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KETOGENIC DIET: NUTRITIONAL THERAPY IN TYPE 2 DIABETES

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Abstract

Type 2 diabetes is recognized as a serious public health concern with a considerable impact on human life and health expenditures, in 2017, approximately 462 million individuals were affected by type 2 diabetes corresponding to 6.28% of the world's population [1].

The term diabetes mellitus describes a metabolic disorder of multiple aetiology: it is characterized by cronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.

The effects of diabetes mellitus include long- term damage, dysfunction and failure of various organs, especially eyes, kidneys, nerves, heart, and blood vessels. Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss.

The most severe clinical manifestations are ketoacidosis or a non-ketotic hyperosmolar state that can lead to dehydration, coma and death in absence of effective treatment [2].

Ketogenic diet promotes glycemic control, elimination / reduction of diabetic medications and weight loss in overweight and obese individuals with type 2 diabetes, as evidenced by the analysis of some recent published papers cited in this narrative review.

Keywords: *Ketogenic diet, diabetes mellitus, Insulin, weight loss.*

Introduction

Type 2 diabetes mellitus is a growing health problem worldwide that affects more than 150 million people at the beginning of the new millennium.

The pathophysiological characteristics of type 2 diabetes mellitus consist of insulin resistance, pancreatic β-cell dysfunction and increased endogenous glucose production.

The optimal treatment aims at the normalization of body weight, glycaemia, blood pressure and lipidemic in order to reduce the marked increase of cardiovascular mortality of type 2 diabetic subjects.

Low-carbohydrate ketogenic diets (KDs) are often implemented to reduce or keep body weight.

The ketogenic diet is a diet rich of fat, adequate proteins, low in carbohydrates leading to the production of ketone bodies and therefore to ketosis.

The ketogenic diet should be individualized according to the patient and based on the patient's needs; therefore, it is nutritionally adequate for each individual, provides 90% of the necessary calories in the form of fat, a minimum of 1.4 g / kg of proteins of ideal weight and minimum carbohydrates. In the classical therapy the ratio of fat to protein and carbohydrate is 4: 1.

To date in literature there are many scientific evidences that relate this type of therapy with type 2 diabetes leading to an overall improvement of the patients hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting due to defects in insulin secretion, insulin action, or both.

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Diabetes is a very complex disease since it is a container of multiple clinical syndromes. There are different diseases united by hyperglycaemia.

The main types of diabetes are the following:

1. type 1 diabetes (also called insulin-dependent)
2. type 2 diabetes (also called non-insulin-dependent)
3. gestational diabetes (appears during pregnancy and usually disappears after birth).
4. monogenic diabetes (ex. MODY, maturity-onset diabetes of the young: a variety of diabetes in which there is a single genetic defect capable of determining hyperglycemia)
5. diabetes secondary to other pathology (ex. pancreatic disease) or drugs (ex. cortisone).

The most known and most frequent varieties of diabetes are type 1 and type 2 diabetes: they are two completely different diseases from the etiological and pathogenetic point of view.

Type 1 diabetes has autoimmune origin and is the consequence of a relatively rapid destruction of the pancreatic cells that don't produce enough insulin.

The destruction is carried out by substances (antibodies, cytokines) produced by the body's immune system cells probably in response to a virus or to one or more toxic substances present in the environment. For this type of diabetes, insulin injection therapy is absolutely necessary because the body no longer produces insulin (absolute lack of insulin). Type 1 diabetes appears mainly in children, adolescents, young adults and rarely starts after age 40. There is a variant of type 1 diabetes called LADA (Latent Autoimmune Diabetes of the Adult) in which the autoimmune attack on insulin-producing cells is slow and less impressive and the disease develops over years: in this type of diabetes there are some clinical features of type 2 diabetes.

Type 2 diabetes develops over many years due to a deficiency in insulin production which, however, does not depend on autoimmunity. Multiple genetic alterations and acquired (environmental) factors are responsible for an insulin deficiency that is generally

associated with a lower efficacy of insulin. In this type of diabetes there is not enough insulin to satisfy the body's needs (relative insulin deficiency). Type 2 diabetes appears above all after the age of 40 years, but the age of onset is decreasing due to the increasing prevalence of obesity even among the youngest.

Among type 2 diabetics there is an extreme etiopathogenetic heterogeneity that is expressed in a variable combination of insulin secretion and insulin resistance deficits. Both defects originate in functional abnormalities in various organs and tissues such as the liver, skeletal muscle, adipose tissue, intestine, brain and the alpha and beta cells of pancreatic islets. In this type of diabetes an important role is exercised by the excess body weight that determines insulin resistance and negatively affects the secretion of the hormone. Most individuals with type 2 diabetes have excess weight. [3]

Type 2 diabetes mellitus is characterized by 4 major metabolic abnormalities: obesity, impaired insulin action, insulin secretory dysfunction, and increased endogenous glucose output (EGO) [4].

Insulin resistance is a condition in which cells don't respond to the normal actions of the hormone insulin. More specifically muscle cells, liver and fat cells have difficulty absorbing glucose from the bloodstream. In order to compensate this condition, the body produces more insulin. Initially, the body is generally able to overcome insulin resistance and blood glucose levels remain at an adequate level. However, as resistance increases, pancreatic beta cells are unable to produce enough insulin to regulate blood glucose. As a result, blood glucose levels can increase and cause pre-diabetes, diabetes and other chronic health disorders such as the metabolic syndrome. [5]

Fortunately, many studies suggest that ketogenic diet can help reverse insulin resistance [6].

Accumulating evidence suggests that low-carbohydrate, high-fat diets are safe and effective to reduce glycemia in diabetic patients without producing significant cardiovascular risks.[7]

In fact, a low-calorie ketogenic diet (VLCKD) is effective not only in weight loss but also to achieve an improvement in glycemic compensation in patients with Type 2 Diabetes Mellitus.[8]

Ketogenic diet

Ketogenic diet is defined as a diet that is able to induce and maintain a chronic state of ketosis, a metabolic condition in which ketone bodies are used as an energy source.

The ketone bodies are mainly three: acetoacetate, beta hydroxybutyrate and acetone.

Ketogenic diet is a high-fat, adequate protein, low-carbohydrate diet designed to produce ketosis through mimicking the metabolic changes of starvation. It is carefully calculated to be nutritionally adequate for each individual, providing 90% of needed calories as fat, a minimum of 1 g/kg of protein, and minimal carbohydrates. The ratio of fats to protein and carbohydrate is classically 4:1.[9]

During fasting, the primary source of carbohydrate reserve is glycogen, but glycogen deposits provide only a reserve of energy from 12 to 14 hours [10]. During prolonged fasting, muscle proteins begin to break down, using glycogen to provide the necessary energy.

During prolonged fasting or during hunger, the main source of human energy is fat stored in adipose tissue. Body fat is readily metabolized by the liver in order to form ketone bodies and these water-soluble compounds get easy access to the central nervous system. As the blood concentrations of ketone bodies increases, their brain metabolism shifts its use of glucose and saves muscle proteins [11, 12].

This deficiency leads to the activation of triglyceride and muscle protein metabolism rather than glucose to produce energy.

Insulin deficiency also produces an excess of glucagon and stimulates the synthesis of ketone bodies, normally inhibited by insulin. Furthermore, hyperglycemia caused by insulin deficiency produces an osmotic diuresis, leading to marked urinary losses of water and electrolytes. Contrary to, the slow start of a ketogenic diet avoids these side effects.

Moreover, the use of ketone bodies for energy purposes is daily present in physiological conditions, such as morning ketosis and ketosis after exertion or physiological ketosis after a rich meal in proteins.

When the intake of carbohydrates is drastically reduced, for example in the case of fasting,

carbohydrate deprivation or excess exercise, the Krebs cycle reduces oxalacetic acid which is consumed to form glucose and is therefore not available for condensation with Acetyl-CoA.

The oxalacetate, to form glucose, implements gluconeogenesis, the reverse way of glycolysis, that needs oxaloacetic acid which, in the absence of carbohydrates, is used for glucogenesis: this causes an excess of Acetyl-CoA whose polymerization leads to the formation of ketone bodies.

These reactions happen inside the liver.

Acetoacetate and ß-hydroxybutyrate come out of the hepatocytes mitochondria because the liver cannot use them because it does not have the enzyme thiophorase able to split the ketone bodies to be used later. So, once they get out of the hepatocytes, they are used by myocardium, brain and muscle.

Much of the Acetyl-CoA comes from the beta oxidation of fatty acids.

The triglycerides stored in lipid droplets of adipose tissue, are split and the fatty acids enter the liver where they undergo beta oxidation.

The ketone bodies from the liver are transported to the bloodstream where they are partly used by extrahepatic tissues and partly, about 20%, are excreted in the urine or can be decomposed to produce acetone that is excreted via the lungs causing the typical halitosis characteristic of this diet.

At the pancreatic level ketone bodies contribute to metabolic improvement in patients with insulin resistance [12,13].

The "threshold" levels that induce these metabolic mechanisms are glucose intakes less than 20-50 g / day. [14,15].

Ketogenic diet in diabetic patients

Over the past 20 years, several studies have shown that the ketogenic diet improves glycemic control and the glycemic model in patients with type 2 diabetes.

In the literature there are several meta-analyzes that have highlighted the correlation between the ketogenic diet and type 2 diabetes: in one of these the researchers examined the results of 20 randomized controlled studies with over 3,000 subjects, the majority some of whom have had type 2 diabetes.

Although the authors concluded that low carbohydrate, low glycemic, Mediterranean and protein diets should be considered a dietary strategy for diabetes treatment, the low carbohydrate diet has proven to be the best solution.

Overall, the results of the studies showed that low-carbohydrate diets caused a significant reduction in the percentage of HbA1c compared to other diets. In some cases, the reduction of HbA1c was similar to the effect obtained by some drugs to treat diabetes.

In one of the meta-analysis studies, subjects who followed a low-carbohydrate diet also had a greater average reduction in triglyceride levels regardless of whether or not they were taking lipid-lowering drugs; triglyceride levels can also be affected by drugs taken for diabetes. However, in a separate analysis of subjects who did not take either diabetes drugs or lipid-lowering drugs a greater reduction in the average triglyceride level was observed. It has been noted that diets low in carbohydrates, with low glycemic content and the Mediterranean diet have led to significant improvements in blood lipids and in particular to a 1-4% reduction in LDL and a 9% reduction in triglycerides.

This review provides evidence that changing the amount of macronutrients can improve glycemic control, weight and lipids in people with diabetes. Low-carbohydrate, low-glycemic, Mediterranean and protein diets have reduced Hb A1c by 0.12-0.5% compared to comparison or control diets. These reductions in Hb A1c were significant, with a 0.5% reduction similar to that obtained with the use of drugs and associated with a lower risk of microvascular complications.

Low-carbohydrate diets limit carbohydrate intake to 20-60 g / d.

These studies compare low-carbohydrate diets with law fat and low GI diets and found that low-carbohydrate diets seemed to provide higher weight loss, glycemic control and lipid profiles than low-fat diets and, in one of the 2 studies, they were

superior to the low glycemic index diet for all 3 variables. [16]

One of the first studies [17] on this topic, conducted by researchers at Duke University Medical Center in 2005, found the impact of a low-carbohydrate and ketogenic diet (LCKD). These researchers recruited 28 overweight participants with type 2 diabetes for a 16-week trial.

Subjects had an average BMI of 42.2, an average age of 56 and were of African American or Caucasian origin. Participants consumed an LCKD diet with the goal of eating less than 20 grams of carbohydrates per day by reducing the dosages of diabetes drugs; in addition, they also received nutritional counseling and drug therapy adjustment every two weeks.

In the 21 subjects who followed a ketogenic diet and successfully completed the study, the scientists observed a 16% reduction in hemoglobin A1c from the baseline measurement to the sixteenth week. Subjects had an average reduction in body weight of 8.7 kg. Furthermore, their average blood glucose levels decreased by 16.6% overall and their average triglyceride levels decreased by 41.6%.

Overall, most subjects have reduced or suspended diabetes drugs. The researchers concluded that "LCKD can be very effective in reducing blood sugar levels".

In another study [18] carried out in 24 weeks the researchers recruited 97 obese subjects with type 2 diabetes and randomly divided them into two groups. The first group of 46 people, of whom 29 completed the study, received a low glycemic index diet with a deficit of 500 calories / day. The second group of 38 subjects, of which 21 completed the study, followed a low-carbohydrate ketogenic diet with less than 20 grams of carbohydrates per day without calorie limits. Both groups were subjected to identical exercise regimes and had the same access to nutritional coaching and at group meetings. Researchers measured the main diabetes indicators including fasting glucose, body mass index (BMI), body weight (kg) and hemoglobin A1c at the start of the study, at the midpoint (week 12) and at the end (week 24).

Both groups found no adverse effects relevant to their health. In the 29 subjects who successfully completed the low-calorie diet, the researchers observed an average 16% reduction in fasting glucose, a reduction of 2.7 in the BMI and a loss of 6.9 kg of body weight. However, in the 21 subjects who successfully completed the very low-carbohydrate ketogenic diet, the subjects recorded an average 19.9% reduction in fasting blood glucose, a 3.9 reduction in BMI and a loss of 11,1 kg of body weight.

Compared to the low-calorie diet, subjects undergoing the ketogenic diet experienced a three-fold reduction in hemoglobin A1C (1.5% vs. 0.5%). In addition to seeing greater improvements in diabetes-related markers, the researchers observed a greater reduction in the use of drugs in subjects undergoing ketogenic dietary treatment. Therefore, due to their overall results, the researchers claimed that "Changing lifestyles with low-carbohydrate interventions is effective for improving and reversing type 2 diabetes."

Based on existing data in the literature, it is clear that the approach of a ketogenic therapy in type 2 diabetes leads to an overall improvement in the patient, even if today there is still a great deal of aversion towards this type of therapy; To find out if carbohydrate restriction can be considered in the most effective type 2 diabetes diet, you need to have an additional results.

Carbohydrate cutting causes a reduction in diabetes-related biomarkers. In some cases the ketogenic diet was even able to completely reverse type 2 diabetes.

In most of these studies it is evident that caloric restriction improves many of the metabolic problems that contribute to this condition, this is because when an excessive amount of calories is consumed, the body is flooded with various sources of energy. This tends to increase energy consumption, fat accumulation and the production of inflammatory molecules. In the short term, the body has no problem managing the energy inflow.

However, when there is constantly a state of energy surplus, cells will respond by becoming insulin resistant. This happens because the cells are not designed to handle a prolonged excess of energy.

To avoid a cellular disaster, they will begin to ignore the insulin message, causing a further increase in blood sugar levels and insulin levels.

One way to reduce insulin resistance and increase insulin sensitivity is to put the cells in a state of "undernourishment" or energy deficit. Probably the most effective way to do this is to maintain a calorie deficit.

Although eating fewer calories is the simplest approach to reducing insulin resistance. It is often not easy for many patients and an alternative is the ketogenic diet.

By eating more fat and limiting carbohydrates, there is a tendency to increase general satiety which leads to a spontaneous reduction in caloric intake. Along with this, the ketogenic diet also helps lose fat, decrease insulin response to meals and reap the benefits of ketones. [19]

Conclusion

Almost all comparative studies on obese subjects suggest that ketogenic diets are superior to low-fat diets in optimizing insulin levels. A ketogenic diet can improve insulin resistant subjects in the following ways:

- Helps to maintain a calorie deficit by increasing insulin sensitivity
- Helps to reduce body fat, reduces inflammation, and consequently helps reverse insulin resistance
- Decreases the glycemic load, helps regulate blood sugar levels and therefore also the body's necessary insulin
- Stimulates the production and use of ketones.

This can help both directly and indirectly the condition of insulin resistance. In summary, lifestyle modification using diets that reduces carbohydrate intake has led to improved glycemic control, elimination / reduction of diabetic medications and weight loss in overweight and obese individuals with type 2 diabetes 2. The diet containing less carbohydrates, the low carbohydrate and ketogenic diet, are much more effective to improve glycemic control than the low glycemic diet.

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