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Prediabetes as opportunity and duty of treatment in people with obesity

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ABSTRACT

Prediabetes, defined as the presence of impaired glucose tolerance, impaired fasting glucose, or both, is considered an intermediate stage between normal glucose tolerance and type 2 diabetes mellitus. During the last decades, the incidence of prediabetes and diabetes has been growing at an alarming rate. Its risk is significantly increased in people with overweight and obesity, mainly abdominal obesity, since these conditions promote endocrine and immune disorders that interfere with insulin action in peripheral tissues and with pancreatic islet cell action. In this context, people with overweight and risk factors for developing diabetes, as well as all individuals older than 45 years, should undergo screening for prediabetes. The objective of the present manuscript is to review the current epidemiologic and pathophysiologic data that has allowed the establishment of standards for the identification and treatment of prediabetes. The realization that structured interventions aimed at modification

RESUMEN

La prediabetes, definida como la presencia de intolerancia a la glucosa (IGT), glucosa de ayuno alterada (IFG) o ambas, se considera un estado intermedio entre la normoglucemia y la diabetes *mellitus* de tipo 2 (DM2). Durante las últimas décadas, la incidencia de prediabetes y diabetes está creciendo de forma alarmante. Su riesgo es significativamente mayor en individuos con sobrepeso u obesidad, principalmente de tipo abdominal, ya que estas condiciones promueven alteraciones endocrinológicas e inmunológicas que afectan a la función de la insulina en tejidos periféricos y la de los islotes pancreáticos. En base a este incremento, es recomendable que las personas con sobrepeso y otros factores de riesgo de desarrollar diabetes, así como las mayores de 45 años, se sometan a una prueba de escrutinio para prediabetes. El objetivo del presente manuscrito es revisar los datos epidemiológicas y fisiopatológicas que han permitido establecer pautas para la identificación y el tratamiento

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of lifestyle and some drugs can delay the incidence of diabetes in this population, or even revert the clinical and biochemical markers of prediabetes, has generated significant importance and research for targeting prediabetes as an opportunity to reduce the impact of diabetes in populations. n conclusion, prediabetes is a condition that increases the risk to develop type 2 diabetes and cardiovascular disease. Overweight and obesity promote its pathophysiology, and therefore, systematic detection practices could be beneficial in certain populations, given that interventions to improve the quality of nutrition and physical activity and the use of drugs such as metformin have proven to reduce the incidence of cardiovascular diseases and certain types of cancer in individuals with this condition. (REV MEX ENDOCRINOL METAB NUTR. 2016;3:189-99)

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de la prediabetes. El reconocimiento de que intervenciones estructuradas para modificar el estilo de vida y algunos fármacos pueden retardar la incidencia de diabetes en esta población, o más aún, revertir los marcadores clínicos y bioquímicos de la prediabetes, ha generado gran interés e investigación en el enfoque hacia la prediabetes como una oportunidad para reducir el impacto de la diabetes en la población. En conclusión, la prediabetes es una condición que incrementa el riesgo de desarrollar DM2 y enfermedad cardiovascular. El sobrepeso y la obesidad promueven su fisiopatología, y, por ende, en ciertas poblaciones las acciones sistematizadas de detección parecen ser benéficas, ya que las intervenciones para mejorar la alimentación y la actividad física, y el empleo de fármacos como la metformina han mostrado resultados favorables en la reducción de las complicaciones micro- y macrovasculares, y de ciertos tipos de cáncer en individuos con esta condición

Palabras clave: Prediabetes. Obesidad. Diabetes *mellitus* de tipo 2 (DM2). Metmorfina.

INTRODUCTION

Prediabetes is considered the intermediate stage between normal glucose homeostasis and the hyperglycemic range of diabetes. Several observational studies and clinical trials have shown that prediabetes often progresses to type 2 diabetes mellitus (T2DM), and that it is associated with increased risk of microvascular and macrovascular complications[1]. The Diabetes Prevention Program showed that approximately 10% of individuals with impaired glucose tolerance (IGT) develop diabetes annually[2]. A cohort study on subjects with IGT, who were the offspring of patients with T2DM at the Joslin Clinic, showed that after eight years of follow-up, 35% had progressed to T2DM, 37% had reverted to normal glucose tolerance, and 29% persisted with IGT. Younger age and higher weight were associated with progression[3]. An analysis of six prospective studies showed that diabetes incidence in subjects with IGT occurred in 23-62% during 2-27 years of follow-up[4]. In the Framingham cohort study, 20% of subjects had impaired fasting glucose (IFG), 5% had IGT, and 6% both, with a likelihood for developing diabetes of 1.3% in the absence of both conditions; 4.3% for those with IGT, 9.2% for those with IFG, and 25.5% for those with both. According to the results of this study, diabetes incidence was predicted by age, sex, family history, body mass index (BMI), blood pressure, and lipids as well as by the presence of IFG and IGT[5].

Nevertheless, IGT and IFG are not identical in terms of pathophysiology and natural history[6]. Patients with IGT present mainly with muscle insulin resistance, while patients with IFG have severe hepatic insulin resistance with mild muscle insulin resistance. Both conditions are characterized by a reduction in early-phase insulin secretion; but IGT is distinguished by the presence of impaired late-phase insulin secretion[6-9]. In skeletal muscle, it has been shown that fatty acids directly inhibit GLUT4 receptors[10] and impair the activation of phosphatidylinositol-3 kinase (PI3K), a mechanism that is increased in subjects with obesity. In the liver, fatty acid-mediated insulin resistance occurs via the activation of protein kinase C (PKC)-ε by diacylglycerol[11].

The present manuscript reviews the current epidemiological and pathophysiological data that have permitted the establishment of standards for the identification and treatment of prediabetes. Also, the principle risk factors for the development of prediabetes are described, as well as the cost-effectiveness of interventions, such as metformin and lifestyle modifications, in the prevention of T2DM.

DEFINITION

The term "prediabetes" includes both fasting glucose and the two-hour value during the oral glucose-tolerance test (OGTT). The World Health Organization (WHO) defines prediabetes by the presence of IGT and/or IFG. The accepted glucose threshold to define IGT is a two-hour plasma glucose level between 140 and 199 mg/dl (7.8-11.0 mmol/l) after a 75 g OGTT; however, the IFG definition still varies between regions. The American Diabetes Association (ADA) recommends fasting plasma glucose (FPG) concentrations ≥ 100 mg/dl (5.6 mmol/l) and < 126 mg/dl (7.0 mmol/l), while the WHO defines IFG by concentrations ≥ 110 and < 125 mg/dl (6.1-7.0 mmol/l)[12]. In 2011 the WHO included a value of glycated hemoglobin A1c (HbA_{1c}) ≥ 6.5% as a threshold to diagnose diabetes, but they did not consider a range to define prediabetes, given the insufficient evidence to determine an exact correlation[13]. In contrast, the ADA included an HbA_{1c} of 5.7-6.4% to their prediabetes definition, and HbA_{1c} values between 6.0 and 6.4% are used by the International Expert Committee and the UK-based National Institute for Health and Clinical Excellence[14]. However, some hemoglobinopathies and diseases that impair the turnover of red blood cells may lead to abnormally low HbA_{1c} levels and hence false-negative diagnoses. There are also racial/ethnic group differences in the hemoglobin glycation or red blood cell survival. In these cases, the use of traditional diagnostic tests based on glucose concentrations is recommended.

The WHO recommends the use of the term "intermediate hyperglycemia" instead of "prediabetes" to avoid any stigma related with diabetes. Moreover, the glycemic levels between normal glucose tolerance and diabetes not only increase the risk for diabetes, but also significantly increase the risk for cardiovascular disease[14].

ASSOCIATION BETWEEN OBESITY AND PREDIABETES: EPIDEMIOLOGICAL AND PATHOPHYSIOLOGICAL ISSUES

Over the last few decades, modifications in dietary habits and a decrease in physical activity levels due to socioeconomic and industrial changes has led to an increase in obesity rates worldwide. In the USA, obesity prevalence has increased from 12% in 1991, to 20.9% in 2001[15], and in 2011-2012 an estimated 34.9% of US adults were reported to be obese[16]. In the same way, the prevalence of T2DM has increased 61% from 1990 to 2001, with an estimated 16.7 million US adults (7.9% prevalence) diagnosed in 2001[17]; this figure has increased to 29.1 million Americans (9.3%) in 2012, with the greatest increases among certain ethnic subgroups, including non-Hispanic black and Hispanic subpopulations and those with high or low levels of schooling[18]. In 2013, the estimated number of cases in adults between 20 and 79 years of age with T2DM worldwide was 382 million, and this figure is estimated to reach 592 million people by 2035[19]. Prediabetes prevalence has also increased and varies across population groups. Some 316 million people worldwide, or 6.9% of adults, are estimated to have IGT, the majority of which (70%) live in low- and middle-income countries; by 2035 this figure is estimated to reach 471 million people (8.0%)[19]. Between 2009 and 2012, the prevalence of prediabetes in adults aged 20 years or older in the USA, on the basis of FPG or HbA_{1c} concentrations, was 37%, of which 51% were aged 65 years or older; the chief risk factors associated with this condition were age, family history of diabetes, and obesity[20]. In 2013, the highest prevalence of IGT in adults was reported in North America (> 14%), followed by regions in Europe, Africa, and South and Central America (12-14%)[19].

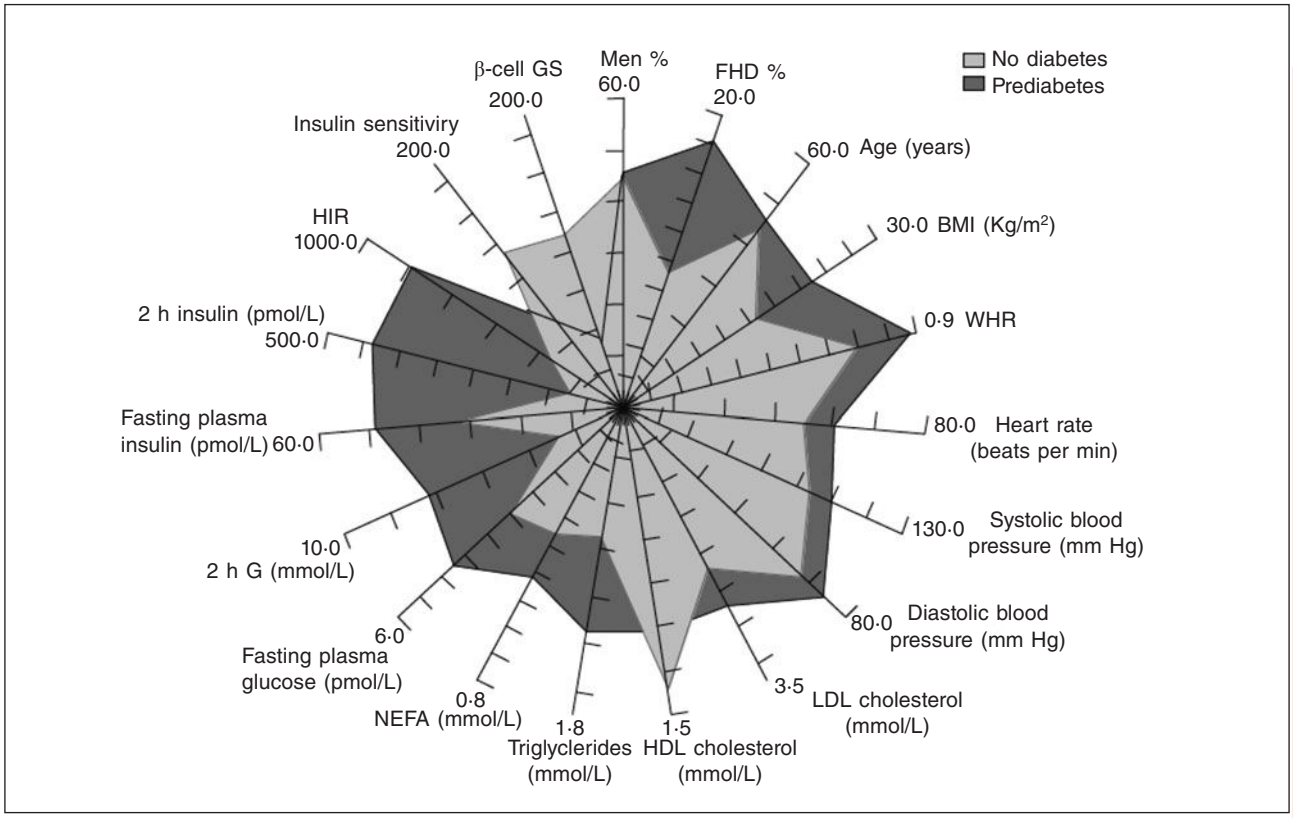

Figure 1. Radial plot with the phenotypic and metabolic characteristics of patients with prediabetes (i.e. impaired fasting glucose and/or impaired glucose tolerance; n = 152) and individuals with normoglycemia (n = 1,159)[24].
BMI: body mass index; NEFA: non-esterified fatty acids; FHD %: percentage of patients with a positive family history of diabetes; WHR: waist-to-hip girth ratio; 2 h G: glucose concentration two hours after an oral glucose load; 2 h insulin: insulin concentration two hours after an oral glucose load; HIR: hepatic insulin resistance index (calculated as the product of fasting endogenous glucose production rate and fasting plasma insulin concentration), in µmol min^{-1} $kg_{FFM}{}^{-1}$pM; Insulin sensitivity: insulin sensitivity index (as the M/I ratio from a hyperinsulinemic euglycemic clamp), in µmol.$min^{-1}kg_{ffm}{}^{-1}nM^{-1}$; β-cell GS: β-cell glucose sensitivity (calculated from the glucose and C-peptide response to an oral glucose load by mathematical modeling), pmol $m^{-2}min^{-1}nM^{-1}$.

Although both IGT and IFG are intermediate states in glucose metabolism that correspond to prediabetes, epidemiological studies indicate that the two categories describe different populations that partially overlap. In general, IFG rates are lower than IGT in the majority of populations, with certain ethnic groups being the exception[21]. There are also differences with respect to sex and age, with an increase in prevalence in both IGT and IFG with age, with women having a higher prevalence of IGT and IFG more frequently than men[21]. In addition, IGT and IFG are also associated with distinct metabolic features. People with IGT show muscle insulin resistance and severe defects in both early- and late-phase insulin responses to intravenous and oral glucose. Conversely, subjects with IFG have severe hepatic insulin resistance and a decreased first-phase insulin secretary response to intravenous glucose and early-phase insulin response to oral glucose. Individuals with both IFG and IGT have a more severe dysglycemia condition and higher risk for developing T2DM[22].

Individuals with IFG and/or IGT tend to be older, with a higher BMI, hyperinsulinemia, dyslipidemia (hypertriglyceridemia and low HDL-cholesterol concentrations), and with a higher arterial blood pressure and heart rate than individuals with normal glucose tolerance (Fig. 1)[23].

Obesity is a risk factor for the development of T2DM; however, not all obese individuals develop T2DM. Obese individuals with normoglycemia have both increased β-cell mass and function, but the failure of these compensatory responses leads to obesity -induced glucose intolerance. Several factors such as genetic predisposition, but also increased insulin secretory demand, among others, play a role in the progressive β-cell dysfunction[24].

Nevertheless, not only the degree of obesity, but the distribution of fat in the body determines the risk for developing diabetes. As a result, the metabolic syndrome, T2DM, and cardiovascular disease are more prominent in the presence of upper body and visceral adiposity[25]. In addition to body fat distribution, the different subtypes of adipose tissue and the coexisting cell types, such as immune cells, have the potential to influence glucose homeostasis and the systematic metabolic processes through endocrine and paracrine signals[26]. Adipose tissue is an active endocrine organ as well as a tissue with the capacity to store energy in the form of triglycerides. Three mechanisms have been proposed that associate obesity with insulin resistance, and hence the development of T2DM.

Firstly, obesity promotes an increased production of adipokines and inflammatory mediators that lead to insulin resistance in several tissues, contributing to intrahepatic and intramyocellular lipid metabolism[27]. Adipokines are specific hormones and cytokines secreted by adipocytes that communicate systemically with other cell types. Their production by adipocytes can contribute to the regulation of energy homeostasis. The adipokine with the most potent insulin-sensitizing activity is adiponectin, which improves insulin action and sensitivity. However, the reduction of adiponectin transcription as a result of the increase of endoplasmic reticulum due to mitochondrial dysfunction[28] provokes an inverse correlation between adiponectin levels and adiposity, promoting ectopic fat deposition[29]. Therefore, individuals who are obese and/or have metabolic syndrome show an altered adipokine profile that leads to changes in insulin sensitivity and other biochemical alterations.

Secondly, there are dysmetabolism sequelae produced by ectopic fat deposition (i.e. non-subcutaneous adipose fat storage) particularly in the liver and skeletal muscle. The abnormal partitioning of lipid between adipose tissue and ectopic fat storage, such as skeletal muscle, liver, heart, pancreas, and blood, is hypothesized to be related to insulin resistance. One hypothesis is that the failure of subcutaneous adipocytes to proliferate and differentiate in the presence of tissue hypoxia could lead to adipose tissue hypertrophy. These enlarged adipocytes cannot accommodate increased energy or dietary intake, leading to triglyceride accumulation in the surrounding organs with an overflow of lipid into visceral fat and non-adipose tissue[29]. Another hypothesis is that as a result of lipolysis, adipose tissue insulin resistance increases the nonesterified fatty acid (NEFA) flux, with a reduction of insulin receptor signaling in liver and muscle[27].

The third mechanism is mitochondrial dysfunction, which results in a decrease in insulin sensitivity and compromises β-cell function[28]. Depending on the anatomical distribution and mitochondrial content (visceral adipocytes are richer in mitochondria than subcutaneous adipocytes), the subcutaneous and visceral white adipose tissues have different metabolic activity. Many metabolic pathways occur in the mitochondria, allowing chemical energy to be converted into adenosine triphosphate (ATP). These include the oxidation of pyruvate, fatty acid β-oxidation, the tricarboxylic acid cycle, and oxidative phosphorylation (OXPHOS). During adipocyte differentiation, ATP consumption is high and even though the biogenesis of mitochondria is stimulated, overall ATP content decreases. Hence, mitochondrial biogenesis has to be properly adjusted during adipogenesis to cover energy needs and lipid and glucose metabolism. Impaired adipose mitochondrial function leads to dysregulation in the homeostasis of adipocyte tissue and can cause insulin resistance and T2DM. Indeed, people with reduced OXPHOS activity usually show insulin resistance and reduced fatty acid β-oxidation, leading to increased cytosolic free fatty acids that alter glucose uptake. All of this is related to impairment in mitochondrial activity[28].

DETECTION OF PREDIABETES

The detection of prediabetes is based on the identification of risk factors and physical examination. Several questionnaires are available to estimate the probability of developing T2DM, the Finnish type 2 Diabetes Risk Score (FINDRISC) being the most frequently used. It was developed in 2001 and consists of eight items (age, BMI, waist circumference, physical activity, diet, use of antihypertensive medication, history of high blood glucose, and family history of diabetes) that give a score and predict the probability of developing diabetes within the following 10 years[30]. Each variable is scored according to the risk that it may confer, resulting in a maximum score of 21 points. The final score can be divided into five risk categories: low (< 7 points), slightly elevated (7-11 points), moderate (11-14 points), high (15-20 points), and very high (> 20 points). This questionnaire has been shown to be useful for identifying individuals who are currently prediabetic and at high risk of developing diabetes. Patients within the high and very high-risk categories (≥ 15 points according to FINDRISC) should be tested for diabetes or prediabetes.

Other validated questionnaires for assessing diabetes risk include Dexlife, CANRISK, and the FINDRISC, all of which are highly predictive[31]. Nevertheless, they are heterogeneous; the ADA therefore recommends screening for prediabetes in people with risk factors[32]. There is no difference between the screening and diagnostic tests for diabetes and prediabetes. The detection and diagnosis of prediabetes is based on FPG, two-hour OGTT, and HbA_{1c} tests[33].

The fasting plasma glucose (FPG) is obtained after the patient has fasted for at least eight hours (except for water). Receiving two blood glucose readings of 126 mg/dl or over usually means the person has diabetes[34]. However, there are several factors that can alter the results, such as pre-analytic and analytic variations, and furthermore this measurement cannot detect postprandial glucose excursions. Therefore, this test is usually used as an intermediate step to identify patients at high risk of diabetes.

The two-hour oral glucose tolerance test (OGTT) is performed in fasting patients (8-12 hours). An initial blood sample is taken to obtain the baseline blood glucose level. Then the patient ingests a liquid that contains 75 g of glucose. If the patient is a pregnant woman, a higher dose of 100 g of glucose is given. Further blood samples are taken at 30 minutes, one and two hours after the ingestion, maintaining the person at rest[35].

A person who does not have diabetes will have a spike in blood glucose levels and then they will quickly return to normal. The blood glucose at two hours during the OGTT in a person without diabetes should be < 140 mg/dl. However, a person with diabetes will not be able to tolerate the glucose drink and their levels will spike and then gradually decrease at a much slower rate (two hour OGTT > 200 mg/dl). If the test shows high levels of blood glucose, the OGTT should be repeated before a formal diagnosis of diabetes is made to ensure there are no outside factors that might have skewed the results. Even though there is high intra-individual variability, the cost, and the need of an appropriate intake of carbohydrates during the previous three days by the patient, this test remains the gold standard in identifying T2DM and impaired glucose tolerance[35].

The HbA_{1c} test evaluates the glycated hemoglobin (i.e. the hemoglobin bonded with glucose) level. The reference method to measure HbA_{1c} is high-performance liquid chromatography (HPLC)[36]. Higher levels of blood glucose glycate higher numbers of red blood cells, and hence result in higher HbA_{1c} levels. Glucose levels and HbA_{1c} are directly related over the 120 days lifespan of the red blood cells, and hence the HbA_{1c} levels reflect a person's blood glucose levels over the previous 8-12 weeks. An HbA_{1c} level < 5.4% corresponds to a person with normal glucose metabolism, while a diabetic individual exhibits values ≥ 6.5%[37]. Some of the advantages of this test are that the results are not altered by variations in glucose levels and fasting is not required for their measurement. Conditions that can cause inaccuracy in the determination of HbA_{1c} are a reduced lifespan of red blood cells, renal impairment, pregnancy, or anemia. In addition, HbA_{1c} should not be used to assess diabetes risk; its predictive power

is poorer than IGT, as well as altered fasting glucose, and its cost is higher[38]. Above all, screening for prediabetes must identify people at high risk who would benefit from treatment. We should evaluate an individual's risk and use the most appropriate test, thus avoiding unnecessary medication and overutilization of already overloaded healthcare systems[39].

CLINICAL PRACTICE ALGORITHM FOR PREDIABETES

The primary goal of prediabetes management, once the patient has been diagnosed with prediabetes, is weight loss. Weight reduction can be effective in preventing progression to diabetes since it can reduce insulin resistance and improve blood lipids and blood pressure in people with IGT[40]. In the Diabetes Prevention Program population, younger age and insulin secretion were key factors in restoring normal glucose tolerance from IGT, in addition to weight loss and intensive management[41]. However, weight loss needs to be significant and sustained to impact the declining ß-cell function[42]. To achieve this, it is necessary to initiate lifestyle modifications, including nutritional counseling to improve the quality of the diet and increase physical activity. The establishment of achievable targets such as a weight loss of 5-10% of total body weight or participation in moderate physical activity (i.e. walking) at least 150 minutes/week can be useful, but maintenance of these goals determines the effectiveness of such interventions. For this reason, long-term behavior modification is a crucial part of these treatments. In the case of persons with significant obesity, weight loss can also be achieved with bariatric surgery, with differing results in the short to long term. Bariatric surgery has been shown to reduce the incidence of T2DM in subjects with morbid obesity, as well resulting in a reduction in macro- and microvascular associated outcomes[43,44].

If weight reduction is accomplished and blood glucose levels are reduced, lifestyle changes should continue and be regularly reinforced, and it is recommended to screen for diabetes every 6-12 months[45]. When weight loss is not achieved or blood glucose levels are still high, it is necessary to consider starting glucose lowering medication[46]. The first-line drug is metformin, which is safe and well tolerated and is estimated to reduce the risk of developing diabetes in prediabetic patients by 25-30%[47]. Thiazolidinediones are estimated to reduce the risk of diabetes by 60-75%; however, they are associated with adverse effects such as peripheral edema and heart failure[48]. Among the drugs approved for obesity management, orlistat, liraglutide, and phentermine/topiramate have shown to reduce progression to diabetes in 37% in 4 years, 79% in 2 years, and 90% in 1 year, respectively[49-51].

However, the effectiveness of prediabetes treatments depends on interdisciplinary interventions, and continues to be influenced by socioeconomic forces and a lack of disease knowledge and skills for management on the part of both patient and doctor. For this reason, it is of great importance to promote the patient's empowerment to self-manage his or her own care. Patients should be provided with tools that include diabetes education, treatment options appropriate for their sociocultural status, behavioral interventions, and problem-solving techniques. In this way, patients can be actively involved in the goal setting process, making informed decisions and taking control of the daily self-management of their condition. Quality of life is related to an improvement in patient empowerment.

REVIEW OF TREATMENTS FOR PREDIABETES AND THE PREVENTION OF THE PROGRESSION TO DIABETES

Initially, the treatment of prediabetes is focused on lifestyle modification in order to lose weight, if overweight or obese, and seeks to increase physical activity. Large-scale studies evaluating the impact of lifestyle intervention have shown sustained reductions in the development of T2DM, but also reductions in traditional diabetes risk factors[52-55]. The Da Qing study[56] obtained a 43% lower incidence over a

20-year period in adults with IGT. This study also demonstrated that a lifestyle intervention that lasted six years prevented or delayed the development of diabetes for up to 14 years after the active intervention. The Finnish Diabetes Prevention Study[57] also showed a reduction of 43% after four years of active intervention and a total follow-up period of seven years in overweight patients with IGT. The Diabetes Prevention Program evaluated the incidence of diabetes in patients with elevated FPG and IGT treated in an intensive lifestyle intervention (ILI) in comparison with usual lifestyle management. After a 10-year follow-up, diabetes incidence was reduced by 34% in the lifestyle intervention group[58]. Moreover, changes in lifestyle not only improve glucose tolerance, but also reduced diabetes-related complications such as cardiovascular disease risk factors including hypertension and dysplipidemia[59,60].

The effect of several pharmacologic treatments on several outcomes like progression to T2DM and weight has been assessed in people with high blood glucose levels[61]. Metformin has low risk of hypoglycemia, durability of its antihyperglycemic effects, and long-term safety, and hence it is recommended as either initial or monotherapy. It is recommended in patients who have both IFG and IGT, and at least one additional risk factor (age < 60, BMI ≥ 35, family history of diabetes in first-degree relative, elevated triglycerides, low HDL, or HbA_{1c} > 6%). Treatment with metformin has shown to be safe, well tolerated, and weight neutral or with moderate weight loss effects in patients of 25 years or older, with a BMI ≥ 24 kg/m^2, elevated FPG, and IGT[62]. Over a 10-year period, metformin was more cost-effective than the lifestyle intervention, even though it was less effective on the primary outcome (incidence of T2DM)[63]. Both lifestyle intervention and metformin have exhibited a reduction in the risk of diabetes by 50% in women with gestational diabetes mellitus[64].

If blood glucose levels are not normalized, other possible medications to consider are glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, or thiazolidinediones (TZD), even though the last two are mainly used for treatment of T2DM. The GLP-1 receptor agonists stimulate insulin secretion from the beta cells, and also reduce glucagon secretion from alpha cells and slow gastric emptying. These drugs are effective in decreasing HbA_{1c} levels, reducing postprandial blood glucose levels, and significantly decreasing body weight. Moreover, they are not associated with hypoglycemia even when associated with gastrointestinal adverse events. The GLP-1 receptor agonists in combination with metformin are a valid alternative to metformin alone in patients that would benefit from weight loss[63]. Liraglutide at doses up to 3 mg is effective in reducing blood glucose levels, body weight, and blood pressure, and hence improves the risk of cardiovascular disease[66]. Liraglutide is a good option of metformin treatment intensification in patients with T2DM treated with metformin with inadequate glycemic control[67]. In order to stabilize endogenous GLP-1, the DPP-4 inhibitors were developed. Sitagliptin, saxagliptin, linagliptin, and alogliptin are four DPP-4 inhibitors approved in the USA, and vildagliptin is approved for use in Europe and Asia.

Another group of drugs are the TZD, which activate the peroxisome proliferator-activated gamma receptors (PPAR-γ), increase hepatic and peripheral insulin sensitivity, preserve insulin secretion, and might promote pancreatic β-cell health. Rosiglitazone is a TZD approved for treatment of hyperglycemia in patients with T2DM. This treatment, together with lifestyle recommendations, is effective in reducing the risk of diabetes or death by 60% and increases the likelihood of regression to normoglycemia in individuals at high risk for diabetes with IGF, IGT or both[68]. Pioglitazone is another TZD effective in lowering HbA_{1c}, with low hypoglycemia risk and possible cardiovascular benefits[69]. However, it presents several side effects such as weight gain and adverse metabolic effects on bone, and has been associated with bladder cancer[70].

COST-EFFECTIVENESS OF PROGRAMS FOR THE PREVENTION OF TYPE 2 DIABETES MELLITUS

In addition to the beneficial effect on weight loss and control of comorbidities, lifestyle interventions

have been proven to be cost-effective[71]. Interventions designed for the prevention of T2DM have an economic impact on the healthcare institutions as well as at the social level[72]. Studies of cost-effectiveness have focused on the effect of lifestyle modification and use of metformin since they have achieved the best results. In the cost-effectiveness analyses that assess prevention of cases of a particular disease, or its delay, as in the effect on gained years with quality of life (QoL), mathematical models are used to calculate the probability of progression from the earlier stages of risk to the development of its complications. These models are built with the data coming from the study and the natural history of the disease. Using such methods, Herman, et al. developed one of the most complete cost-effectiveness analyses of the Diabetes Prevention Program. In this study it is assumed that if the entire cohort were to be prescribed placebo, approximately 50% of them would develop T2DM at the end of seven years; if they were to receive an ILI, 50% of the participants would develop T2DM after 18 years; and if the intervention was metformin, 50% would progress to T2DM in 10 years. In conclusion, the ILI reduced the absolute risk to develop T2DM by 20% and treatment with metformin reduced it by 8%, which corresponds to a reduction in the relative risk (RR) of 24 and 10%, respectively[73]. Likewise, it was found that the lifestyle intervention increased lifespan by 0.5 years and reduced the incidence of blindness by 39%, end-stage kidney disease by 38%, amputations by 35%, stroke by 9%, and coronary heart disease by 8%. Metformin increases life expectancy by 0.2 years and reduced blindness by 16%, end-stage kidney disease by 17%, amputations by 16%, stroke by 3%, and coronary heart disease by 2%. With such assumptions, in comparison with placebo, the yearly direct cost on gained QoL is US$ 1,100 for the ILI, and US$ 31,300 for the treatment with metformin. In participants 50 years old or older, the cost of the ILI increased to US$ 4,137 and treatment with metformin to US$ 36,327. From another Diabetes Prevention Program analysis, from a social perspective that includes indirect costs, it was estimated that lifestyle interventions and metformin have a cost of US$ 24,000 and US$ 34,500, respectively, for each new case with T2DM prevented or delayed; for each quality-adjusted life year (QALY) a cost was estimated of US$ 51,600 for the ILI, and US$ 99,200 for treatment with metformin. In this analysis, it is determined that, in comparison with placebo, 6.9 participants with IGT will require an ILI for three years and 14.3 years of treatment with metformin to prevent or delay one incident case of T2DM. During the Diabetes Prevention Program, the ILI had a cost of US$ 15,700 and the intervention with metformin was US$ 31,300 for each case of T2DM prevented. From the healthcare system perspective, the ILI has a cost of US$ 31,500, and the intervention with metformin of US$ 99,600 for each QALY. Finally, the cost of the ILI for each T2DM case prevented was US$ 4,300 lower for subjects 65 years old or older, in comparison with individuals 45 years old or younger. From this standpoint, the cost of the intervention with metformin was US$ 22,400 higher in subjects aged 65 years or older in comparison with subjects younger than 45 years. In conclusion, lifestyle interventions and treatment with metformin are efficacious and cost-effective from the point of view of the prevention policies for diabetes, especially in people younger than 45 years[74]. Nevertheless, the cost-effectiveness relationship depends on the health system. In countries where there are insufficient healthcare services to treat people with diabetes and people with low-risk, the use of treatment programs for prediabetes is insufficient[75]. Their implementation requires the availability of multidisciplinary treatment groups, and their effects will be observed in the mid-term.

CONCLUSIONS

Individuals with impaired glucose homeostasis, but with glucose levels not high enough for the diagnosis of T2DM are considered to have prediabetes. It is defined by impaired glucose tolerance and impaired fasting glucose, although these terms are not equivalent and different international criteria can be used, which has important implications for the healthcare systems.

The impact of socioeconomic and industrial changes during the last decades has lead to alarming rates of obesity and diabetes. Obesity is one of the main risk factors for the development of diabetes, given the metabolic role that adipose tissue has in addition to storing of energy. It is linked with T2DM by promoting proinflammatory cytokine release, insulin resistance, deranged fatty acid metabolism, and cellular disorders such as mitochondrial dysfunction.

People with overweight and other risk factors for developing diabetes, such as family history of diabetes, physical inactivity, or hypertension, should be screened for the presence of prediabetes, in addition to screening all individuals for T2DM at 45 years.

Individuals diagnosed with prediabetes should initiate lifestyle modifications to reduce body weight, if necessary, and increase physical activity. Other treatments with antihyperglycemic medication or weight-loss medication are also recommended. Metformin is usually the first option of medication. It is effective in reducing the risk to develop diabetes. Other treatments with thiazolidinediones, glucagon-like peptide-1 receptor agonists, and dipeptidyl peptidase-4 inhibitors are also effective in reducing the risk to develop diabetes, with different safety profiles.

To meet the universal screening recommendation and lifestyle interventions, it is necessary to use clinical criteria and adequate use of the healthcare resources to better address the burden of T2DM on populations.

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