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REVIEW ARTICLE

Prediabetes: Clinical Relevance of an Important Risk Marker

Pré-diabetes: A Relevância Clínica de um Importante Marcador de Risco

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ABSTRACT

The term prediabetes refers to subjects with impaired fasting glucose and/or impaired glucose tolerance who are at increased risk for type 2 *diabetes mellitus*. Although both types of patients are at increased risk for developing type 2 *diabetes mellitus* and cardiovascular disease, they manifest distinct metabolic abnormalities. Large, randomized prospective studies with lifestyle intervention and/or various modes of pharmacotherapy have demonstrated successful delay of diabetes. Several issues in the management of prediabetes remain controversial, such as the role of pharmacotherapy and when to escalate treatment. Lifestyle modification may be considered an ideal method of diabetes prevention because of beneficial effects on the cardiovascular risk profile as well as benefits related to weight loss and an improved diet. However, long-term adherence to such intervention remains potentially a limiting factor to widespread implementation, and pharmacological therapy to prevent type 2 diabetes may be an important therapeutic modality in those patients in whom lifestyle interventions fail, are not sufficiently potent, or are not feasible. In this review, we offer an overview of some of the issues surrounding the identification and treatment of prediabetes, with an interpretation of the available data to help guide management.

Keywords: Prediabetic State; Hyperglycemia; Disease Prevention

RESUMO

O termo pré-diabetes refere-se a indivíduos com glicemia de jejum alterada (GJA) e/ou tolerância a glicose diminuída(TGD) e que possuem risco aumentado para *diabetes mellitus* tipo 2. Embora em ambos os casos exista alto risco de desenvolver diabetes e doença cardiovascular, eles manifestam alterações metabólicas distintas. Grandes estudos prospectivos randomizados com intervenção no estilo de vida e/ou várias formas de tratamento farmacológico demonstraram sucesso nos resultados, prevenindo ou retardando a progressão para o diabetes. Várias opiniões sobre condutas em pré-diabetes permanecem controversas, tais como o papel da farmacoterapia e quando considerar esse tratamento. Modificações do estilo de vida devem ser considerados um método ideal de prevenção devido aos efeitos benéficos sobre o risco cardiovascular assim como benefícios relacionados a perda de peso e melhora na dieta. Entretanto, a aderência a longo prazo de tais intervenções permanece um fator limitante para sua ampla implementação, podendo a terapêutica farmacológica ser uma importante abordagem para prevenir diabetes tipo 2 em indivíduos cujas intervenções no estilo de vida falharam ou não foram suficientemente potentes ou possíveis. Nesta revisão, nós reportamos alguns trabalhos envolvidos na identificação e tratamento do pré-diabetes, interpretando os dados disponíveis que poderão nos auxiliar na condução desses casos.

Palavras-chave: Estado Pré-Diabético; Hiperglicemia; Prevenção de Doenças

INTRODUCTION

Prediabetes is characterized by impaired fasting glucose and/or impaired glucose tolerance. It is classified as an intermediate category between normal glucose tolerance and type 2 diabetes.[1,2] Blood glucose levels are strictly controlled, were considered normal between 70 and 99 mg/dL, when individuals have been fasting for eight hours. Thus, normal glucose tolerance is defined as fasting glucose concentrations below 100 mg/dL and and glucose concentrations below 140 mg/dL after drinking a glucose solution containing the equivalent of 75 g anhydrous glucose (oral glucose tolerance test [GTT]). In prediabetes, impaired fasting glucose (IFG) is defined as glucose concentrations in the blood above or equal to 100 mg/dL and below 126 mg/dL in the fasting period, whereas impaired glucose tolerance (IGT) is defined as glucose concentrations above or equal to 140 mg/dL and below 200 mg/dL in OGTT.[1,2]

In 15 to 20% of all cases of prediabetes both conditions are associated. According to data from the International Diabetes Federation (IDF), it is estimated that by 2025, about 472 million people will have prediabetes. Factors such as ethnicity and age influence the onset of IGT and IFG, as suggested by epidemiological studies. Age is a decisive factor for greater prevalence of IGT. IGT is also more frequent in women than in men and IFG is twice more common in men than in women. These individuals are considered at high risk for developing type 2 *diabetes mellitus*, and up to 70% of them develop the disease. Individuals who have both conditions are at two times greater risk of developing type 2 diabetes than individuals who have only one of these conditions.[2,3,4]

Some studies have shown that the cumulative incidence of diabetes in five to six years was: 4-5% in individuals with normal fasting glucose and normal OGTT; 20-34% in individuals with IFG or IGT; and 38-65% in individuals with both IFG and IGT. Because the disease is slow and insidious, this progression has been greatly contributing to the increased prevalence of undiagnosed cases of type 2 diabetes, as well as of its chronic degenerative complications, particularly cardiovascular disease.[3] It is known that individuals with type 2 diabetes are at two to three times higher risk of developing cardiovascular disease than non-diabetics, and coronary artery disease is the leading cause of morbidity and mortality and a major cause of medical costs in this population.[4,5] Given these facts, it is not surprising that attempts have been made to determine the possibilities benefits of strategies to prevent or at least delay the onset of type 2 diabetes, especially when taking into account that the high prevalence of diabetes is directly related to the contemporary lifestyle. Some randomized studies, however, have demonstrated that IGT and IFG progression into type 2 diabetes and its complications can be prevented by lifestyle interventions or even additional pharmacological therapy, when appropriate. In addition to these observations, individuals with prediabetes are at a 50% higher risk of having a fatal outcome from cardiovascular disease than people with normal glucose tolerance.[5,8] As disclosed by some studies, IGT alone is a greater risk factor for the development of cardiovascular diseases than is IFG. There is strong evidence that dysglycemia and cardiovascular disease are associated. This contributed to the implementation of new guidelines for prediabetes management, admitting that prediabetes states may be related to a higher risk of such complications and should be closely monitored even in asymptomatic individuals by OGTT testing.[6,7]

Finally, In view of the expected increase in the coming years of the prevalence of *diabetes mellitus* and taking into account that acute coronary syndromes will be the leading cause of mortality in this population, It becomes increasingly necessary to join efforts in order to modify this expected panorama. The huge impact of diabetes on public health and the impressive progress made to the understanding and treatment of prediabetes in recent years drove us to conduct this review study. Paying attention to prediabetes is considered the most cost-effective alternative for avoiding the various consequences of diabetes, particularly cardiovascular disease. If not treated many of these individuals will develop type 2 diabetes within 10 years and a large proportion of them will suffer from micro and/or macrovascular diseases. Thus, it is necessary that this condition is properly recognized and valued by health professionals, so that the benefits of early intervention are obtained and this disturbing scenario can be changed.[6]

METABOLIC CHANGES IN PREDIABETES - PATHOPHYSIOLOGY

Prediabetes is an easily understood term, which indicates that glucose is not being properly processed in the body, but frank diabetes has not yet presented. However, the pathophysiological bases of IFG and IGT are not the same. This is because the determinants that elevate fasting glucose levels are different from those that elevate 2-hour glucose in OGTT, i.e., they are heterogeneous conditions with regard to etiopatogenic mechanisms and reflect distinct pathological disturbances in glucose homeostasis when occurring alone.[8,9]

It is related to obesity, sedentary lifestyle and diets rich in saturated fats and carbohydrates with high- glycemic index values, which in turn trigger the development of hepatic and peripheral insulin resistance (muscle). In addition, the inability of cells b to compensate for this insulin resistance is also an early change observed in prediabetes states.[8,9] Insulin resistance is characterized by changes in

various parts of the insulin signaling pathway, reducing concentration, phosphorylation and activity of insulin receptors (tyrosine kinase), decreasing intracellular translocation of glucose transporter 4 (GLUT-4) and also reducing activity of intracellular enzymes. Several studies have shown that subjects with IFG have predominantly hepatic insulin resistance, while those with IGT show predominantly moderate to severe muscle insulin resistance, and only a slight increase in hepatic insulin resistance.[8,9,10,11,12,13] The increase in insulin resistance in subjects with prediabetes is accompanied by a variety of metabolic abnormalities, including obesity, hypertension and dyslipidemia. All these abnormalities are considered risk factors for cardiovascular disease. This clinical constellation is referred to as metabolic syndrome. Epidemiological studies have shown that individuals with prediabetes have a two to three times higher prevalence of metabolic syndrome than do individuals with normal glucose tolerance.[8]

The pattern of pancreatic insulin secretion also differs in the two groups. The importance of the first phase of insulin secretion is the inhibition of endogenous hepatic glucose production in the postprandial period, which contributes to the maintenance of glucose levels at about 150 to 160 mg/dL within the first 60 min of the OGTT. The second phase of insulin secretion is responsible for the progressive decline in blood glucose levels until values lower than 140 mg/dL to 120 mg/dL. Patients with IFG alone show a reduction in the first phase of insulin secretion and a greater increase in glucose levels than normal individuals at 60 and 30 min. Late response following glucose ingestion in OGTT is normal when compared to patients with IGT alone. The latter usually show changes both in the first and in the late phase of secretion. Changes in the second phase (or late phase) of insulin secretion associated with muscle insulin resistance that occurs in IGT alone prevent the decline in glucose levels after 60 min, and they remain elevated at 120 min during OGTT.[8,9,10,12,13,15] While beta-cell failure mechanisms are poorly known, a progressive reduction of the sensitivity of β-cell to glucose has been observed as postprandial blood glucose increases.[8,9]

Incretins are intestinal hormones. GLP-1 (Glucagon-like peptide 1) and GIP (gastric inhibitory polypeptide) are key incretins. These hormones usually act on β-cells by enhancing insulin secretion stimulated by glucose, promote the regeneration of β-cells and stimulate the reduction of apoptosis. Decreased levels of these hormones or resistance to them - as observed in both diabetic and prediabetic individuals - might contribute to the reduction of insulin secretion in the postprandial period.[9,13,14] This finding led to the development of incretin-based therapies for type 2 *diabetes mellitus*.[14]

DIAGNOSIS

As mentioned above, the diagnosis of prediabetes can be done by fasting glucose or OGTT testing. This test is a laboratory method that is based on evaluating pancreatic insulin release capacity upon glucose load. Prior to the test, patients should fast for at least eight hours. Their fasting blood glucose levels will be measured then and their blood glucose levels will be obtained again two hours after drinking a solution containing 75g of anhydrous glucose. The diagnostic criteria adopted by the SBD (Brazilian Society of Diabetes) and ADA (American Diabetes Association) are described in Table 1.[1,16,17]

Table 1 - *Fasting glucose levels and glucose levels 2h after loading with 75g glucose (post-load glucose).*

Clinical condition	Fasting glucose	Glucose levels 2h after loading
normal	<100mg/dL	<140mg/dL
IGT	<100mg/dL	140-199mg/dL
IFG	100-125mg/dL	<140mg/dL
IGT + IFG	100-125mg/dL	140-199mg/dL
Diabetes	≥125mg/dL	≥200mg/dL

According to the new recently published ADA standards for clinical practice in diabetes,[17] the glycated hemoglobin (A1C) test is now indicated as a parameter for the diagnosis of diabetes and prediabetes. A diagnosis of diabetes can be done if the A1C level is higher than 6.5%. Values between 5.7% and 6.4% are now indicative of a diagnosis of prediabetes.

The ADA recommends screening for prediabetes in:[17]

1) Asymptomatic adults at any age, provided that are overweight or obese, and have one or more additional risk factors for diabetes (Table 2).

Table 2 - *Risk factors for type 2 diabetes. Adapted from ADA*

Age ≥ 45 years.
Overweight.
Family history of diabetes.
Sedentary lifestyle.
Ethnicity (e.g., Asian Brazilians).
Individuals with IGT or IFG.
Previious history of gestational diabetes or macrosomia.
Hypertension (≥140/90 mmHg)
HDL-C ≤35 mg/dL and/or triglycerides ≥250 mg/dL.
Polycystic ovary syndrome.
History of vascular disease.

2) Persons with no risk factors: only after 45 years of age.

3) Women with gestational diabetes: screening tests for diabetes should be performed between six and 12 weeks after birth.

TREATMENT

Indeed, prediabetes treatment should be based on the adoption of really effective measures for the prevention of type 2 *diabetes mellitus*.[1,7,18] Large randomized controlled trials have shown that interventions in lifestyle and the various types of pharmacotherapy are essential in this context. Their real benefits in contributing to the prevention of the development of *diabetes mellitus* have been demonstrated.[18,19]

The Diabetes Prevention Program (DPP) study was carried out to investigate whether changes in lifestyle (CLS) and/or use of metformin could be associated with the prevention of diabetes. After a mean follow-up period of three years, the incidence of diabetes was found to be 58% lower in the group of patients who changed their lifestyle and 31% lower in the metformin group, when compared to the placebo group. Moreover, compared to the metformin group, the incidence of diabetes was found to be 39% lower in the group of patients who changed their lifestyle.[20,21,22]

The *Finnish DPS* (Finnish Diabetes Prevention Study) was another study conducted in five Finnish centers. After five years of follow-up, the authors found that modifications in the standard diet of patients and their engagement in at least four hours of physical activity per week resulted in a 58% reduction in the risk of diabetes. Interestingly, in this population, the effects in reducing the risk of diabetes remained for four years after the end of the study, and there was a 35% reduction in new cases of type 2 diabetes in subjects with IGT.[23]

The STOP-NIDDM study (Study TO Prevent Non-Insulin-Dependent *Diabetes Mellitus*) included patients at high risk of developing type 2 diabetes. These patients were treated with acarbose (300 mg/day) or placebo. After an approximate follow-up period of three years, the group of patients who took acarbose showed a 25% decrease in the relative risk for developing diabetes.[24]

The study with the longest follow-up reported thus far is the Da Qing Diabetes Prevention Outcome Study. In the 20-year period of the study, participants who changed their lifestyles showed a 43% reduction in the incidence of diabetes.[25]

In the *DREAM* (Diabetes Reduction Assessment with Ramipril and Roziglitazone Medication) study, the use of rosiglitazone reduced the incidence of diabetes and death by 60% within three years of observation.[26] The most recent study reported was the *ACT NOW* (ACTos NOW for the prevention of diabetes) study, which showed a 81% reduction in the conversion of prediabetes to type 2 diabetes in a period of two years and six months. The authors compared pioglitazone and placebo effects.[27] Nevertheless, the increased risk of weight gain, congestive heart failure, and the costs associated with the use of glitazones must be weighed against their potential benefits in treating prediabetes.[13,19]

A recent study evaluated the regression of prediabetes to normal glucose tolerance by using DPP data. The authors concluded that, in addition to changes in lifestyle, the restoration of insulin secretion plays a key role in reversing this situation.[28] It has been experimentally demonstrated that GLP-1 analogs can stimulate the proliferation and neogenesis of insulin-producing cells in animals. This presents a possible future direction for the treatment of prediabetes.[13,28]

The results of these studies are consistent and encouraging. Studies conducted with the highest risk populations and with the implementation of healthy lifestyle programs have shown to be potentially effective in reducing the risk of progression of prediabetes to diabetes. However, longer follow-ups of patients on these programs are necessary in order to analyze outcomes such as cardiovascular

disease and even death, and demonstrate the real benefits of such programs. Likewise, the results assessed during periods of interruption of studies will help us determine if the improvements found occurred only in the intervention period.[29]

Although some aspects regarding the treatment of prediabetes remain controversial, such as the role played by pharmacological therapy and when treatment should be started, the recommendations in the literature differ only slightly. The ADA basically recommends changes in lifestyle through modifications in diet - in order to achieve a moderate weight loss of five to 10% of body weight - and physical exercise - at least 150 minutes/week of moderate activity, e.g.: walking. The use of metformin, widely supported due its cost-effectiveness and relative safety, would be recommended for individuals at high risk of progression to diabetes, in whom lifestyle interventions have failed, have not been powerful enough or have not been possible. Patients making changes in their lifestyles should be annually monitored and patients being treated wtih metmorfin should be monitores every six months.[1,17]

FINAL CONSIDERATIONS

There is obviously a need to clarify erroneous concepts that consider prediabetes to be a minor condition and forget that it has been proven to be associated with coronary artery disease. Moreover, its diagnosis and treatment are inexpensive and should be made in order to prevent diabetes. It seems clear that prevention of diabetes remains the best policy and should be preferred to lifelong complex treatments and the appearance of serious and debilitating chronic complications brought about by established diabetes. Therefore, it is critically important to raise the threshold of awareness of prediabetes among health authorities, and encourage the implementation of education programs with strategies to disseminate the concept of prediabetes and the importance of its treatment. With regard to pharmacological interventions, a careful analysis seems to be worth carrying out, especially if we consider that prediabetes, like diabetes, have become a worldwide epidemics. Therefore, taking into account ethical, financial and practical issues, should all prediabetic patients be treated with long-term drug therapy? Anyway, we know that the recognition of this condition will make us at least encourage these patients to change their lifestyles through the adoption of a healthy diet and the abandonment of sedentary life, as these changes bring benefits beyond the prevention of diabetes. As evidenced in the studies reviewed here, these interventions are still considered to be the best safety measures with the best cost-effectiveness for preventing type 2 diabetes. Although this evidence is widely scattered, the major hurdle remains its application in daily clinical practice. We all agree that health professionals cannot compete with the industrialized and mechanized society that promotes a sedentary lifestyle and the consumption of foods high in calories and saturated fat - habits directly implicated in the development of diabetes and atherosclerosis. Despite all the difficulties and limitations, some educational, social and behavioral strategies as well as some policies are being implemented in order to raise awareness about the importance of prevention.[28,29] After all, the prevention of diabetes is the only alternative available to minimize the current - and future - epidemics, as well as its complications.

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