by OMS or NCEP criteria allows to predict the appearance of DM2 and CD.

MS, as defined by NCEP criteria allows to better predict the appearance of CVD when associated with determinations of insulin resistance.

#### References

1. Stern SE, Williams K, Ferrannini E, DeFronzo RA, Bogardus C, Stern MP. Identification of individuals with insulin resistance using routine clinical measurements. *Diabetes*. 2005; 54: 333-9.
2. Smith SC, Anderson JL, Cannon RO, Fadi YY, Koenig W, Libby P, et al. CDC/AHA Workshop on markers of inflammation and cardiovascular disease. *Circulation*. 2004; 110: e550-e3.

# Nutrition principles and recommendations in diabetes mellitus

## 1. Introduction

Nutrition recommendations and the establishment of a diet for the control of patients with diabetes *mellitus* (DM) associated with changes in lifestyle, including physical activity, are considered first-choice therapies (A, 1)<sup>1,3,8,16</sup>.

This association has proved to promote improvement of insulin sensitivity, decrease glucose plasma levels, expressively reduce abdominal circumference and visceral fat, improving the metabolic profile with reduction in LDL-C and triglyceride levels and increase in HDL-C<sup>8,12</sup>.

Management regarding nutrition therapy and physical exercises as treatment of patients with DM and is founded on several studies which will be presented below.

## 2. Nutrition therapy

Adoption of a healthy food plan is fundamental in the treatment of DM<sup>1,16</sup>. In order to establish nutrition needs of the individual, the first step is to perform a detailed nutrition evaluation, including determination of body mass index, abdominal circumference. In addition, the determination of the metabolic profile is very important for the establishment of DM nutrition therapy.

The food plan should be individualized and supply a total caloric value (TCV) compatible with the obtention and/or maintenance of the desirable body weight. For obese diabetics, the diet should be hypocaloric with a reduction of 500 kcal to 1,000 kcal of the predicted total daily energy expenditure (TEE) or food anamnesis, with the purpose to promote weight losses of 0.5 kg to 1 kg/week. A practical method for the calculation of TEE is to use 20 kcal to 25 kcal/kg present weight/day (A, 1). Diets below 800 kcal should not be used, since they are ineffective for weight reduction (C,4)<sup>1,3,16</sup>.

In insulin-resistant individuals, reduction of energy intake and moderate weight loss improve insulin resistance and blood glucose in the short term<sup>1,5,6,7,16</sup>.

Structured programs which emphasize changes in lifestyle, including nutritional education, reduction in fats (less than 30% energy intake) and energy intake, regular physical activity and regular contact with professionals may produce an approximately 5%-7% body weight loss in the long term (A, 1)<sup>1,8,12,16</sup>. Thus, exercises and behavioral modification are very useful as adjuncts to other strategies for weight loss and maintenance of weight (A, 1)<sup>1,3,16</sup>.

Using a standard diet alone for weight reduction is

insufficient to produce weight loss in the long term (A, 1)<sup>1,8,16</sup>. Recommendations for calorie and macronutrient intake are summarized in the Table.

### 2.1. Carbohydrates

Adoption of the dietary model Dietary Approaches to Stop Hypertension (DASH) associated with an intervention in lifestyle may increase insulin sensitivity. For carbohydrates, the use of greens, legumes, whole grains and fruits which should be consumed within the context of a healthy diet is recommended (A, 1). Table sugar or products containing sugar (fructose source) may eventually be ingested within the context of a healthy food plan (A, 4). Since sucrose does not increase blood glucose more than isocaloric starch amounts, sucrose and food containing sucrose do not need to be restricted for people with DM; however, they should be substituted for another source of carbohydrate or, if added, should be compensated with additional insulin doses or other hypoglycemic medication (A, 1). Non-nutritious sweeteners are safe when consumed up to acceptable daily intake level as established by the Food and Drug Administration (FDA) (A, 1)<sup>1,3,5,6,16</sup>.

Regarding the glycemic index of carbohydrates, we may state that the amount of carbohydrate in meals or snacks is more important than the source or type of carbohydrate (A, 1)<sup>13</sup>. Although diets with low glycemic index may reduce postprandial glycemia and the lipid profile, the ability of the individual to maintain these diets in the long term is not well established. No sufficient evidence is found to recommend the use of foods of low glycemic index as a primary strategy in the food plan (B, 2)<sup>1,3,6,16</sup>.

Carbohydrate and monounsaturated fat together should constitute 60%-70% of the energy intake<sup>6</sup>. However, the metabolic profile and the need for weight reduction should be considered when determining the amount of monounsaturated fat in the diet (B, 4)<sup>1,3,4,7,11,16</sup>.

### 2.2. Fibers

Consumption of at least 20 gram fibers in the form of greens, legumes, whole grains and fruits which supply minerals, vitamins and other nutrients for a healthy life is recommended. Although high amounts of fibers (50 g/day) show beneficial effects on glycemia and lipid control, it is not known if palatability and gastrointestinal side effects would be acceptable to the population (A, 1). Thus, diet fiber consumption should be encouraged for the pop-

**Table. Composition of the food plan recommended for individuals with diabetes mellitus.**

Macronutrients	Recommended intake
Total caloric value (TCV)	According to the individual's needs
Carbohydrates (CH) <sup>1</sup>	60% to 70% CH + monounsaturated fatty acids (MIFA)
Sucrose	Without restriction
Fructose	No addition to food is recommended
Food fibers <sup>2</sup>	Minimum of 20 g/day
Total fat (TF) <sup>3</sup>	~30% of TCV or 80% to 85% CH + TF
Saturated fatty acids <sup>4</sup> (SFA)	<10% total calories
Polyunsaturated fatty acids <sup>5</sup> (PIFA)	Up to 10% total calories
MIFA <sup>6</sup>	60% to 70% CH + MIFA
Cholesterol <sup>7</sup>	<300 mg/day
Protein <sup>8</sup>	15% to 20%

<sup>1</sup>The total daily portions of this group of food varies according to the TCV of the prescribed food plan. Considering that a carbohydrate portion corresponds to a slice of white bread, or half roll, or half straining spoon of rice or spaghetti, or half medium-sized potato, or half ladle of bean, for example women with BMI >27 kg/m<sup>2</sup> and sedentary should receive only six portions/day, while active normal-weight men may have an intake up to 11 portions/day; <sup>2</sup>select whole or minimally processed food with low glycemic index; <sup>3</sup>in general fatty food such as fatty meats, sausages and the like, whole milk products, fried foods, cocoa nut fat, gravies, creams and fatty sweets and foods braised with excess oil or fat; <sup>4</sup>include saturated fatty acids (C<sub>8</sub>-C<sub>16</sub>) and trans fatty acids. Recommend up to 7% if LDL-C is >100 mg/dL; <sup>5</sup>include omega-3 fatty acids which are found in fish such as salmon, sardine, mackerel and herring; <sup>6</sup>olive oil has 77% MIFA and its consumption is predominant in the Mediterranean diet; <sup>7</sup>some individuals with LDL-C >100 mg/dL may benefit from a less than 200 mg/day daily cholesterol intake; <sup>8</sup>corresponds to two small portions of lean meat/day which may be substituted for legumes (soya, chick pea, beans, lentil, etc.) and two to three daily portions of skimmed mild or low-fat cheese. Intake of fish should be stimulated because of their high content of omega-3 fatty acids. Eggs also may be used as substitutes for meat, observing the limit of two yolks/week in function of their cholesterol content. Protein excess should be avoided.

ulation as a whole but there is no reason to recommend that people with DM should consume a higher fiber amount than others (A, 2)<sup>1,3,16</sup>.

### 2.3. Fats

Fat intake is inversely associated with high insulin sensitivity, not only due to the positive relation to body weight but also because of the quality of fatty acid supply (A, 1). Less than 10% of the daily energy intake should be derived from saturated fats<sup>1,12,14,16</sup>. Some people (individuals with LDL-C higher than or equal to 100 mg/dL) may benefit from reduction in saturated fat intake to less than 7% of daily energy intake (A, 1). In order to reduce LDL-C, energy intake derived from saturated fats may be reduced when weight loss is desirable, or substituted for carbohydrate or monounsaturated fat when weight loss is not a goal (B, 2)<sup>1,3,4,16</sup>.

Polyunsaturated fat intake should constitute approximately 10% of the daily energy intake (B, 3). Omega-3 polyunsaturated fatty acids may be especially beneficial in the treatment of severe hypertriglyceridemia in people with type 2 diabetes mellitus (DM2). Two or three portions of fish/week should be recommended (B, 2)<sup>1,3,16</sup>.

In some situations, such as in hyperglyceridemia or when HDL-C is below that desirable, it may be advisable

to increase monounsaturated fat amount, in this case reducing carbohydrate supply<sup>4,11</sup>. This substitution should happen, but it should be attempted to incorporate monounsaturated fatty acids in the food plan in an additive way, since it may promote weight gain. Use of fats in quotas of less than 15% TCV may reduce HDL-C and increase glucose, insulin and triglyceride plasma levels (B, 2)<sup>1,3,3,16</sup>.

*Trans* fatty acids increase LDL-C and triglycerides and reduce the HDL-C fraction. The greatest contribution of these fatty acids in the diet stems from consumption of hydrogenated oils and fats, hard margarines and shortenings (industrial fats present in ice-creams, chocolates, bakery products, snacks, salad sauces, mayonnaise, creams for deserts and oils for industrial frying) and, to a lesser extent, milk products and bovine and caprine meat (A, 2)<sup>1,3,16</sup>.

Diets with reduced amounts of lipids, when maintained for a long time, contribute to a slight weight loss and improvement of the lipid profile (A, 2)<sup>1,12,16</sup>.

### 2.4. Protein

A daily protein intake of 15%-20% TCV is recommended. In individuals with controlled DM, protein intake does not increase plasma glucose concentration, although protein is a potent insulin secretion stimulator, to the same

extent as carbohydrate (A, 2). For people with DM, especially those who have not an optimal glucose control, the need for protein may be greater than that advocated by the Recommended Dietary Allowance (RDA), but never greater than the usual intake (B, 2)<sup>1,3,5,16</sup>.

For people with DM there is no evidence that suggests that habitual protein intake (15% to 20% daily energy needs) should be modified in the case renal function is normal (A, 4)<sup>1,3,16</sup>.

The long-term effects of diets with high-protein and low carbohydrate content are unknown. Although those diets may promote weight loss and improvement of glycemic profile in the short term, it has not yet been established if this weight loss will be maintained for a longer period of time. The effect of such diets on plasma LDL-C profile is also a matter of interest (B, 4)<sup>1,3,16</sup>.

## 2.5. Vitamins and minerals

The food plan should provide for the daily consumption of two to four portions of fruits, with at least one being rich in vitamin C (citric fruits) and of three to five portions of raw and cooked greens. Preference for whole food, whenever possible, is recommended. There is no clear evidence regarding the benefit of mineral and vitamin supplementation in people with DM who do not present deficiencies, except for folate, for the prevention of birth defects and for calcium, in order to prevent bone disease (C, 2). Routine supplementation of the diet with antioxidants is not advised because of uncertainties related to efficacy and safety in the long term (C, 2)<sup>1,3,16</sup>.

## 2.6. Cooking salt

Should be limited to 6 g/day. Processed foods, such as sausages and the like, preserved, canned, and smoked foods and packaged snacks should be avoided. Contrariwise, natural spices such as parsley, chives and aromatic herbs are recommended instead of industrialized seasonings (A, 1)<sup>1,3,16</sup>.

## 2.7. Alcohol

If the individual chooses to ingest alcoholic beverages, he/she should do it up to the limit of one dose for women and two for men. One dose is defined as 360 mL beer, 150 mL wine or 45 mL distilled beverage (C, 2). In order to reduce the risk of hypoglycemia, they should be consumed together with foods (C, 2)<sup>1,3,9,16</sup>.

## 2.8. Supplementary food recommendations

The division of the food plan into 6 meals, three main and three snacks, is recommended. Regarding the way of food preparations, grilled, roasted, vapor-cooked or even

raw, should be preferred. Diet and light foods may be indicated in the context of the food plan, and not used exclusively. Individual preferences and the patient's and family's purchasing power should be respected (C, 4)<sup>1,16</sup>.

## 3. Special situations

### 3.1. Children and adolescents

Individualized food plans and intensive insulin regimens may provide flexibility for children and adolescents with DM to reconcile irregular eating times and schedules, situations of varying appetite and levels of physical activity (A, 4). Need for nutrients in children and adolescents with type 1 and 2DM seem to be similar to other individuals of the same age (B, 4)<sup>1,3,16</sup>.

### 3.2. Pregnancy and lactation

Nutritional needs during pregnancy and lactation are similar for women with or without DM (A, 4). Thus, nutritional therapy for gestational DM and the severely diabetic patient focuses on food choices which warrant an adequate weight gain, normoglycemia and absence of ketone bodies (A, 4). For some women with gestational DM, a modest energy and carbohydrate restriction may be beneficial (B, 4)<sup>1,10,16</sup>.

### 3.3. The elderly

Energy requirements in the elderly are less than in young adults (B, 1). Physical activity should be encouraged (A, 1). In the elderly, undernourishment is more common than excess weight, therefore attention is called when prescribing diets for weight loss (B, 4)<sup>1,3,16</sup>.

### 3.4. Hypertension

A slight weight loss affects blood pressure in a beneficial way (A, 1). The goal should be reduction of sodium intake to 2,400 mg or sodium chloride to 6,000 g per day (B, 4)<sup>1,3,5,16</sup>.

### 3.5. Dyslipidemias

For individuals with elevated LDL-C levels, saturated fatty acids and saturated *trans* fatty acids should be limited to less than 10% and, perhaps, to less than 7% energy intake (B, 2). For individuals with elevated plasma triglycerides and reduced small and dense particle HDL-C and LDL-C (metabolic syndrome), improvement of glycemic control, slight weight loss, increase in physical activity, restriction of saturated fats and incorporation of monounsaturated fats in the diet might be beneficial (B, 2)<sup>1,3,5,14,16</sup>.

### 3.6. Nephropathies

In individuals with microalbuminuria and in those with kidney disease, reduction in dietary proteins from 0.8 to 1 g/kg present body weight per day and a decrease to 0.8/kg present body weight per day, respectively, may reduce the progression rate of the disease (B, 3)<sup>1,3,15,16</sup>.

### 3.7. Catabolic diseases

Energy required by most hospitalized patients may be met when 25 to 30 calories per day per kg present weight are supplied (A, 4). Protein requirement is between 1 and 1.5 g daily per kg present weight, this being the upper limit given to patients with the highest metabolic stress (A, 4)<sup>1-3,16</sup>.

## References

- American Diabetes Association (ADA). Nutrition principles and recommendations in diabetes. *Diabetes Care*. 2004; 27 Suppl 1: S36-S46.
- Clement S, Bralhwatte SS, Magee MF, Ahmann A, Smith EP, Schafer RG, et al. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care*. 2004; 27: 553-91.
- Franz MJ, Bantle JP, Beebe CA, Brunzell JD, Chiasson J, Garg A, et al. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care*. 2002; 25: 148-98.
- Garg A. High-monounsaturated-fat diets for patients with diabetes mellitus: a metaanalysis. *Am J Clin Nutr*. 1998; 67: 577S-82S.
- Grundy SM, Hansen B, Smith Jr. SC, Cleeman JI, Kahn RA. Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung and Blood Institute/American Diabetes Association Conference on Scientific Issues Related to Management. *Circulation*. 2004; 109: 551-6.
- Kelley DE. Sugars and starch in the nutritional management of diabetes mellitus. *Am J Clin Nutr*. 2003; 78: 858S-64S.
- Kelley DE, Kuller LH, Mckolanis TM, Harper P, Mancino J, Kalhan, S. Effects of moderate weight loss and orlistat on insulin resistance, regional adiposity and fatty acids in type 2 diabetes. *Diabetes Care*. 2004; 27: 33-40.
- Klein S, Sheard F, Pi-Sunyer X, Daly A, Wylie-Rosett J, Kulkarni K, et al. Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies: a statement of the American Diabetes Association, the North American Association for the Study of Obesity and the American Society for Clinical Nutrition. *Diabetes Care*. 2004; 27(8): 2067-73.
- Luz PL, Coimbra SR. Wine, alcohol and atherosclerosis: clinical evidences and mechanisms. *Braz J Med Biol Res*. 2004; 37: 1275-95.
- Reichelt AJ, Oppermann MLR, Schimidt MI. Recomendações da segunda Reunião do Grupo de Trabalho em Diabetes e Gravidez. *Arq Bras Endocrinol Metabol*. 2002; 46: 574-81.
- Ros E. Dietary *cis*-monounsaturated fatty acids and metabolic control in type 2 diabetes. *Am J Clin Nutr*. 2003; 78: 617S-25S.
- Sartorelli DS, Sciarra EC, Franco LJ, Cardoso MA. Primary prevention of type 2 diabetes through nutritional counseling. *Diabetes Care*. 2004; 27: 3019.
- Schulze MB, Hu FB. Dietary approaches to prevent the metabolic syndrome: quality versus quantity of carbohydrates. *Diabetes Care*. 2004; 27: 613-4.
- Tanasescu M, Cho E, Manson JE, Hu FB. Dietary fat and cholesterol and the risk of cardiovascular disease among women with type 2 diabetes. *Am J Clin Nutr*. 2004; 79: 999-1005.
- Ueda H, Ishimura E, Shoji T, Emoto M, Morioka T, Matsumoto N, et al. Factors affecting progression of renal failure in patients with type 2 diabetes. *Diabetes Care*. 2003; 26: 1550-34.
- World Health Organization (WHO). Diet, nutrition and the prevention of chronic diseases. Report of a joint FAO/WHO Expert Consultation. Geneva: Technical Report Series 916, 2003.

# How to prescribe exercise in the treatment of diabetes mellitus

## 1. Recommendations for physical exercise in type 2 diabetes mellitus

There is consistent evidence regarding the beneficial effects of exercise on type 2 diabetes mellitus (DM2):

1. it improves glycemic control, reducing glycosylated hemoglobin, independent of body weight reduction;
2. it reduces cardiovascular risk;
3. it contributes to the weight reduction program;
4. it improves self-esteem.

In addition, regular exercise may prevent emergence of DM2 in high-risk individuals (A, 1) (Table 1).

## 2. Definitions used in this document

The terms exercise and physical activity are usually used in a similar way, but they have different definitions, although they are used for the same situation. Physical activity corresponds to body movement in routine activities, while exercise is a planned, structured, repeated activity in order to improve or maintain physical performance such as, for instance, to walk, run, ride a bicycle, swim, among several sports. These terms will be used in the text according to the definition.

Resistance exercise corresponds to movements which use muscle force to move a weight or against a load. Examples include weight lifting and exercises using equipment with weights.

**Table 2. Evaluation of the patient with DM before beginning an exercise program.**

### Recommendations for stress test in DM

Sedentary lifestyle with one of the following risk factors:

Age >35 years with or without other cardiovascular risk factors besides DM

Age >25 years and >15 years DM1 or >10 years DM2

Arterial hypertension

Dyslipidemia

Smoking

Nephropathy, including microalbuminuria or renal insufficiency

Proliferative and preproliferative retinopathy

Autonomic neuropathy

In the absence of contraindication, for obtention of HRmax in all individuals with DM, determine the objectives of intensity and functional capacity (Sigal *et al.*) (grade B2, level 4).

**Table 1. Exercise intensity.**

	Percent VO <sub>2</sub> max	Percent HRmax
Moderate	40-60	50-70
Vigorous	>60	>70

VO<sub>2</sub>max, maximum O<sub>2</sub> consumption; HRmax, maximum heart rate in ergometric test or calculated by 220 – age.

## 3. Recommendation

In some patients with DM, performance of a stress test is needed before beginning an exercise program (Table 2).

### 3.1. Type

Aerobic exercise as, for instance, walking, cycling, running, swimming, dancing, among others (A, 1).

### 3.2. Frequency

Three to five times a week (A, 1).

### 3.3. Duration

Per day, 30 to 60 minutes or continuous 150 min/week (A, 1).

### 3.4. Intensity

Moderate (Table 1) (A, 1). Exercise with 50% to 70% VO<sub>2</sub>max has a more significant effect on glycosylated hemoglobin (A, 1), but is difficult and often not very safe to be reached in DM2. Thus, moderate activity is recommended and the possibility of increase in intensity is considered for additional benefit of glycemic control.

### 3.5. Prescription of resistance exercise

Three times a week, including the great muscles groups, progressing to three series of eight to ten repetitions with weight until not tolerating such repetitions. Less intensive exercises are useful but with less metabolic effects (Dunstan *et al.*<sup>3</sup>; Castaneda *et al.*<sup>2</sup>)(A, 1).

### 3.6. Exercise in DM2 prevention

Physical exercise increment and slight weight loss reduce DM2 incidence in individuals with reduced glucose tolerance. At least 150 minutes a week of moderate exercise associated with moderate diet regarding energy restriction are indicated for DM prevention in individuals at risk (A, 1).

**Table 3. Factors which influence the response to exercise.**

Exercise: intensity, duration and type

Level of performance

Time and content of last meal

**Specific factors of the individual:**

Time of last insulin dose

Insulin type

Metabolic control

Presence of complication

Phase of menstrual cycle in women

**Table 4. Suggestion for ultrarapid-acting insulin dose reduction of the meal before the exercise as related to duration and intensity of the exercise**

Intensity of exercise (%VO <sub>2</sub> max)	Percent of insulin dose reduction	
	30 min exercise	60 min exercise
25	25	50
50	50	75
75	75	-

Source: Rabase Lhoret et al.<sup>7</sup>.

#### 4. Recommendations for physical exercise in type 1 diabetes mellitus (DM1)

The effect of exercise on improvement of glycosylated hemoglobin in DM1 is still controversial, but it should be indicated, since it reduces cardiovascular mortality and improves self-esteem (A, 1). It is impossible to establish precise management protocols for all patients with DM1 who begin an exercise program, since the metabolic response to exercise depends on several factors (Table 3).

The highest risk in the practice of exercise in DM1 is hypoglycemia which may occur during, immediately after or hours after end of exercise. Intensive insulin administration allows adequate treatment adjustments, making different exercise levels, including the competitive, feasible. Blood glucose monitoring is the basis for adaptation of the treatment to the exercise and should be conducted before, during (when duration > 45 minutes) and after the exercise. By monitoring capillary blood glucose, some rules may help in treatment adaptation.

#### 5. Treatment adaptation

##### 5.1. Insulin

The precise reduction in insulin dose varies from person to person. As a general rule:

1. reduce the ultrarapid-acting (lispro or aspart) or rapid-acting (regular) insulin dose of the meal before the exercise (Table 4);
2. reduce the dose of intermediate-acting or prolonged-acting insulin (NPH, glargine or detemir) or that basal of the pump after the exercise when this is of longer than the usual duration;
3. use ultrarapid-acting insulin for bolus<sup>7</sup>(B, 3).

##### 5.2. Carbohydrate

The type of indicated carbohydrate (CH) depends on factors such as exercise duration and intensity and blood glucose level before and during the exercise. Simple CH (candy, juices, cooling drinks, isotonic solutions) should be used with slight lowering blood glucose and/or hypoglycemia during the exercise. If the patient does not present tendency to lowering blood glucose, a fiber-rich complex CH may be used, such as energetic cereal bar. Before long-lasting events the athlete should use CH to avoid hypoglycemia and to restore hepatic and muscle glycogen (B, 4).

#### 6. General recommendations for DM1 and DM2

##### 6.1. Exercise and hyperglycemia

In the absence of insulinopenia, light to moderate exercise may reduce glycemia. Thus, if the patient feels fine and ketonuria is negative, there is no need to delay the exercise because of hyperglycemia, even if 300 mg/dL. If glycemia is >250 mg/dL with ketosis, exercise should be avoided (B, 4).

##### 6.2. Exercise and hypoglycemia

If the patient uses insulin or a secretagogue, he/she should replace carbohydrate if glycemia is <100 mg/dL. But, if he/she is treated with diet, metformin, alpha-glycosidase inhibitors or thiazolidinedione without insulin or secretagogue, no supplementation with CH is needed (B, 4).

##### 6.3. Retinopathy

Aerobic or resistance exercise of high intensity is contraindicated in the presence of proliferative retinopathy due to the risk of vitreous hemorrhage or retinal detachment. Three to six months after photocoagulation, start or continuation of exercise is recommended<sup>1</sup>(B, 4).

##### 6.4. Peripheral neuropathy

In the presence of neuropathy with reduction in sensi-

tivity of the lower limbs, activity without the effect of gravity, such as swimming, riding a bicycle or upper limb exercises should be stimulated (B, 4)<sup>13</sup>.

### 6.5. Autonomic neuropathy

Patients with autonomic neuropathy may present a smaller cardiac response to exercise, an alteration of thermoregulation, impairment of thirst and gastroparesis with delay in nutrient absorption. These patients should be submitted to a more intense cardiac evaluation with myocardial scintigraphy (B, 4)<sup>12</sup>.

### 6.6. Microalbuminuria and nephropathy

There is no restriction of specific exercises for patients with renal alteration, including even prescription of resistance exercise. But, since microalbuminuria and proteinuria are associated with cardiovascular disease, the performance of a stress test before the start of a more intense than the usual exercise is important (B, 4).

## References

1. Aiello LP, Wong J, Cavallerano JD, Bursell SE, Aiello LM. Retinopathy. In: Ruderman N, Devlin JT, Schneider SH, Kriska A, editors. Handbook of exercise in diabetes. 2 ed. Alexandria, VA, American Diabetes Association, 2002. p. 401-13
2. Castaneda C, Layne JE, Munoz-Orians L, Gordon PL, Walsmith J, Foldvari M, et al. A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. *Diabetes Care*. 2002; 25: 2335-41.
3. Dunstan DW, Daly RM, Owen N, Jolley D, de Courten M, Shaw J, et al. High-intensity resistance training improves glycemic control in older patients with type 2 diabetes. *Diabetes Care*. 2002; 25: 1729-36.
4. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002; 346: 393-403.
5. Levin ME. The diabetic foot. In: Ruderman N, Devlin JT, Schneider SH, Kriska A, editors. Handbook of exercise in diabetes. 2 ed. Alexandria: American Diabetes Association; 2002. p. 385-99.
6. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and Diabetes Study. *Diabetes Care*. 1997; 20: 537-44.
7. Rabase-Lhoret R, Bourque J, Ducros F, Chasson JL. Guidelines for pre meal insulin dose reduction for postprandial exercise of different intensities and durations in type 1 diabetic subjects treated intensively with basal-bolus insulin regimen (ultralent-lispro). *Diabetes Care*. 2001; 24: 625-30.
8. Colberg S. The diabetic athlete prescriptions exercise and sports. 2001. Ed. Human Kinetics.
9. Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C. Physical activity/exercise and type 2 diabetes (technical review). *Diabetes Care*. 2004; 27: 2518-39.
10. Stevens RJ, Kothari V, Adler AI, Stratton IM. The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). *Clin Sci (Lond)*. 2001; 101: 671-9.
11. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001; 344: 1343-50.
12. Valensi P, Sachs RN, Harfouche B, Lormeau B, Paries J, Cosson E, Paycha F, Leutenegger M, Attali JR. Predictive value of cardiac autonomic neuropathy in diabetic patients with or without silent myocardial ischemia. *Diabetes Care*. 2001; 24: 339-43.
13. Vinik AI, Erbas T. Neuropathy. In: Ruderman N, Devlin JT, Schneider SH, Kriska A, editors. Handbook of Exercise in diabetes. 2 ed. Alexandria: American Diabetes Association; 2002. p. 463-96.
14. Zinman B, Ruderman N, Campaigne BN, Devlin JT, Schneider SH. Physical activity/exercise and diabetes mellitus (position statement). *Diabetes Care*. 2003; 26 Suppl. 1: S73-S77.

# Oral drugs in the treatment of diabetes mellitus

How to select them according to the patients' clinical characteristics

## 1. Introduction

When the patient with type 2 diabetes *mellitus* (DM2) does not respond or stops to respond adequately to non-pharmacological measures, one or more antidiabetic agents should be indicated, with the purpose to control blood glucose and to promote fall in glycated hemoglobin (B, 2)<sup>1</sup>. The mechanisms of insulin resistance (IR), progressive  $\beta$ -cell failure, multiple metabolic disorders (dysglycemia, dyslipidemia and vascular inflammation) and micro- and macrovascular repercussions which accompany the natural history of DM2 are also objectives to be remembered.

Epidemiologic studies support the hypothesis of a direct and independent relationship between glucose blood levels and cardiovascular disease (CVD) (A, 1)<sup>1-23</sup>. Therefore, absence of a glycemic threshold in diabetic individuals and persistence of this relation in non-diabetics suggests that glycemia is a continuous risk variable, similarly to other cardiovascular risk factors (A, 1)<sup>2-28,30</sup>. Thus, the goal of the treatment is normoglycemia with good available strategies for its maintenance in the long term. To be true, one of the essential objectives in the treatment of DM should be obtention of glycemic levels as close as possible to normality as can be reached in clinical practice<sup>49</sup>.

To reach this, antidiabetic agents should be indicated when fasting and/or postprandial glycemic values above those required for DM diagnosis are found<sup>1-28,30</sup>.

## 2. Oral antidiabetic agents

Are substances whose aim, when ingested, is to lower glycemia and maintain it at normal values (fasting <100 mg/dL and postprandial <130 mg/dL)<sup>4</sup>.

In view of this comprehensive concept, oral antidiabetics may be divided, according to their mechanism of action, into: drugs that increase pancreatic insulin secretion (sulfonylureas and glinides); reduce glycosides (alpha-glucosidase inhibitors); decrease hepatic glucose reduction (biguanides); and/or increase peripheral glucose utilization (glitazones).

However, practically, oral antidiabetics may be classified into two main categories: those which increase insulin secretion (hypoglycemics) and those which do not (antihyperglycemics).

### 2.1. Agents which increase insulin secretion

Are insulin secretagogues and comprise sulfonylureas that develop a more prolonged hypoglycemic action during the whole day (chlorpropamide, glibenclamide, gliclazide, glipizide and glimepiride) and promote a 1.5% to 2% fall in glycated hemoglobin; and the glinides, with less time of action, mostly in the postprandial period, with a reduction in glycated hemoglobin of 1% in the case of nateglinide and from 1.5% to 2% with repaglinide<sup>1,3-5,36-38</sup>.

### 2.2. Agents that do not increase insulin secretion

These drugs when used as monotherapy are usually related to a very low hypoglycemia risk. Therefore they may be used safely from the beginning of the disease. To this group belong:

- acarbose (alpha-glucosidase inhibitor);
- metformin (biguanide);
- rosiglitazone and pioglitazone (thiazolidinediones or glitazones) (Table).

Acarbose reduces intestinal glucose absorption velocity; therefore it acts at an earlier phase still in the digestive tract, predominantly on postprandial glycemia (and afterwards also on fasting glycemia), with a 0.7% to 1% reduction in glycated hemoglobin<sup>1,3-5,25-29,33-35</sup>.

The major antihyperglycemic action of metformin, that is, decreasing hepatic glucose production is accompanied by a slighter peripheral sensitizing action. On average, metformin reduces glycated hemoglobin by 1.5% to 2%<sup>1,3-5,31,32</sup>.

Glitazones act predominantly on peripheral insulin resistance of the muscle, adipocytes and hepatocytes, sensitizing the action of insulin produced by the patient him(her)self. Theoretically, as the performance of endogenous insulin improves, without increase in its secretion, glitazones would have the potential to preserve the beta cell and to postpone cardiovascular deterioration (although such evidence still is in need of studies in great samples). Glitazones reduce glycated hemoglobin by 1% to 2.2% on average<sup>1,3-5,33-35,43-47</sup>.

## 3. Choice of the oral antidiabetic agent

Choice of the medicament should take into account:

- fasting and postprandial glucose and glycated hemoglobin values;

**Table. Treatment of DM2 with antidiabetic agents**<sup>1,3-5,25-29,31-40,43</sup>

Drugs (dosage mg)	Mechanism of action	Reduction in fasting blood glucose (mg/dL)	Reduction in HbA1c (%)	Contra-indication	Side effects	Other beneficial effects
<b>Sulfonylureas</b>						
Chlorpropamide 125 to 500 Glibenclamide 2,5 to 20 Glipizide 2.5 to 20 Gliclazide 40 to 320 Glicazide MR 30 to 120 Glimepiride 1 to 8 One to two times/day	Increase in insulin secretion	60-70	1.5-2	Pregnancy, Renal or hepatic failure	Hypoglycemia and weight gain (chlorpropamide favors increase in blood pressure and does not protect against retinopathy)	
<b>Glinides</b>						
Repaglinide 0.5 to 16 Nateglinide 120 to 360 Three times/day	Increase in insulin secretion	20-30	0.7-1	Pregnancy	Hypoglycemia and slight weight increase	Reduction in medium intimal carotid thickening (repaglinide)
<b>Biguanides</b>						
Metformin 1,000 to 2,550 Two times/day	Reduces hepatic glucose production with less sensitizing action on insulin action	60-70	1,5-2	Pregnancy, renal, hepatic, cardiac, pulmonary failures and severe acidosis	Abdominal discomfort, diarrhea	Decrease in cardiac events DM2 prevention Improvement of lipid profile Weight loss
<b>Alpha-glucosidase inhibitors</b>						
Acarbose 50-300 Three times/day	Delay in carbohydrate absorption	20-30	0.7-1	Pregnancy	Meteorism, flatulence and diarrhea	Decrease in cardiovascular events DM2 prevention Reduction of medium intimal carotid thickening Improvement of lipid profile
<b>Glitazones</b>						
Rosiglitazone 4 to 8 Pioglitazone 15 to 45 Once/day	Increase in insulin sensitivity in muscle, adipocyte and hepatocyte (insulin sensitizing agents)	35-65*	1-2.2*	Class III and IV heart failure Hepatic failure Pregnancy	Edema, anemia and weight gain	DM2 prevention Reduction of medium intimal carotid thickening Improvement in lipid profile Reduction of liver fat

\*Mean fasting blood glucose and HbA1c reduction for monotherapy. In the case of combined therapy, a synergic effect may occur with potentiation of reduction in glycemic levels.

- patient's weight and age;
- presence of complications, other metabolic disorders and associated disease;
- possible interaction with other drugs, adverse reactions and contraindications.

### 3.1. General recommendations based on glycemia

- With blood glucose less than 150 mg/dL, drugs which do not promote increase of insulin secretion, specially if the patient is obese, are indicated (D, 5)<sup>1,3-5</sup>.
- When fasting glucose is above 150 mg/mL, indication

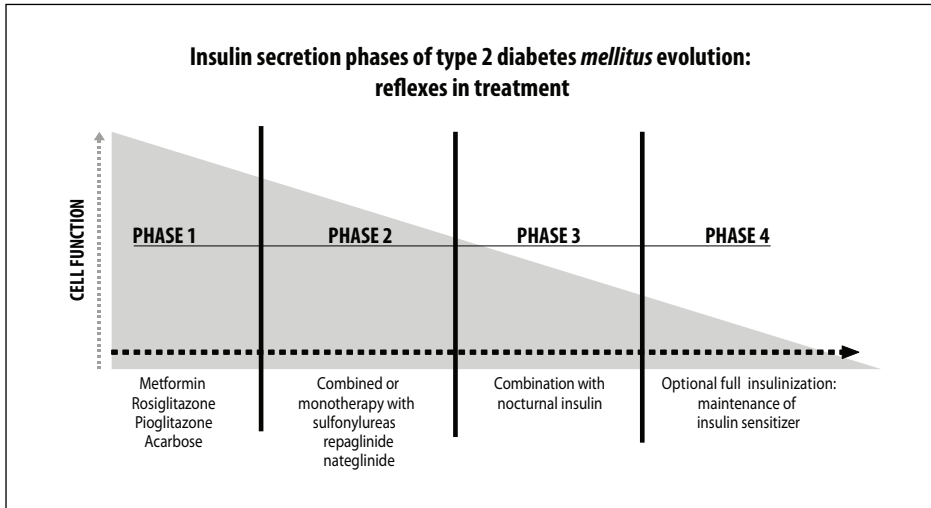


Figure 1. Therapeutic algorithm for DM2 management according to the disease evolution phase.

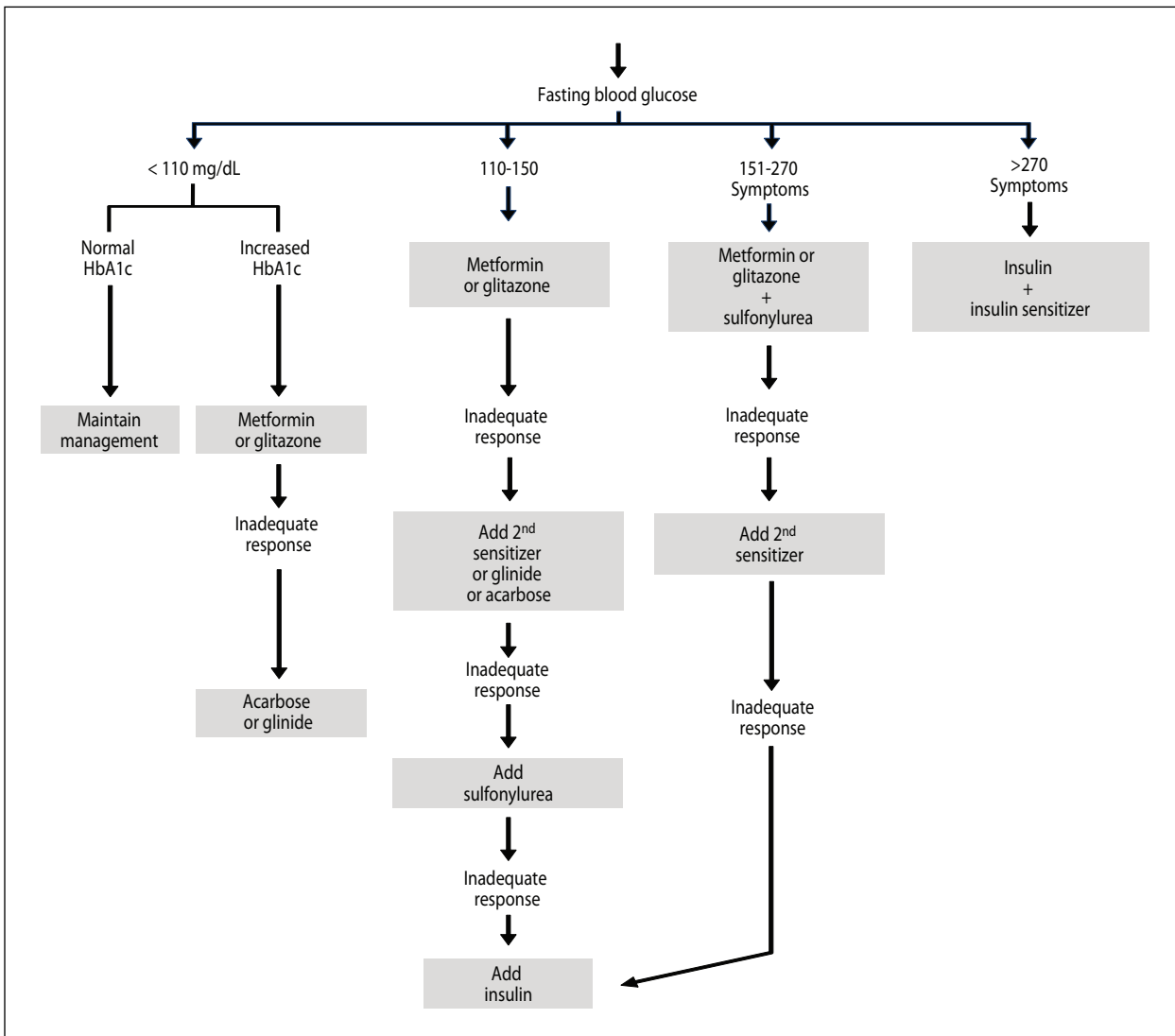


Figure 2. Therapeutic algorithm for DM2 management according to fasting blood glucose (SBD, 2005).

of oral antidiabetic monotherapy will depend on pre-dominance between insulin resistance or insulin deficiency/beta-cell failure (D, 5)<sup>1,3-5</sup>.

### 3.2. General recommendations based on the clinical presentation

- In most DM2 cases, the clinical phenotype is soon characterized by the presence of obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), arterial hypertension, among other typical stigmata of the so-called *metabolic syndrome*. These stigmata indicate the presence of insulin resistance and, in this case, antihyperglycemic agents are more appropriate, improving endogenous insulin action with a better metabolic control and avoiding excessive weight gain (A, 1)<sup>1,3-5,25-35</sup>.
- Association between hyperglycemia and weight loss is a sign of insulin deficiency and usually of an advanced or more unbalanced stage of the disease. Under these circumstances, secretagogues are usually indicated (sulfonylureas or glinides) either as monotherapy or combined therapy (D, 5)<sup>1,3-5,36-38</sup>.
- For those patients with normal fasting blood glucose, but with above normal glycated hemoglobin (HbA1c) the use of antihyperglycemics (metformin or glitazones)<sup>44</sup> or those which act more on postprandial glycaemia is indicated<sup>1,3-5,32,25-29,38</sup>.
- With years or decades of DM2 evolution, a progressive reduction in the insulin secreting capacity by the beta cells occurs, and monotherapy may fail to maintain a good metabolic control<sup>1,2-5,32,36,37,39,40</sup>. Thus, there is a need to combine oral drugs (ideally with different mechanisms of action) and sometimes a third oral drug has to be added. At this time the analysis of cost/benefit ratio of the treatment is important, since opportune introduction of insulin (which is not the subject of this article) can also be efficient.

### 3.3. Practical general recommendations

In practice, a patient may attend the first visit, at the beginning of DM2 evolution, when insulin resistance predominates, or else, with many years of disease evolution where the main characteristic is insulinopenia. Best therapy depends heavily on the secreting ability of his/her pancreas (Figures 1 and 2).

In phase 1, initial DM2 period characterized by slight dysglycemia, obesity and insulin resistance, the best indication is drugs which do not increase insulin secretion.

In phase 2, with insulin secretion decrease, the indication of a secretagogue is correct, possibly in combination with insulin sensitizers.

In phase 3, with progress of insulin secretion loss, usually after some decades of disease evolution and already with weight loss and/or present co-morbidities, usually association of a long-acting insulin injection with the oral drugs is required before the patient goes to sleep (opportune bedtime insulinization).

Finally, in phase 4 when clear insulinopenia predominates, the patient should receive one or two applications of a depot insulin (NPH or long-acting analogs) one before breakfast and another before dinner or at bedtime, alone or combined with a rapid- and a very rapid-acting insulin<sup>41,42</sup>. In this phase 4, an oral sensitizing agent, combined with insulinization, usually reduces insulin doses and helps metabolic control improvement.

### References

1. Sociedade Brasileira de Diabetes. Consenso Brasileiro sobre Diabetes 2002. Diagnóstico e classificação do diabete melito e tratamento do diabete melito do tipo 2. Rio de Janeiro: Diagraphic Editora, 2003.
2. Report of the Expert Committee on Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 1997; 20: 1183-97.
3. Lebovitz HE, editor. *Therapy for diabetes mellitus and related disorders*. American Diabetes Association. 4 ed. Alexandria, VA, USA; 2004.
4. Oliveira JEP, Milech A, editors. *Diabetes mellitus: clínica, diagnóstico e tratamento multidisciplinar*. São Paulo: Atheneu; 2004.
5. Oliveira JEP, Monteiro JBR, Araújo, CGS. *Diabetes melito tipo 2: terapêutica clínica prática*. Rio de Janeiro: Med Line; 2003.
6. McCance DR, Hanson RL, Charles MA, Jacobsson LTH, Pettit DJ, Bennett PH, et al. Comparison of tests for glycated haemoglobin and fasting and twohour plasma glucose concentration as diagnostic methods for diabetes. *BMJ*. 1994; 308: 1323-8.
7. Engelgau MM, Thompson TJ, Herman WH, Boyle JP, Aubert RE, Kenny SJ, et al. Comparison of fasting and 2-hour glucose and HbA1c levels for diagnosing diabetes: diagnostic criteria and performance revisited. *Diabetes Care*. 1997; 20: 785-91.
8. Stamler J, Vaccaro O, Neaton JD, Wentworth D, for the Multiple Risk Factor Intervention Trial Research Group. Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*. 1993; 16: 434-44.
9. Kuusisto J, Mykkänen L, Pyörälä K, Lasskso M. NIDDM and its metabolic control are important predictors of stroke in elderly subjects. *Stroke*. 1994; 25: 1157-64.
10. Hanefeld M, Fischer S, Julius U, et al. Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study: 11- year follow-up. *Diabetologia*. 1996; 39: 1577-83.
11. Barrett-Conner E, Ferrara A. Isolated postchallenge hyperglycemia and the risk of fatal cardiovascular disease in older women and men: the Rancho Bernardo Study. *Diabetes Care*. 1998; 21: 1236-9.
12. Rodrigues B, Lau N, Burchfiel C, et al. Glucose intolerance and 23-year risk of coronary heart disease and total mortality: the Honolulu Heart Program. *Diabetes Care*. 1999; 22: 1262-5.
13. Shaw J, Hodge A, de Courten M, Chitson P, Zimmet P. Isolated post-challenge hyperglycemia confirmed as a risk factor for mortality. *Diabetologia*. 1999; 42: 1050-4.
14. Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose: the Fumagata Diabetes Study. *Diabetes Care*. 1999; 22: 920-4.

15. Bakau B, Shipley M, Jarrett R, Pyörälä K, Pyörälä M, Forhan A, et al. High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men: 20-year followup in the Whitehall Study, the Paris Prospective Study and Helsinki Policemen Study. *Diabetes Care*. 1998; 360-7.
16. DECODE Study Group. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet*. 1999; 354: 617-21.
17. Coutinho M, Gerstein H, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events: a meta-regression analysis for published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care*. 1999; 22: 232-40.
18. DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med*. 2001; 161: 397-405.
19. Stratton IM, Adler AL, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000; 321: 405-11.
20. Wahab NN, Cowden EA, Pearce NJ, Gardner NJ, Merry H, Cox JL on behalf of the ICONS Investigators. Is blood glucose an independent predictor of mortality in acute myocardial infarction in thrombolytic era? *J Am Coll Cardiol*. 2002; 40: 1748-54.
21. Del Prato S. In search of normoglycaemia in diabetes: controlling postprandial glucose. *Int J Obes Relat Metab Disord*. 2002; 26 Suppl 3: S9-S17.
22. Jackson CA, Yudkin JS, Forrest RD. A comparison of the relationship of the glucose tolerance test and the glycated haemoglobin assay with diabetic vascular disease in the community: the Islington Diabetes Survey. *Diabetes Res Clin Pract*. 1992; 17: 111-23.
23. Beks PJ, Mackay AJC, de Neeling JND, de Vries H, Bouter LM, Heine RJ. Peripheral arterial disease in relation to glycaemic level in elderly Caucasian population: the Hoorn Study. *Diabetologia*. 1995; 38: 86-96.
24. Knowler WC, Barrett-Connor E, Fowler SE, Hammar RF, Lechin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002; 346: 393-403.
25. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Laakso M. Acarbose for prevention of type 2 diabetes: the STOP-NIDDM randomized trial. *Lancet*. 2002; 359: 2072-7.
26. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance. The STOP-NIDDM Trial. *JAMA*. 2003; 290: 486-94.
27. Hanefeld M, Cagatay M, Petrowitsch T, Neuser D, Petsinna D, Rupp M. Acarbose reduces the risk for myocardial infarction in type 2 patients: meta-analysis of seven long-term studies. *Eur Heart J*. 2004; 25: 10-6.
28. Hanefeld M, Chiasson JL, Koehler C, Henkel E, Schaper F, Temelkova-Kurktschiev T. Acarbose slows progression of intima-media thickness of the carotid arteries in subjects with impaired glucose tolerance. *Stroke*. 2004; 37: 1073-8.
29. Ogawa S, Takeuchi K, Ito S. Acarbose lowers serum triglycerides and post-prandial chylomicron levels in type 2 diabetes. *Diabetes Obes Metab*. 2004; 6: 384-90.
30. Buchanan TA, Xiang AH, Peters RK, Siri KL, Marroquin A, Goico J, et al. Preservation of pancreatic beta cells function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes*. 2002; 51: 2796-803.
31. Cusi K, DeFronzo RA. Metformin: a review of its metabolic effects. *Diabetic Rev*. 1998; 6: 89-130.
32. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998; 352: 854-65.
33. Koshiyama H, Shimono D, Kuwamura N, Minamikawa J, Nakamura Y. Inhibitory effect of pioglitazone on carotid arterial wall thickness in type 2 diabetes. *J Clin Endocrinol Metabol*. 2001; 86: 3452-6.
34. Parulkar AA, Pedergrass ML, Granda-Ayala R, Lee RT, Fonseca VA. Non-hypoglycemic effects of thiazolidinediones. *Ann Intern Med*. 2001; 134: 61-71.
35. Tiikkainen M, Hakkinen AM, Korshennikovova E, Tuulikki N, Sari M, Yki-Jarvinen H. Effects of rosiglitazone and metformin on liver fat content, hepatic insulin resistance, insulin clearance, and gene expression in adipose tissue in patients with type 2 diabetes. *Diabetes*. 2004; 53: 2169-76.
36. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998; 352: 837-53.
37. UK Prospective Diabetes Study Group. (UKPDS 24). A 6-year, randomized, controlled trial comparing sulfonylurea, insulin, metformin therapy in patients newly diagnosed type 2 diabetes that could not be controlled with diet therapy. *Ann Intern Med*. 1988; 128: 165-67.
38. Espósito K, Giugliano D, Nappo F, Marfella R. Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. *Circulation*. 2004; 110: 214-9.
39. Turner RC, Cull CA, Frighi V, Holman RR, UKPDS Group. Glycemic control with diet, sulfonylurea, metformin or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). *JAMA*. 1999; 281: 2005-12.
40. Wright A, Burden ACF, Paisey RB, Cull CA, Holman RR, UKPDS Group. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the UKPDS (UKPDS 57). *Diabetes Care*. 2002; 25: 330-6.
41. Yki-Jarvinen H, Kauppila M, Kujansuu E, Lahti J, Marjanen L, Rajala S, et al. Comparison of insulin regimens in patients with non-insulin dependent diabetes mellitus. *N Engl J Med*. 1992; 327: 1426-33.
42. Yki-Jarvinen H, Riysi L, Nikkile K, Tuloks Y, Vanano R, Heikkilä OM. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. *Ann Intern Med*. 1999; 130: 386-96.
43. Yu JG, Kruszynska YT, Mulford MI, Olefsky JM. A Comparison of troglitazone and metformin on insulin requirements in euglycemic intensively insulin-treated type 2 diabetic patients. *Diabetes*. 1999; 48: 2414-21.
44. Sociedade Brasileira de Diabetes. Atualização Brasileira sobre Diabetes 2005. Síndrome metabólica. Rio de Janeiro: Diagraphic Editora, 2005.
45. Wyne K, et al. The effects of rosiglitazone in poorly-controlled, drug-naive patients with type 2 diabetes mellitus. In: 64<sup>th</sup> Annual Meeting of ADA, 2004, Orlando. Proceedings Orlando: ADA, 2004. Poster 639.
46. Chou H, et al. Rosiglitazone and metformin fixed-dose combination provides superior glycaemic control compared to metformin and rosiglitazone monotherapies and was well tolerated in drug-naive type 2 diabetes patients. In: 41<sup>st</sup> Annual Meeting of EASD, 2005, Atenas. Proceedings Atenas: EASD, 2005. Poster 766.
47. Rosenstock J, et al. Rosiglitazone/metformin (RSG/MET) fixed dose combination (FDC) is effective and well-tolerated in drug-naive type 2 diabetes mellitus (T2DM) subjects with severe hyperglycemia. In: 65<sup>th</sup> Annual Meeting of ADA, 2005, San Diego. Proceedings San Diego: ADA, 2005. Poster 515.
48. Haffner SM, et al. Insulin sensitivity in subjects with type 2 diabetes. Relationship to cardiovascular risk factors: the insulin resistance atherosclerosis study. *Diabetes Care*. 1999; 22(4): 562-8.
49. American Diabetes Association. *Diabetes Care*. 2003; 26: S28-S32.

# Use of insulin in the treatment of type 2 diabetes mellitus

## 1. Introduction

Type 2 diabetes *mellitus* (DM2) is characterized by two main pathophysiologic defects: insulin resistance, resulting in increase of hepatic glucose production and reduction in its peripheral utilization, and impairment of the basal secreting function of the beta cell, stimulated by the substrate, mainly glucose. Loss of the acute response to a glucose overload is the defect that occurs early in the natural history of the disease, in general when fasting blood glucose reaches 115 mg/dL, leading to postprandial hyperglycemia. When fasting blood glucose reaches a level of 140 mg/dL, approximately 75% islet function has been lost. The progressive loss of function and volume of the beta cell is associated with an amyloid deposit, a product of the amyloid polypeptide co-secreted normally with insulin by the beta cell. It should be noted that hyperglycemia, *per se*, when present chronically, impairs beta-cell function and increases insulin resistance, being called glycototoxicity, in opposition to similar effects of high circulating fatty acid values in DM, known as lipotoxicity.

DM2 may be present nine to 12 years before the diagnosis when, with sometimes a frequent 50% loss of beta-cell function, indicating the important role of its dysfunction, together with insulin resistance, in the pathogenesis of DM2. The progressive loss of insulin function with time is associated with glycemic deterioration, occurring independently of the therapy, including insulin, with the possible exception of glitazones which could induce beta-cell recovery<sup>1</sup>. Thus, the difficulty to maintain glycated hemoglobin at the desired level with time could be related to different behavioral factors (e.g.: lack of compliance with diet, exercise, prescribed medication), but reflects primarily the progressive decline in beta-cell function<sup>2</sup>.

## 2. Intensive insulin therapy in the short term for the treatment of newly diagnosed DM2

For newly diagnosed DM2, with high blood glucose, usually above 250 mg/dL, an intensive therapy is indicated with rapid-acting (regular) or ultrarapid-acting insulin (lispro or aspart) before each meal and basal insulin of intermediary action (Neutral Protamine Hagedorn [NPH]), or long-acting (glargine) in one or more daily doses. The total insulin dose for the beginning of treatment in these patients not previously treated with insulin would be 0.4 U/kg weight, 50% being basal and the remaining 50%

rapid-acting or ultrarapid-acting insulin preparations. Capillary glycemia (fingertip) before meals, particularly before breakfast, should reach a value lower than 110 mg/dL, and less than 130-140 mg/dL 2 hours after meals. NPH or glargine dose should be regulated according to fasting capillary glycemia, increasing or decreasing this dose by 2-3 U/day, the same applying to the use of regular or ultrarapid-acting insulin. Obviously the other measures, mainly dietetic, will be indicated. Within two or three weeks, glycemia control will reach and maintain the desired values, and insulin therapy can then be discontinued. In a recently published study<sup>3</sup> using the above mentioned scheme and using only NPH and regular insulin, it was shown that the benefit of a better glycemia control was maintained for at least one year with diet alone or also with an oral hypoglycemic agent, while the mean blood glucose levels were maintained in the range of 120 mg/dL. It is interesting to mention that the authors observed in most studied patients (15/16) an evident recovery of insulin secretion during the glucose tolerance curve at the end of the study, probably related to the association between glyco- and lipotoxicity which was still greater one year after the end of intensive insulin therapy. This study, despite being performed with a small number of patients, could be a basis for a good glycemic control in the long term in DM2 with elevated initial glycemia levels.

The newly diagnosed DM2 patients could receive insulin via continuous subcutaneous infusion pump, the basal and bolus insulin doses being adjusted so that the pre- and postprandial glycemias are within the above mentioned limits, usually within one week. A marked beta-cell-function improvement was observed, particularly reduction of proinsulin (indicating improved insulin secretion quality) and a significant fall in endogenous hormone resistance. In this study, the patients who maintained glycemic control without drug therapy for more than one year (group in remission) showed a higher recovery of beta-cell function than those who did not maintain euglycemia (group without remission, approximately half of the studied patients) when they were also evaluated after the end of continuous insulin infusion<sup>4</sup>.

## 3. Insulin therapy in chronic DM2 treatment

If fasting blood glucose is persistently high (>160 mg/dL) and glycated hemoglobin remains above the

**Table 1. Mostly used premixed combinations of human NPH and regular insulins.**

Combination	Time of administration before meals (min)	Activity peak after administration (hours)
Novolin 70/30 (Novo Nordisk) (70% NPH and 30% regular)	30	4.2±0.39
Humulin 70/30 (Lilly) (70% NPH and 30% regular)	30-60	4.4 (1.5-16)

**Table 2. Mostly used combination of ultrarapid-acting analogs bound to protamine and premixed soluble analogs.**

Combination	Time of administration before meals (min)	Activity peak after administration (hours)
Novo Mix (Novo Nordisk) (70% aspart/protamine and 30% aspart)	10-20	2.2 (1-4)
Humalog Mix 25 (Lilly) (75% lispro/protamine and 25% lispro)	15	2.6 (1-6.5)

desirable maximum value ( $\geq 7\%$ ) despite the fact that the patient is receiving maximum doses of oral therapy with two or three oral antidiabetic agents, showing their total or partial inefficiency, and while maintaining oral drugs at least in the beginning, insulin therapy should be started earlier than usual during the natural diabetes evolution, as soon as a more marked glycemic unbalance is clinically observed, thus performing the so-called opportune insulinization<sup>5</sup>.

### 3.1. Oral antidiabetic agents + basal insulin

The patient should continue with oral agents and the same dosage (eventually reduced) and a single bedtime NPH or glargine insulin dose is prescribed (begin with 15 U or 0.2 U/kg in the more obese). Adjustment by 2, 4 or 6 U of the insulin dose is made every 3 days, preferable by the patient him/herself, (depending on consistently higher than 120, 140 or 160 mg/dL fasting capillary glycemia, respectively) until reaching the goal of less than 110-120 mg/dL fasting blood glucose, in the case no nocturnal hypoglycemia occurs.

### 3.2. Full DM2 therapy with insulin

When fasting capillary glycemia reaches the value of 120 mg/dL or less (100-110 mg/dL) and the 2-h postprandial glycemia persists above the goal ( $>180$  mg/dL, according to the American Diabetes Association [ADA], or 135 mg/dL in our experience of evaluation of a great number of normal, young and not obese individuals and in agreement with the International Diabetes Federation [IDF]), this is an indication that oral drugs, even at maximum doses do not control blood glucose levels during the day, indicating a more marked insulin deficiency. Therefore the need to provide a rapid-acting (regular) or ultrarapid-acting insulin during the day to cover the meals, and discontinuation of the use of oral secretagogues is then usual; but to continue with insulin sensitizers in combination

with insulin therapy may prove beneficial. Thus combined insulin plus metformin therapy or insulin and thiazolidinediones (rosiglitazone or pioglitazone) has allowed an effective glycemic control with lower insulin doses. However, combined thiazolidinedione and insulin therapy is associated with increase in body weight and edema as compared to insulin + metformin therapy. Cost/benefit ratio of the better glycemic control *versus* weight gain should be considered on an individual basis. Weight gain and edema have been associated with a greater incidence of heart failure in patients treated with thiazolidinediones and insulin, to the point that the European Agency for Analysis of Medical Products considers insulin therapy a contraindication for the use of thiazolidinediones, although there is no convincing reason for this.

For the patients who need basal and prandial insulin but who do not wish to receive multiple daily insulin injections, simulating its physiological secretion, rapid-acting (regular) or ultrarapid-acting (insulin analogs: lispro or aspart) insulin mixtures with intermediary-acting insulins would be indicated. Available premixed insulins on the market may be classified into two groups:

- B1 – premixed NPH human and regular insulin: the available mixtures on the market are indicated in Table 1;
- B2 – premixed ultrarapid-acting analogs bound to protamine and soluble analogs. These preparations are indicated in Table 2.

There is an essential difference between insulin premixed with human insulin (NPH + regular) and of a soluble analog with protamine analog. Actually, in the first, the actions of both components are added during a relatively long period and, consequently, the resulting action of the premixed insulins is not present as two well-differentiated phases, as would be desirable, there being only a prolongation of the rapid action during the initial 6 hours. On the other hand, in the mixtures of analogs, the actions of both

**Table 3. Mostly used schemes for insulinization of DM2 and initial basal and prandial insulin doses.**

Before breakfast	Before lunch	Before dinner	Bedtime
<b>1.R/Ur 2x/day + NPH 2x/day</b>			
2/3 total dose			1/3 total dose
2/3 NPH	–	1/2 R/Ur	1/2 NPH
1/3 R/Ur			
<b>2.R/Ur 3x/day + NPH 2x/day</b>			
1/2 total dose		1/2 total dose	
2/3 NPH			1/3 NPH
1/3 R/Ur	1/3 R/Ur	1/3 R/Ur	
<b>3.R/Ur 3x/day + NPH 3x/day</b>			
1/3 NPH	1/3 NPH		1/3 NPH
1/3 R/Ur	1/3 R/Ur	1/3 R/Ur	
<b>4. Basal regimen –with NPH bolus</b>			
	70% total dose		30% total dose
30% R/Ur	20% R/Ur	20% R/Ur	NPH
<b>5. Basal regimen – bolus with NPH</b>			
	50% total dose		50% total dose
15% R/Ur	20% R/Ur	15% R/Ur	Glargine
<b>6. Premixed insulins with ultrarapid-acting analogs 2x/day</b>			
50% total dose		50% total dose	
<b>7. Premixed insulins with ultrarapid-acting analogs 3x/day</b>			
30% total dose	40% total dose	30% total dose	

R, regular insulin; Ur, ultrarapid-acting insulin analog (lispro or aspart).

components are complementary. Due to the shorter action of lispro or aspart, the actions of the rapid- and slow-acting components are clearly maintained separate, resulting in an actually biphasic absorption. Thus the use of premixed insulins containing ultrarapid-acting insulin analogs (lispro or aspart) showed lower postprandial glucose levels and improvement of global glycemic control as compared to premixed human regular and NPH insulin-containing preparations. The available premixed insulins, preferably insulin analogs, may be administered two or three times daily, before breakfast and before dinner or before the three main meals. In the case of two doses, if glucose levels are high after lunch, complementation with an ultrarapid-acting analog can be made before this meal. The combinations of fixed insulin doses in the premixed insulins is the easiest way to provide basal and prandial insulins but does not allow that doses of each component may be separately adjusted. In these conditions, variable regular and intermediate-acting (NPH) human insulin can be mixed by the patient in the same syringe, thus allowing a better control of postprandial glycemia levels. The other possibility is to mix an ultrarapid-acting analog with NPH insulin which, however, is not usually recommended ex-

cept if the mixture is used immediately because it is not stable, since there is a tendency to formation of several associations between the components. However, there is a difficulty in reaching the exact measure of the volumes of the components of the mixture to be prepared, particularly in the elderly. With the availability of very precise pens for insulin application, providing separately rapid-acting or ultrarapid-acting and intermediate-acting insulin may be attempted, NPH about 30-45 and lispro or aspart about 15 minutes before the start of the meal.

In order to stimulate physiologic insulin secretion, multiple daily applications ( $\geq 3$ /day) of ultrarapid-acting before meals and intermediate-acting (NPH) or prolonged-acting insulin (glargine or detemir, the latter available in Brazil since February 2006) may be used for basal supplementation, with improvement of glycemic control. Actually, increase in the number of injections may reduce the incidence of hypoglycemia by supplying a more physiologic insulin profile.

The different schemes of utilization of basal and prandial insulin as well as premixed insulins and suggestion for their distribution as related to the total dose of daily insulin are shown in Table 3. In the treatment to attain the

7% (ideally <6.5%) glycated hemoglobin goal, the basal bedtime insulin dose has varied from 0.4 to 0.5 U/kg per day. For DM2, the total daily insulin dose has varied from 0.5 to 1.0 U/kg per day, depending on the degree of insulin resistance, particularly the degree of obesity. Adjustment of insulin doses should be made on an individual basis, depending on self-monitoring of capillary glycemia.

A particularly useful observation for DM2 is that providing the greatest part of intermediate-acting insulin in the morning, as established in the past and still used by many physicians could induce a risk of hypoglycemia before lunch and, frequently, at the end of the afternoon, requiring snacks at approximately 10 o'clock and in the afternoon at 4 – 5 o'clock, resulting in a higher caloric intake and worsening of diabetes control. Regarding dose adjustment for DM2 for the performance of exercises, unfortunately little followed by this type of patient, in general the diabetic individual does not have exercise-induced hypoglycemia or need for supplementary carbohydrate which, if provided, may counterbalance the attempt of weight loss.

In our experience, when prandial insulin is provided, and the postprandial value is still unsatisfactory, association of rapid- or ultrarapid-acting insulin with an acarbose supply at the dose of 25 mg may be attempted, increasing progressively up to a maximum of 100 mg each time, avoiding undesirable gastrointestinal effects.

## References

1. Ovalle F, Bell DS. Effect of rosiglitazone versus insulin on the pancreatic beta-cell function of subjects with type 2 diabetes. *Diabetes Care*. 2004;27:2585-9.
2. UK prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. UK Prospective Diabetes Study Group. *Diabetes*. 1995;44:1249-58.
3. Ryan EA, Imes S, Wallace C. Short-term intensive insulin therapy in newly diagnosed type 2 diabetes. *Diabetes Care*. 2004;27:1028-32.
4. Li Y, Xu W, Liao Z, Yao B, Chen X, Huang Z, et al. Induction of long-term glycemic control in newly diagnosed type 2 diabetes patients is associated with improvement of beta-cell function. *Diabetes Care*. 2004;27:2597-602.
5. Riddle MC. Timely initiation of basal insulin. *Am J Med*. 2004;116 Suppl 3A:3S-9S.

# Combined treatment

## Oral agents and insulin in type 2 diabetes *mellitus*

### 1. Introduction

Innumerable observations demonstrated that good glycemic control in general prevents the appearance of chronic complications which constitute the main causes of mortality, morbidity and worsening of quality of life of the patient with diabetes *mellitus* (DM)(A, 1)<sup>1</sup>. However, persistent glycemia maintenance at levels reflecting the physiological one is difficult to obtain, since this requires lifestyle changes, intensifying physical exercise, greater discipline and attention regarding nutrition, loss and maintenance of body weight and a strict daily control of glycemia, which usually is not obtained and not valued by the patients and professionals who treat them because of lack of, or few symptoms associated with moderate hyperglycemia. Despite the fact that many patients succeed in maintaining normal or near normal glycemic values for a long time by following diets, increasing exercise and using oral antidiabetic drugs (OAD), the vast majority is not able or fails to maintain glycemic control as the disease persists, even increasing or combining several OAD in function of worsening of the beta-cell secreting ability which would be part of DM natural history (B, 1)<sup>2</sup>. In this phase, introduction of oral antidiabetic drugs would allow a better and more adequate insulin availability to the patient who would benefit from the actions of oral drugs. From the clinical viewpoint, the rational justification for combination of insulin therapy with OAD would be based on the obtention of a better and adequate glycemic control, reduction of administered insulin doses, less weight gain and lower incidence of hypoglycemia. A secondary justification would be based on a higher receptivity of the patient to the use of insulin, considering the occurrence of barriers to an earlier introduction of insulin therapy in patients with type 2 DM (DM2).

There are several published randomized and prospective studies in the last decade associating one or more insulin doses with sulfonylurea, glitazones, metformin and acarbose, showing variable degrees of glycemic control improvement, reduction of doses and even of the number of insulin applications, less weight gain and hypoglycemia (A, 1)<sup>3-7</sup>. However, studies that evaluate the beneficial potential of this combined therapy in the prevention of cardiovascular diseases are lacking. We selected five review studies: the first three, performed in the last decade, analyzed only comparison of insulin use combined with sulfonylurea or placebo in patients who already used insulin

previously or those using sulfonylurea with a poor glycemic control and who would need insulin, who were compared to those with insulin therapy alone<sup>3</sup>. While Peters' study<sup>3</sup> (B, 2) concludes that combined treatment (CT) presents only a slight improvement of glycemic control, the other two studies<sup>4,5</sup> recommend it in conjunction with sulfonylurea because this showed to be more efficient than that with insulin alone (B, 2). Due to the fact that these studies did not analyze other oral antidiabetics and did not present well-defined objectives and study criteria, we focused our attention on two more recently published meta-analysis studies, where only results of randomized studies with at least a 2-month duration and published regarding the potential advantage of combined therapy in relation to each of the above mentioned variables were analyzed.

### 2. Glycemic control and reduction of insulin requirement

In a review study, Yki-Jarvinen<sup>6</sup>, on comparing the use of insulin alone with CT in insulin-naïve (IN) patients to those who previously used insulin (PI), observed in the former that in 15 comparisons (ten studies) glycemic control was similar in most comparisons (11/15) and with a better control in the combined group in four comparisons (B, 2). In all patients it was observed that the daily insulin dose was lower for combined therapy as compared to insulin therapy alone. PI patients, most with CT (19/25), presented a better glycemic control. Glycemic control of all patients with previous use of insulin was improved by the combined use with glitazones. In a meta-analysis study of the Cochrane Library, Goudswaard<sup>7</sup> (B, 2) evaluating 1,911 patients of 13 controlled and randomized studies (21 comparisons) between insulin therapy alone and sulfonylureas and/or metformin, observed no significant benefit to glycemic control with insulin therapy (two or more daily injections) as compared to combined OAD with a single nocturnal Neutral Protamine Hagedorn (NPH) insulin dose. Yki-Jarvinen's study<sup>6</sup> (B, 2) combining insulin with metformin observed a better glycemic control associated with reduction of the daily insulin dose. CT resulted in significantly lower glycosylated hemoglobin levels in comparison with insulin monotherapy once a day. When compared to insulin therapy which used more than one injection a day, CT did not show glycosylated hemoglobin level reduction and,

depending on the isolated scheme of multiple doses, showed to be more efficient in obtaining a better glycemic control. In general, CT was associated with a relative 46% decrease of the daily insulin requirement as compared to insulin monotherapy. When compared to NPH regimens applied daily two or three times, the insulin sparing effect of sulfonylurea CT associated or not with metformin showed to be superior to the use of metformin alone. Because it allows a glycemic control similar to that of insulin therapy with one daily dose, CT with a bedtime NPH insulin injection showed to be potentially useful from the practical viewpoint of the clinical physician who assists the individual with DM2 as a form to overcome barriers to the introduction of insulin therapy.

### 3. Hypoglycemia

In his review, Yki-Jarvinen<sup>6</sup> observed in five comparisons of IN patient groups a lower hypoglycemia frequency despite the better glycemic control when using CT with metformin. When metformin was associated with sulfonylurea in the combined treatment, no reduction of hypoglycemia frequency was observed. Combined treatment with only sulfonylureas did not disclose difference in five and showed increased hypoglycemia in seven comparisons regarding frequency. In three groups utilizing glitazones, a higher frequency of hypoglycemia and improvement of glycemic control was observed on CT. In the meta-analysis study of the Chocrane Library<sup>7</sup>, in 22 comparisons (14 studies) no statistically significant difference of hypoglycemia between CT and insulin therapy alone was shown, except for one comparison.

### 4. Weight gain

Yki-Jarvinen<sup>6</sup> observed reduction of weight gain in two of the three groups who used metformin in CT; no alteration of weight gain in 16 comparisons of patients using sulfonylurea; and increase of weight gain with improvement of weight control in the three groups that used glitazones. In the meta-analysis study, Goudswaard<sup>7</sup> (B, 2) observed, in 13 comparisons (ten studies) that on CT there was a significantly lesser weight gain when using metformin alone or associated with sulfonylurea. In the other comparisons no differences were observed regarding weight gain between insulin monotherapy and CT.

### 5. Other parameters

In all CT studies there were few patients who presented some adverse effect, with no worsening of quality of life and alterations of triglyceride and other lipid and lipoprotein levels being observed. There is a lack of studies indicating advantages in the development of macro- and microvascular complications.

### 6. Conclusions

Insulin CT with OAD allows a comparable or superior control than insulin use alone, especially when performed with one daily dose. Some studies indicate that combined treatment with metformin would be more effective to obtain a better glycemic control associated with less weight gain and lower hypoglycemia frequency. Compared to insulin monotherapy, CT reduces the daily insulin requirement, especially when using sulfonylurea or glitazone. CT with a nocturnal insulin dose may help the clinician to overcome the patient's resistance to insulin use. In spite of the innumerable studies and potential advantages of its use, there is a lack of more solid evidence in order to recommend a certain form and treatment regimen based on CT with OAD and insulin.

### References

1. Intensive blood glucose control with sulfonylurea or insulin compared with conventional treatment and risk of complications in type 2 diabetes mellitus (UKPDS 33). UK Prospective Study (UKPDS) Group. *Lancet*. 1998; 352(9131): 837-53.
2. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies. UK Prospective Study (UKPDS) Group. *JAMA*. 1999; 281(21): 2005-12.
3. Peters AL, Davidson MB. Insulin plus sulfonylurea agent for treating type 2 diabetes. *Annals of Internal Medicine*. 1991; 115(1): 45-53.
4. Pugh JA, Davidson MB, Sawyer J, Ramirez G, Tuley M, Friedberg SJ. Is combination sulfonylurea and insulin useful in NIDDM patients? A meta-analysis. *Diabetes Care*. 1992; 15: 953-9.
5. Johnson JL, Wolf SL, Kabadi UM. Efficacy of insulin and sulfonylurea combination therapy in type II diabetes. A meta-analysis of the randomized placebo-controlled trials. *Archives of Internal Medicine*. 1996; 156(3): 259-64.
6. Yki-Jarvinen H. Combination therapies with insulin in type 2 diabetes. *Diabetes Care*. 2001; 24(4): 758-67.
7. Goudswaard NA, Furlong NJ, Valk GD, Stolk RP, Rutten GEHM. Insulin monotherapy versus combination of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus (Cochrane review). Oxford: Cochrane Library, Issue 1; 2005.