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The role of lifestyle interventions in preventing diabetes in high risk populations

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Abstract. Diabetes mellitus (DM) represents a group of metabolic disorders characterized by hyperglycemia that produces long-term dysfunctions, at many levels, especially in the eyes, kidneys, cord, blood vessels and nervous system. Through its microvascular (retinopathy, nephropathy, neuropathy) and macrovascular complications (myocardial infarction, stroke, peripheral arterial disease), diabetes is a major cause of increased morbidity and reduced quality of life and life expectancy.
If in 2000 the prevalence of diabetes worldwide was 2.8% (171 million people) it is projected that in 2030 the prevalence of diabetes will be 4.4% (366 million people). It thus justifies the growing interest for early diagnosis and active screening of patients with DM, which is the first step to implementing early intervention, primary prevention of this disease being a goal of major interest.
In recent years it increasingly emerged the idea of excess metabolic and cardiovascular risk in patients currently considered normo-glycemic but with a high value of 1 hour post load blood glucose in the oral glucose tolerance test OGTT. Several studies have investigated the hypothesis that subjects with normal glucose tolerance and 1hour blood glucose in OGTT as high as patients with impaired glucose tolerance (IGT) is an intermediate category of patients presenting an altered metabolism translated by increased insulin resistance and reduced β cell susceptibility to glucose. Cardiovascular risk and the subsequent risk of the development of DM in this group of patients was found to be equal to that of patients diagnosed with IGT by current standards. These subjects at increased risk for future type 2 diabetes are the ones that effective prevention programs target.
There are overwhelming data that prove the fact that lifestyle modifications, both diet and multiple physical activity are highly successful in preventing diabetes and cardiovascular morbidity in high-risk populations. Clinical guidelines are needed for the optimal community implementation of evidence-based diabetes prevention programs
Key words*: diabetes, oral glucose tolerance test, one hour glucose, early prevention*.
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Diabetes: a public health problem

Diabetes mellitus (DM) represents a group of metabolic disorders characterized by hyperglycemia that produces long-term dysfunctions, at many levels, especially in the eyes, kidneys, cord, blood vessels and nervous system. The common element is hyperglycemia, resulting from the combination of a secretory defect and a defect of insulin action in varying proportions (1).
Through its microvascular (retinopathy, nephropathy, neuropathy) and macrovascular complications (myocardial infarction, stroke, peripheral arterial disease), diabetes is a major cause of increased morbidity and reduced quality of life and life expectancy (2).
Diabetes mellitus is a current important public health problem, which is reinforced by the rapid growth in the number of patients with diabetes in the recent decades, and we could now speak of a "pandemic" of diabetes globally. A number of factors have led to this situation: obesity, sedentary lifestyle, increased life expectancy, ageing (3).
Another cause for concern is the fact that DM is still underdiagnosed, the number of patients diagnosed with diabetes is actually almost doubled by the number of patients with diabetes or prediabetes and undiagnosed.
If in 2000 the prevalence of diabetes worldwide was 2.8% (171 million people) it is projected that in 2030 the prevalence of diabetes will be 4.4% (366 million people). A study conducted in 2004 by Swild et al (4) showed that these predictions are true while the obesity rate would remain constant. However, given the continuous increase in the prevalence of obesity, it is possible that these figures understate the actual prevalence of DM in the future.
Unfortunately, the figures provided by the International Diabetes Federation (IDF) in 2014 exceeded the most pessimistic forecasts.

IDF is calling DM "a growing problem", while producing worrying figures: 387 million people worldwide have diabetes and this number is expected to rise in 2035 to 592 million, which represents an increase of 53%. It was concluded that, even at the level of information and access to diagnostic methods of the year 2014, the number of undiagnosed cases remains very high (46.3% of patients) (5).

The costs associated with this disease are enormous, as diabetes is a major cause of morbidity and disability. Every seven seconds a person dies due to diabetes, diabetes causing approximately 4.9 million deaths per year, 50% of these occurring in persons under the age of 60 years (5).

In addition, diabetes is rarely identified as the main cause of death, statistics showing that 35-40% of the deceased who had diabetes had had mentioned this condition on the death certificate and only 10- 15% of them mentioned DM as the cause of the death (6).

Morbidity associated with this disease is important, diabetes is the main cause of blindness, end-stage chronic kidney disease, nontraumatic limb amputations and cardiovascular morbidity and mortality (7). Studies conducted in the US (6) showed a marked increase in cardiovascular risk in diabetic patients: hypertension was diagnosed in 71% of patients with diabetes, dyslipidemia in 65%, cardiovascular morbidity was 1.7 times higher in patients with diabetes, hospitalization for acute myocardial infarction was 1.8 times more common and for stroke 1.5 times higher than in subjects without DM. The same large-scale studies brought alarming data: 4.2 million (28.5%) of adults with diabetes over the age of 40 studied between 2005 and 2008 showed diabetic retinopathy; DM has been identified as the main cause of renal failure in 44% of all cases diagnosed in 2011. Also, 60% of nontraumatic lower limb amputations are due to diabetes.

All these data speak for themselves about the huge costs and complications of diabetes, this condition being a real economic and social burden.

It thus justifies the growing interest for early diagnosis and active screening of patients with DM, which is the first step to implementing early intervention, primary prevention of this disease being a goal of major interest.

Criteria for the diagnosis of diabetes: the role of 1-hour plasma glucose in detecting high risk-population

There is still controversy regarding the role of the oral glucose tolerance test (OGTT) versus fasting glucose in practice. The OGTT shows the disadvantages of a higher cost, a low reproducibility and a certain discomfort for the patient. Advantages compared with DM diagnosis only through fasting glucose, however, are multiple. Since the number of patients with undiagnosed DM almost double that of patients diagnosed with diabetes and since studies have shown that the fasting and 2-hour post load glucose not always identify the same patients with diabetes, it seems logical that both methods are used in order to diagnose a large number of patients with this disorder. This goal is particularly important since it is proven that early intervention leads to a much better metabolic control and prevents or delay the onset of the so dreaded complications. In addition, only OGTT can identify an important group of patients, patients with impaired fasting glucose (IFG) and those with impaired glucose tolerance (IGT), two categories of patients at high risk for DM and cardiovascular complications. These two conditions are known as “prediabetes” and could benefit at most of early interventions.

The DECODE study (8) showed that, in a group of 1517 patients newly diagnosed with DM 1, only 28% have fulfilled both criteria of diagnosis (fasting blood glucose $\geq$ 126 mg/dl and 2 hours glucose $\geq$ 200 mg/dl), while 40% of patients met only fasting glucose criteria and 31% only the 2 hours criteria. It is thus obvious that, by using only the fasting blood glucose levels at diagnosis, approximately 30% of the patients are lost.

This situation is even more striking is the elderly. A study led by Barrett-Conner et al (9) showed that 70% of women and 48% of men studied, aged between 50 and 89 years old were diagnosed with DM only on 2 hours blood glucose criteria. It is necessary to actively detect patients with diabetes and prediabetes (IFG, IGT), given that early intervention is vital for these patients.

Active detection of patients with diabetes and prediabetes requires testing of certain categories of asymptomatic patients, but with increased risk (1).

We'll refer to overweight or obese patients with additional risk factors: inactivity; first degree relative with diabetes; certain ethnicities that are considered to be at high risk: Hispanic, African-

American, native- Americans, Asian- Americans, Pacific Island natives; women who were diagnosed with gestational diabetes during pregnancy or have given birth to a baby weighing more than 4kg; hypertensive (TA≥ 140/90mmHg or on antihypertensive therapy); patients with dyslipidemia (HDL-cholesterol <35 mg/dl and/or triglycerides> 250 mg/dl); HbA1c≥ 5.7% or previously diagnosed patients with IFG; women diagnosed with polycystic ovarian syndrome; other conditions associated with insulin resistance (acanthozis nigricans, severe obesity); history of cardiovascular disease.

For all such patients testing should begin at the age of 45 and should be repeated every 3 years (annually in patients with prediabetes).

In terms of the glucose tolerance status, the OGTT identifies three categories of patients: patients with normal glucose tolerance (NGT), patients with prediabetes (IFG and/or IGT) and patients with diabetes (Table II). An important category of patients to whom early prevention can be applied extensively, with particularly good results is represented by patients with prediabetes. IFG and IGT are entities with a major risk for future development of DM and positively correlated with the patient's cardiovascular risk. They are associated with obesity, especially abdominal obesity, dyslipidemia (characterized by low HDL cholesterol and high triglycerides) as well as hypertension.

At present, IGT diagnosis is determined by 2-hours blood glucose ≥ 140mg/dl. Moreover, patients diagnosed with diabetes using a value of 2-hours post load blood glucose ≥ 200 mg/dl were found to have an increased risk for cardiovascular disease and complications, so much worse prognosis than patients diagnosed with DM based on fasting glucose values of ≥ 126 mg/dl. Analyzing data from three large longitudinal studies, Shaw et al (10) reported a 2.7-fold increase in the risk of all-cause mortality in men and 2 times in women in a population of patients with newly diagnosed DM using 2 hours post load glucose criteria when compared to a population with normal glucose tolerance. This excess risk was not observed in the group of patients with newly diagnosed DM using fasting glucose criteria. All the studies take into account a value of 2 hours post load glucose of ≥ 140 mg/dl in the case of IGT and ≥ 200 mg/dl in the case of DM.

In recent years it increasingly emerged the idea of excess metabolic and cardiovascular risk in patients currently considered normo-glycemic but with a high value of 1 hour post load blood glucose in OGTT.

Several studies have investigated the hypothesis that subjects with normal glucose tolerance and 1 hour blood glucose in OGTT as high as patients with IGT is an intermediate category of patients presenting an altered metabolism translated by increased insulin resistance and reduced β cell susceptibility to glucose. Cardiovascular risk and the subsequent risk of the development of DM in this group of patients were found to be equal to that of patients diagnosed with IGT by current standards.

The RISC (European Relationship Between Insulin Sensitivity and Cardiovascular Risk) study (11), examined the metabolic phenotype of individuals with NGT who had high 1h plasma glucose excursions. The RISC study was a prospective (3- and 10-year follow-up), observational, cohort study performed on 1205 healthy subjects with no history of diabetes, hypertension or hyperlipidemia. They were performed an OGTT and the results identified a subgroup of patients with NGT by current standards but increased 1h plasma glucose (>8.95 mmol/l), increased insulin resistance and β cell dysfunction.

A new glucose tolerance subgroup of patients were thus identified, patients who could benefit from targeted lifestyle advice.

Another study that examined the relation between 1 hour blood glucose and future diabetes risk is San Antonio Heart Study (12). In this study, an OGTT was performed on a cohort of 1611 participants. One-hour plasma glucose strongly correlated with hepatic and muscle insulin resistance indices and β-cell failure. The correlation exceeded the one offered by 2-h plasma glucose. In this study 16.7% of participants with normal glucose tolerance (NGT) with 1-h plasma glucose concentration >155 mg/dl developed type 2 diabetes over a 7 to 8 year period. A 1h cutoff point of 155 mg/dl during the OGTT stratifies individuals into high and low risk for future development of type 2 diabetes. It was demonstrated that 1-h plasma glucose is a better predictor of future type 2 diabetes than 2-h plasma glucose with a 13.1-fold increased OR for developing the disease in subjects with higher 1-h plasma glucose (>155 mg/dl). These subjects at increased risk for future type 2 diabetes are the ones that effective prevention programs target.

There are also examples in the literature of 1-h plasma glucose being predictive of the risk of myocardial infarction and coronary heart disease (13, 14) in type 2 diabetes.

The importance of early intervention (lifestyle intervention: diet and exercise) in preventing or delaying the onset of diabetes

Nevertheless, studies have shown that targeted treatment of IGT can reduce progression to type 2 diabetes, and the risk of cardiovascular disease or future diabetes seems to be continuous across the glucose range.

It is a well known fact that obesity and low level of physical activity are important independent and modificable risk factors for the development of DM.

The Diabetes Prevention Program (DPP) (15) was a randomized clinical trial performed on 3,234 subjects who were at high risk for diabetes. Subjects were ≥25 years old, having a BMI ≥24 kg/m^2 (≥22 kg/m^2 in Asian Americans), having a fasting plasma glucose concentration of 5.3–6.9 mmol/l (≤6.9 mmol/l in the American Indian clinics), and attaining a 2-h glucose of 7.8–11.0 mmol/l during a 75-g oral glucose tolerance test. All subject had IGT.

They were randomized in three groups of intervention: 1) lifestyle interventions, 2) metformin twice daily and standard lifestyle recommendations, or 3) placebo twice daily and standard lifestyle recommendations.

The goal of the study was: subjects had to achieve and maintain a weight reduction of at least 7% of their initial body weight through a healthy low-calorie, low-fat diet and physical activity of moderate intensity, such as brisk walking, for at least 150 min per week (15).

Physical activity was assessed semiannually with the Modifiable Activity Questionnaire (16).

The physical activity level was calculated as the product of the duration and frequency of each activity (in hours per week) weighted by an estimate of the metabolic equivalent (MET) of that activity and summed for all activities.

Usual daily caloric intake during the previous year, including calories from fat, carbohydrate, protein, and other nutrients, was assessed at baseline and at 1 year later.

Lifestyle intervention and metformin both have been shown to be effective strategies for diabetes prevention. There was no surprise in the finding that lifestyle intervention alone restored normal glucose tolerance significantly more frequently than did placebo. Lifestyle intervention and metformin both were proved to reduce insulin resistance but this fact did not explain alone the results of the study. There are also other mechanisms, beyond insulin sensitization that led to reducing diabetes risk.

The most important intervention that led to regression to normal glucose tolerance seemed to be weight loss: every 1 kg lost was associated with a 16% reduction in diabetes risk (17). Apparently, weight loss and exercise mobilized fat from the visceral depot, with favorable metabolic results.

There are many large- scale randomized controlled trials that have used a lifestyle intervention (changes in nutritional intake, physical activity, or both) in populations at high risk of developing DM.

The goal of these trials was to reduce the rate of the development of diabetes and to ameliorate the cardiovascular risk in these populations (19).

Baker et al published in 2011 the results of a large meta-analysis that investigated this important objective. 5825 subjects were investigated in seven major studies: Diabetes Prevention Program (DPP), U.S.A; Diabetes Prevention Study (DPS), Finland; Da Qing IGT and Diabetes Study (DQS), China; Diabetes Prevention Program (IDPP), India; Diabetes Prevention Program (DPP); Asti Diabetes Prevention Program (ADPP), Italy and Vasterbotten Intervention Program (VIP), Swedwen

These studies recruited their subjects from the general community. DPP was the only one that recruited from patients being routinely screened at a medical facility.

Participants in all studies were individually advised to increase physical activity: 150 min/week at moderate intensity (DPP, ADPP, and VIP), up to 30-40 min/day (i.e. 210–280 min/week) at moderate intensity (DPP). Moderate intensity aerobic activity were the primary form of exercise. If exercises were performed in a more vigorous way, it was allowed a reduction in exercise volume.

The DPP study included moderate intensity progressive resistance training, and in the DPS study moderate intensity progressive resistance training and power training were included. The VIP study included muscle strengthening exercise twice a week.

Logs were kept of physical activity, caloric intake and fat intake. Participants in all studies were individually advised to modify their dietary

intake. Reviewed studies included a reduction in energy intake with all studies recommending a reduction of fat intake, commonly to 20–30% of total energy intake (DPP, DPS, DQS, and VIP). In four studies (DPS, IDPP, ADPP, and VIP), specific increases in dietary fiber intake were recommended. All studies advised an increased intake in fiber-rich foods such as fruits and vegetables.

The common elements in all studies were energy reduction and energy density shift. Subject were advised to keep these diet and exercises logs and to attend organized exercises sessions.

The control groups received usual care, and in some cases written material relevant to healthy lifestyle: general information about diabetes, general instructions for diet and exercise. In the DPP, controls received written instructions on the Diet and Food Pyramid (20) but control subjects did not receive any contact from researchers between outcome assessment time-points and for them there were no organized exercise sessions.

All studies were successful in reducing incident T2D. Results from the DPP and DPS both indicate a RRR of 58% (95% CI 48–66, $p<0.001$ and $p<0.001$, respectively) (21,22) in the incidence of T2D as a result of intensive lifestyle modification incorporating both diet and exercise when compared to the rate in controls. The greatest reduction in incidence was reported by the VIP and ADPP with a RRR of 74 and 75% compared to controls (23, 24).

There are overwhelming data that prove the fact that lifestyle modifications, both diet and multiple physical activity are highly successful in preventing diabetes and cardiovascular morbidity in high-risk populations (25).

Clinical guidelines are needed for the optimal community implementation of evidence-based diabetes prevention programs.

Table I. OGTT interpretation (adapted after ADA)

	ADA (American Diabetes Association) 2003	WHO (World Health Organization) 1999
Diabetes		
Fasting glucose	≥ 7 mmol/l (126 mg/dl) or	≥ 7 mmol/l (126 mg/dl) or
2- hour glucose	≥ 11,1 mmol/l (200 mg/dl)	≥ 11,1 mmol/l (200 mg/dl)
IFG		
Fasting glucose	5,6 - 6,9 mmol/l (100 mg/ dl-125 mg/dl)	6,1 - 6,9 mmol/l (110 mg/dl- 125 mg/dl)
2- hour glucose	-	
IGT		
Fasting glucose	-	< 7 mmol/l (126 mg/dl)
2- hour glucose	≥7,8mmol/l (140 mg/ dl) and < 11,1 mmol/l (200 mg/dl)	≥7,8mmol/l (140 mg/dl) and <11,1 mmol/l (200 mg/dl)

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