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Remission of type 2 diabetes: a real perspective for clinical practice

Remissão do diabetes tipo 2: uma perspectiva real para a prática clínica

Remisión de la diabetes tipo 2: una perspectiva real para la práctica clínica

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ABSTRACT

The type 2 diabetes (T2D) is probably the biggest challenges of global public health. In United States, 4% of all Gross Domestic Product is spent with the diabetes complications. Despite the progress on studies to refrain the diabetes complications, the most effort is target for iniciatives like a search with new pharmacological oportunities and there is less interest in the cientific comunity and governments to study plausible and applicable strategies of lifestylechanges in diabetes. Even so, the publication of Diabetes Prevention Program study, that demonstrated the expressive reduction in the primary outcome, diagnosis of diabetes, was a Mark that starts a series of studies looking for the remission of T2D. The DiRECT study is the most strong evidence to demonstrate the remission of T2D in humans with lifestyle changes with results until 89% in patients that reduced their weight in 15% of initial. the objective of this review is present and discuss the lifestyle medicine as a real possibility for diabetes type 2 remission.

Keywords: diabetes mellitus type 2, diabetes, obesity, lifestyle medicine.

RESUMO

O diabetes tipo 2 (DT2) é provavelmente o maior desafio da saúde pública global. Nos Estados Unidos, 4% de todo o Produto Interno Bruto é gasto com complicações do diabetes. Apesar do avanço nos estudos para conter as complicações do diabetes, a maior parte dos esforços está voltada para iniciativas como a busca de novas oportunidades farmacológicas e há menor interesse da comunidade científica e dos governos em estudar

estratégias plausíveis e aplicáveis de mudanças de estilo de vida no diabetes. Mesmo assim, a publicação do estudo do Programa de Prevenção do Diabetes, que demonstrou a redução expressiva no desfecho primário, o diagnóstico de diabetes, foi um marco que inicia uma série de estudos buscando a remissão do DM2. O estudo DiRECT é a evidência mais forte para demonstrar a remissão do DM2 em humanos com mudanças no estilo de vida, com resultados de até 89% em pacientes que reduziram o peso em 15% do inicial. O objetivo desta revisão é apresentar e discutir a medicina do estilo de vida como uma possibilidade real para a remissão do diabetes tipo 2.

Palavras-chave: diabetes mellitus tipo 2, diabetes, obesidade, medicina de estilo de vida.

RESUMEN

La diabetes tipo 2 (DT2) es probablemente el mayor desafío de la salud pública mundial. En Estados Unidos, el 4% de todo el Producto Interno Bruto se gasta en complicaciones de la diabetes. Apesar de los avances en los estudios para frenar las complicaciones de la diabetes, el mayor esfuerzo se dirige a iniciativas como la búsqueda de nuevas oportunidades farmacológicas y hay menos interés por parte de la comunidad científica y de los gobiernos por estudiar estrategias plausibles y aplicables de cambios de estilo de vida en la diabetes. Aún así, la publicación del estudio del Programa de Prevención de la Diabetes, que demostró la expresiva reducción en el resultado primario, el diagnóstico de diabetes, fue una marca que inicia una serie de estudios buscando la remisión de la diabetes tipo 2. El estudio DiRECT es la evidencia más contundente para demostrar la remisión de la diabetes tipo 2 en humanos con cambios en el estilo de vida con resultados de hasta el 89% en pacientes que redujeron su peso en un 15% del inicial. El objetivo de esta revisión es presentar y discutir la medicina del estilo de vida como una posibilidad real para la remisión de la diabetes tipo 2.

Palabras clave: diabetes mellitus tipo 2, diabetes, obesidad, medicina del estilo de vida.

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Introdução

Type 2 diabetes mellitus (T2DM) in association with obesity are the most important diseases with epidemiological impact today. The incidente's increase becomes evident when society's expenses with its treatment and complications are analyzed: in 2012 the cost of the disease was estimated at 240 million dollars and in 2017, 327 million dollars, that is, an increase of 36% in 5 years [1]. Currently, it is estimated that 30 million Americans have a diagnosis of diabetes, the vast majority of whom are type 2 diabetics and another 84 million Americans have a clinical state of "pre-diabetes". Of all health spending in the United States (USA), which in 2017 was equivalent to 17% of the Gross Domestic Product (GDP), a quarter of this amount was allocated to treating diabetes and its complications, which means 4.2%, that is, for every 100 dollars of wealth produced in the USA, 4.2 dollars are spent on the treatment of diabetes and its complications.

In Brazil, the VIGITEL [2] study, surveillance of risk and protective factors for chronic diseases by telephone survey, is an initiative of the Brazilian Ministry of Health that, despite methodological limitations such as the fact that the interviews are self-reported by telephone contact, the study has the advantage of maintaining a historical series since 2006, which allows an analysis of changes in the epidemiological profile of the population over the years. In its most recent publication with data from 2023, a progressive increase in the percentage of the population with diabetes increased from 5.5% in 2006 to 10.2% in 2023, the study's overweight rate increased from 42.6% to 61,4% and obesity (Body Mass Index, BMI, greater than or equal to 30) from 11.8% to 24,3%. This upward curve in the growth of obesity and overweight is accompanied by a progressive increase in the incidence of diabetes and there are no signs of slowing down for now. Despite this results only 6,0% of patients answered that estimate negatively their health state.

To treat diabetes as a public health problem is essential aproacho through 3 fundamental points os view: how to prevent, treat and, if possible, reverse the condition.

A historic perspective of diabetes intervention through the prism of lifestyle medicine

The United Kingdow Prospective Study (UKPDS) [3, 4] published in 1998, leaves a legacy about the importance of good glycemic control to prevent diabetes complications. In this study, strict glycemic control was able to reduce the microvascular complications of diabetes, that is, diabetic neuropathy, diabetic nephropathy and diabetic retinopathy without significantly reducing the incidence of macrovascular events such as acute myocardial infarction (AMI) and Stroke. However, in long-term follow-up, the group that received strict glycemic control during the intervention also had a lower incidence of both microvascular and macrovascular events [4].

Over the years, other studies such as the Action to Control Cardiovascular Risk in Diabetes Study Group (ACCORD) showed that despite the importance of glycemic control, this could not be an isolated goal to be established at any cost, as events such as hypoglycemia would also be harmful [5].

With this understanding, and a consensus regarding the most appropriate goals, in the first decades of the 21st century, diabetes studies societies and the pharmaceutical indutries worked to develop new classes of antidiabetics that emerged and positioned themselves in relation to glycemic control, efficacy, safety and reduction of diabetes complications.

The LOOK AHEAD study published in 2007 highlighted the positive impact of weight loss through interventions to change lifestyle on good glycemic control [6]. However, the percentage of patients who stopped using hypoglycemic drugs was small, attributed to a possible selection bias of patients with longer diabetes and also a fraction of the participants were insulin users. Despite the comments of the study, about some possible bias, there is other robust evidence of the importance of a healthy lifestyle with better nutrition and physical exercise to prevent diabetes and as a fundamental component of treatment in all guidelines, despite this element being neglected in the practice of most professionals [7]. The question this article is dedicated to reviewing is: could lifestyle intervention reverse the diagnosis of diabetes? And It would be a plausible perspective to clinical pratice?

In 2002, the Diabetes Prevention Program (DPP) [8] study was dedicated to comparing the impact of using metformin versus prescribing lifestyle changes in pre-diabetic patients. This group was guided through a program called Lifestyle Balance that involved nutritional support, with the objective of losing 7% of initial body weight, as well as guidance on moderate physical activity, group support and individual behavioral therapy. The prescribed diet was basically hypocaloric with carbohydrate restrictions, whose estimated caloric supply was between 1200 and 2000Kcal. The outcome assessed was diagnosis of T2DM and expected follow-up was 3 years.

DPP demonstrated that the group that underwent the lifestyle change program showed greater weight loss compared to patients who received metformin (5.6kg vs 2.1kg) with statistical significance in reducing the incidence of diabetes in favor of the group that prescribed lifestyle modifications (58% vs 31%). After this, all patients in the "metformin" group were invited to receive same therapy after a medication washout period and the result in long-term follow-up was equality between the groups with weight reduction and consequent improvement in serum levels of glycated hemoglobin in these patients [9].

The Counterpoint [10] study demonstrated a real possibility of improving laboratory tests in diabetic patients within 4 years of diagnosis and who were submitted to a calorie-restricted diet. Patients had a reduction in blood glucose levels in the second week with a reduction in liver fat deposition with full restoration of beta cell function in the fourth week of intervention.

The results in reducing the progression of diabetes resulting from the UKPDS study and the new therapeutic options promoted accommodation among the physicians, which began to work hard in pursuit of goals for managing DM2, with great emphasis on research and prescription of medications with few studies. focused on a non-pharmacological approach to DM2. If analised together, the information from the DPP and the Counterpoint study brings a bolder horizon for patients, demonstrating that there would be the possibility of progress in the hypothesis that the true first line of approach for diabetic patients should be a more aggressive dietary approach with psychosocial support and prescription of physical activity with the aim of reversing the pathophysiology of the disease.

Information from studies with patients undergoing bariatric surgery already supported evidence of the possibility of reversing DM2.

This mechanism was partially elucidated in the study by Cheng et al. [11] in animals. The group used db/db mice, which are animals with a specific mutation in the leptin receptor gene. These rats present severe hyperglycemia and hyperinsulinemia and develop pancreatic failure until approximately 4 months of age when they die. The study consisted of offering the animals weekly cycles of a diet that mimicked fasting, the Fasting Mimicking Diet (FMD), lasting 4 days from the twelfth week of life.

The results demonstrated that from 90 days onwards, the animals showed improvement in pancreatic function until restoration of beta-cell function. During the investigation, the authors found an increase in the expression of mRNA related to the activity of NGN3+ cells, which are progenitor cells located predominantly in the pancreatic islets and have the capacity to generate all endocrine cell lineages, including insulin-producing beta cells.

Lifestyle medicine approach for treating diabetes in humans

In humans, the DiRECT [12] study is the main study working on the concept of diabetes reversal. An open and controlled clinical trial with the objective of evaluating the results of an intensive intervention consisting of a dietary program, called Counter Weight, psychosocial support and prescription of physical activity.

The Counter Weight program was designed using the same rationales described in the studies so far. Basically, it was aimed at calorie restriction, with the patient undergoing a Very Low Carb Diet (VLCD) in a modality called Very Low Energy Liquid Diet (VLED). In it, the first stage lasted 12 weeks or until the loss of 20kg, whichever occurred first, and the patient received a liquid diet with a progressive reduction in caloric supply up to a dose of 800KCal per day for 2 weeks. Despite being hypocaloric, the distribution of macronutrients was the same as a regular diet, with a distribution made up of 59% of calories from carbohydrates, 13% from fats, 26% from proteins and 2% from fibers. The lowest caloric intake would be the peak of the program with slow and progressive food reintroduction accompanied by a team already trained in this type of approach in severely obese people [13].

As the study was intended to treat, despite providing for a 12-week approach in the first phase, some patients were maintained on VLCD/VLED for up to 5 months, depending on weight loss and the patient's tolerance to the diet.

As in the first phase, food reintroduction also did not restrict any specific food group, with a diet composition of 50% of calories from carbohydrates, 35% from fat and 15% from proteins with all follow-up within a weight maintenance program structured.

A peculiarity of the DiRECT study was the suspension of oral antidiabetics and antihypertensives from the first day of calorie restriction. For this methodology to be carried out safely, only non-insulin-dependent diabetics with up to 6 years of diabetes diagnosis and patients with glycated hemoglobin below 12% were selected.

Regarding exercise prescription, in the first phase of the VLCD diet, patients were encouraged to maintain their usual dose of physical activity and as they progressed through the dietary program, they received pedometers during the food reintroduction phase and were then instructed to walk as much as possible. of steps possible, ideally greater than 15 thousand steps per day.

The primary outcomes were weight loss of more than 15kg and maintenance of glycated hemoglobin for 12 months with levels below 6.5%, which, according to the authors, would be considered remission or reversal of DM2.

The results demonstrated that in the intervention group, the loss of 15kg or more was 24% versus 0% in the control group. Regarding DM2 remission, 46% in the intervention group versus 4% in the control group. In the subgroup analysis, among patients who managed to lose 15kg, they had a type 2 diabetes remission rate of 89%.

The 2-year follow-up study of DiRECT [13] was published in 2018 and demonstrated that the intervention group maintained a success rate in relation to sustaining weight loss of 15kg or more of 11% versus 2% in the control group and with a rate of type 2 diabetes remission of 35% versus 2%. Among the patients who were successful in losing weight in the original study, that is, they lost 15kg with the original intervention, the diabetes remission rate reduced from 89% to 70%, also demonstrating a very significant result in the intervention group with weight loss. weight of 15kg or more.

The epidemiological chalenge

In January 2019, the Obesity Commission of the Lancet [14] published a report that treats the problem of obesity as a pillar of what it calls the

Global Syndemic, which would be the union of three pandemics: obesity, malnutrition and climate change. These pandemics have their own characteristics, but they are completely correlated as they interact with each other and share their determinants, exerting mutual influences on their burden on society.

The population's dietary pattern and the way governments relate to it goes through notable commercial conflicts of interest, from agroindustry, which has an indelible economic importance for Brazil, for example, to the understanding how to implement primary health care programs that have a deep connection with society to the point of being able to influence the population's food choices, school menus and the promotion of physical activity in the communities in which they are located.

In parallel to the discussion about how to review and treat the basis of the Global Syndemic problem, we must understand that the major public health problem in relation to diabetes will not be solved only with the administration of new powerfull and more expensive medicines. Despite the excellent progress that the UKPDS has brought to the understanding and management of diabetes (DM), knowledge is still limited to damage control of DM complications which is insufficient to solve the public health problem that society faces now and what is yet to come, given the changes in the population's habits that have occurred over the last 30 years.

In May 2019, Taylor, Al-Mrabeh and Sattar [15] published an extensive review discussing the pathophysiological mechanisms of reversal of type 2 diabetes. According to the authors, as the pathophysiological basis is linked to positive caloric balance, fatty infiltration of the liver and pancreas mainly, which causes beta cell dysfunction, intensive interventions, such as the Couter Weight program, that result in weight loss in addition to a physical activity program and adequate cognitive behavioral support could point to a path towards reversing the pathophysiological process of DM2 and consequently reversing the DM2. The DiRECT study clearly demonstrates this hypothesis in humans.

In clinical practice, there is the challenge of naming this process, which is often called “DM2 reversal”. What is observed is a sustained improvement in glycemic levels. From there, the question arises: Would a cure for diabetes be possible? In 2009, the American Diabetes Association (ADA) [16] published a position on what this possible cure for diabetes would be after a broad meeting with experts from different areas of medicine.

In this discussion, the main challenge of calling this phenomenon a cure would be related in analogy to what occurs in cancer and other chronic degenerative diseases, which are diseases with a high rate of recurrence. Therefore, in analogy to how terminologies are used in oncology, diabetes could present partial remission if fasting glycemia remains between 100 and 125 mg/dl, total remission in the case of sustained fasting glycemia <100 mg/dl and in the case of improvement in glycemic indexes for more than 5 years, prolonged remission.

There was also a consensus that no matter the means by which DM has achieved remission, that is, either through bariatric surgery or through lifestyle measures, the definition of remission is given by laboratory results below the thresholds of what is defined by diabetes in the absence of medication and not the means by which the results were achieved, always understanding that literature data related to DM2 deals with weight loss and sustained calorie restriction for a long period. In this position, the ADA does not mention a minimum time for glycemic improvement in the absence of medication for this patient to be classified as "in remission".

A new consensus report by ADA [17] reforces the concept about T2DM Remission and points 3 therapeutics possibilities: lifestyle changes, bariatric and metabolic surgery and pharmacological obesity treatment.

Also the Association of British Clinical Diabetologists (ABCD) and the Primary Care Diabetes Society (PCDS) jointly published a document to take a position on the topic [18]. In this document, the authors reinforce the recognition of the phenomenon of DM2 remission and classify the patient as "in remission" when they have glycated hemoglobin lower than 6.5% for more than 6 months in the absence of medication.

Despite the successful results of the DiRECT study, the implemented diet is not very feasible in clinical practice identicaly as CounterWeight Project proposes with limits to the implementation of this program in almost all services.So,these studies should be considered as proofs of concept, and based on the understanding that the main learning brought by the result is the importance of sustained weight reduction, it is up to the clinician at the time of diagnosing DM2, evaluating the best data in available literature, clarify and offer the patient the possibility of diabetes remission.

Conclusion

Lifestyle medicine proposes to approach the patient beyond the disease and treats the real cause of the chronic disease, which is the way the

patient lives their life, therefore, in addition to being completely aligned with the proposed non-drug approach, it also brings with it behavioral approach concepts that favor the best results obtained in the clinical trials proposed so far.

Is fundamental to health services and providers, both public and private, to understand the relevance of these data from an epidemiological point of view to develop effective and intensive multidisciplinary programs to combat the Global Syndemic and thus bring benefits beyond the improvement of DM2, with the reduction of incidence of other comorbidities related to obesity and overweight, in addition to the great long-term economic benefits.

It is essential to understand that this public health problem will not be solved with medication, but with effective lifestyle measures both at the management level and in care practice.

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