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THE EFFECTS OF A LOW-CARBOHYDRATE DIET ON OBESITY AND ASSOCIATED COMORBIDITIES

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Abstract

Obesity is undoubtedly one of the leading health problems today. According to some authors, the main cause of obesity is a high intake of carbohydrates. This hypothesis has contributed to the creation of a large number of diets with limited carbohydrate intake, including the keto diet.

Considering the great popularity of this diet and the large number of contradictory attitudes related to it, the aim of this paper is to review the effectiveness of a ketogenic diet in the treatment of obesity and associated comorbidities.

A search of databases (KoBSON, Google Scholar, MEDLINE, PEDro, DOAJ, PubMed) has identified 1197 studies on the relevant topic, and a further application of the set criteria, the final analysis included 37 studies. Using a descriptive and analytical method for processing the selected literature, we found that a ketogenic diet compared to a diet high in carbohydrates and low in fat, leads to initially greater weight loss, but in the long run, later results are equalized.

Moreover, most studies show the positive effects of this diet on the cardiovascular system and lipid profile in terms of lowering systolic and diastolic blood pressure, as well as the values of triglycerides and cholesterol and increasing high-density lipoprotein cholesterol levels. In addition, the results show a positive effect in the treatment of insulin resistance and type 2 diabetes. On the other hand, a ketogenic diet can also lead to vitamin, mineral and dietary fiber deficiencies, electrolyte imbalances, dehydration, increased uric acid and the risk of gout, metabolic acidosis, as well as cognitive impairment.

Overall, the ketogenic diet has its place in diet therapy, but its proper indication and implementation is very important in order to minimize the side effects.

Keywords: keto diet, lipid profile, body composition, metabolic diseases.

Introduction

Obesity is one of the main health issues today, because it reaches epidemic proportions and leads to a large number of cardiovascular, metabolic and other diseases [*Di Angelantonio E et al., 2016*]. According to some authors, the main cause of this phenomenon is a high intake of carbohydrates (CHO), especially the simple ones. Namely, throughout the history, the consumption of carbohydrates in humans was low, especially in the Paleolithic (~ 1,500,000 years). It was only with the advent of agriculture (10,000 years ago) and the industrial revolution (200 years ago) that higher carbohydrate intake was enabled, but these periods are significantly shorter compared to the previous ones, and therefore have little impact on human genetics and still cannot ensure the adequate adaptation to such a diet [*Eaton S, Konner M, 1985; Westman E et al., 2003*].

This hypothesis has resulted in a large number of diets that have limited the intake of carbohydrates (Paleo, Atkinson, Steelman, Dukan, Protein diet, etc.), as well as the Keto diet, which is especially popular nowadays. The keto diet originally began to be used in the 1920s for the treatment of epilepsy [*Kessler S et al., 2011*], but today it is widely used both in the treatment of obesity and in a wide range of different diseases [*Paoli A et al., 2015*]. It is characterized by high fat intake> 70% and low carbohydrate intake (often less than 50 *g/day*). However, the keto diet should be distinguished from a low-carbohydrate diet (LCD). A low-carbohydrate ketogenic diet (LCKD) leads to ketosis, which means increased production of ketone bodies,

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while a low-carb diet (LCD) is any diet that reduced their intake (usually below 200*g*), but it does not necessarily lead to ketosis [*Westman E et al., 2007; Greene DA et al.,2018*]. This way of eating has caused a lot of controversies and polemics, both in the general population and in the academic community. LCKD is glorified and its positive effects in the treatment of obesity, cardiovascular diseases, diabetes, etc. are stated, while on the other hand, the harmful effects are stated and the preferred option is higher carbohydrate content either through today's standard diet or some other also represented directions, such as a vegetarian or vegan diet. Most studies just compare a low-carb diet with a low-fat, high-carbohydrate diet to see the effectiveness of one type of diet over another.

Given the great popularity of this diet and the large number of contradictory attitudes associated with it, the aim of this narrative work is to get the facts straight by reviewing the previous research in a systematic way and in accordance with the physiological and biochemical laws of the human body. The explanations of both the positive and negative functioning of this diet will be provided, in case of obesity and associated comorbidities.

Material and methods

The paper used a descriptive and analytical method, while the following electronic databases were used for collecting the papers: KoBSON, Google Scholar, MEDLINE, PEDro, DOAJ and PubMed. The key words used to find the papers are: keto diet, a diet with low carbohydrate content, obesity, weight loss, body composition, cardiovascular diseases, lipid profile, diabetes, metabolism, ketone bodies.

The titles of the identified studies, their abstracts and whole texts were read and analyzed. The research was conducted by several authors, and the studies were analyzed in detail based on the set criteria.

Inclusion criteria:

•Studies that used a low-carbohydrate diet or a ketogenic diet with a carbohydrate intake of less than 150 *g* per day;

•Studies that have compared a low-carb diet with other diets;

•Studies that have analyzed changes in body composition;

•Studies that followed the changes in the risk factors of cardiovascular and metabolic diseases (lipid profile, glucose, insulin, HbA1c, etc.);

•Studies written in English.

Exclusion criteria:

•Studies in which the intake of carbohydrates on the ketogenic diet was higher than 150 *g*

•Studies not written in English

A search of electronic databases identified 1197 studies on a relevant topic. After further analysis and application of the set criteria, in accordance with the objectives of this study, the final analysis included 37 studies while the additional 33 studies were used for further discussion and explanation.

Theoretical consideration of the problem

Metabolism of ketone bodies

The metabolism of ketone bodies implies their production (ketogenesis) and utilization (ketolysis). In healthy adults, the liver can produce 185 *g* of ketone bodies per day. Most ketone bodies are formed by the breakdown of fatty acids from adipose tissue, most often during starvation or after adrenergic stress. After fatty acids are released from adipose tissue, they go to the liver, where they are transformed by the process of β-oxidation into acetyl-CoA, which can be oxidized in the citric acid cycle or used to obtain ketone bodies. By a further process and action of certain enzymes, three ketone bodies are formed, that is, acetic acid is formed first, followed by beta-hydroxybutyric acid and acetone. Ketolysis is the departure of ketone bodies through the bloodstream to certain organs, where through enzymes they are converted back to acetyl-CoA and thus used as energy [*Sumithran P, Proietto J, 2008*].

Adaptation to ketosis implies the ability of the organism to adapt to the increased amount of production of ketone bodies and their utilization. We can say that if after the initial increase in ketone levels, their value then decreases to medium and low levels, that the body has adapted to ketosis, because it effectively uses ketones as energy sources and for these reasons there are not too many of them in the blood. It usually takes about 2-3 weeks for the body to reach a stable state and optimal values that are between 1.5-3.0 *mmol/L* [*Mitchell G et al., 1995*]. The period of transition to the keto diet is known in the slang as "keto flu" because during this period, symp-

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

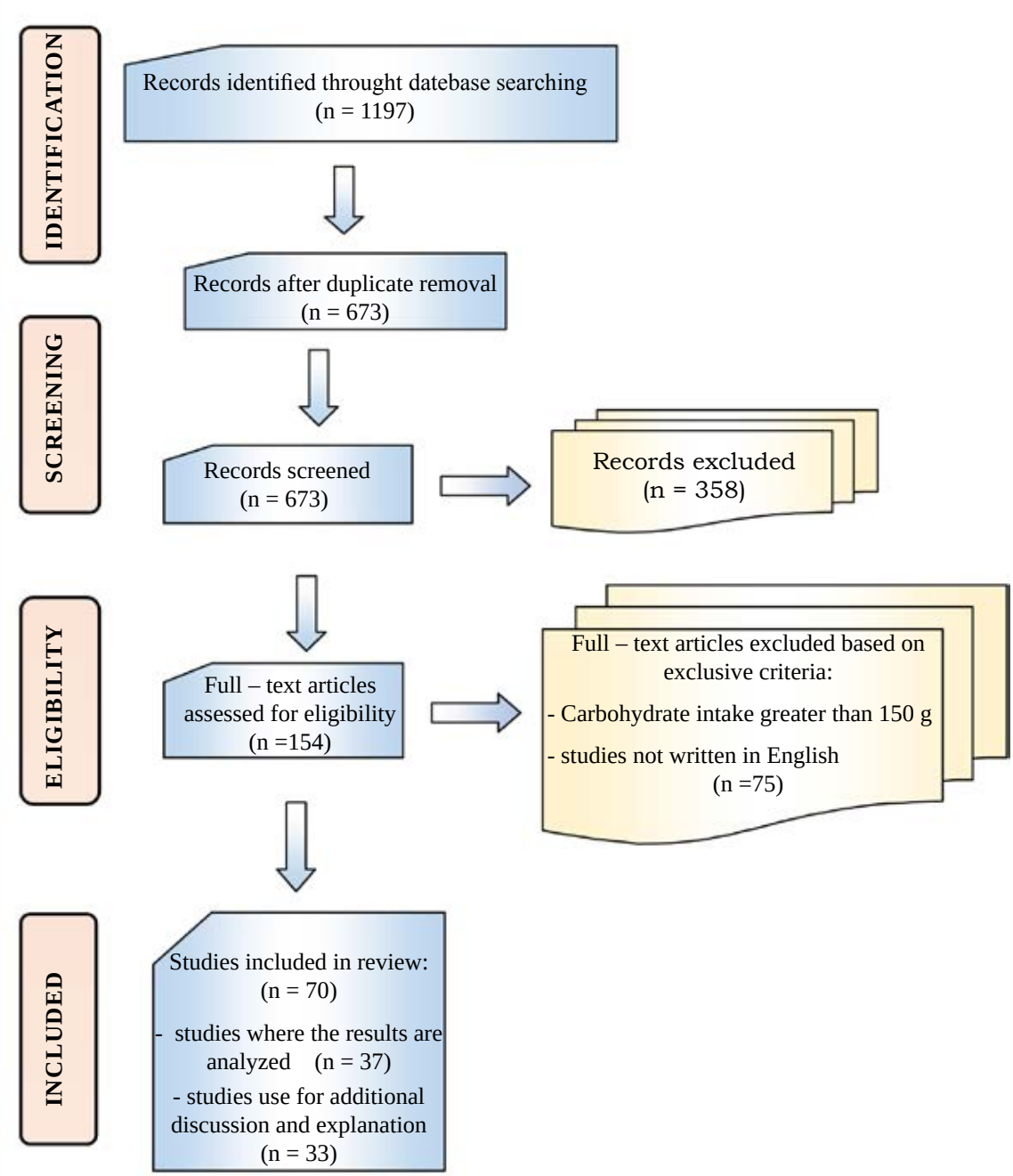

Figure 1. *PRISMA flow chart illustrating the selection process of articles for this narrative review.*

toms such as headache, fatigue, drop in energy and concentration, diarrhea, constipation, etc. are often manifested, but after the adaptation, these symptoms withdraw [*Sumithran P, Proietto J, 2008; Bostock E et al., 2020*].

Restriction of carbohydrates leads to general changes in metabolism by directing it from "glucocentric" to "adipocentric", i.e. there is a reduced use of glucose as an energy source, and increased use of fatty acids and ketone bodies (from dietary fats, proteins and adipose tissue) [*Westman E et al., 2003*]. The tissues for whose functioning glucose is necessary (red blood cells, retina, lens, kidney medulla) obtain it through gluconeogenesis and glycogenolysis. Even though carbohydrates are not ingested at all, the body will produce 200g of glucose per day through the liver and kidneys alone, mostly from amino acids and to a lesser extent from glycerol, pyruvate and lactic acid [*Westman E et al., 2007*]. Also, cells that cannot use fatty acids, such as brain and nerve cells, rely less on glucose and more on ketone bodies [*Westman E et al., 2003*]. The extent to which these metabolic pathways will take place depends on the degree of restriction of carbohydrates. With higher level of restriction, there is lower utilisation of glucose and

higher production of free fatty acids and ketones from adipose tissue.

In addition, there are certain hormonal changes which are reflected in increased levels of testosterone [*Silva J, 2014; Michalczyk M et al., 2019*], growth hormone (GH) [*Johannessen A et al., 1981; Michalczyk M et al., 2019*], insulin-like growth factor 1 (IGF-1) [*Harber M et al., 2005*], adrenaline, cortisol [*Langfort J et al., 1996*], glucagon, and, on the other hand, there is a drop in insulin levels [*Westman E et al., 2003; Volek J, Sharman M, 2004*].

Influence of low-carbohydrate ketogenic diet on weight reduction

It was generally accepted that the effects of diets and thus LCKD as well manifested due to spontaneous caloric deficit, given that it is common knowledge that caloric deficit, regardless through which macronutrient it is achieved, will result in weight loss [*Freedman M et al., 2001*]. However, contrary to this view, a large number of studies have shown that subjects on LCKD, over a period of 3-6 months, lose more weight than subjects on a standard diet [*Foster G et al., 2003; Nordman A et al., 2006*] when caloric intake was balanced [*Brehm B et al., 2003*] or even smaller in the HC (high carb) group [*Samaha F et al., 2003; Greene P et al., 2003*]. For example, in a study by Brehm B. and co-authors (2003), although both groups showed the same caloric deficit, subjects on LCKD lost 8.5 kg and on LFD (low fat diet) 4.2 *kg* over 6 months ($p<0.001$). In a study by Samaha F. and colleagues (2003), the LCKD group lost more pounds than the LFD group over 12 weeks (5.8 vs 1.9; $p<0.05$) although they ingested 54 *Kcal* more per day. These results indicate that LCKD achieves certain metabolic benefits, which contribute to greater weight loss. The initial weight loss is explained by diuresis, which is increased due to the loss of glycogen and ketonuria, which results in greater excretion of water and sodium from the body. About 100 *g* of glycogen is stored in the liver and about 400 *g* in muscle, each stored gram entails 2 *g* of water [*Denke M, 2001*]. In addition, LCKD subjects appear to find it easier to ingest optimal amounts of calories because there is the evidence to suggest that ketone bodies themselves reduce appetite [*Nickols-Richardson S et al., 2005; McClernon F et al., 2007*] and regulate the level of the hormones leptin and ghrelin [*Sumithran P et al., 2013*], and in addition, the large saturating power of protein contributes to the reduction of appetite [*Westerterp-Plantenga M et al., 2009*]. Also, proteins increase thermogenesis, even up to 100% [*Johnston C et al., 2002*], so extra calories are expended on their digestion. Additional calories are consumed due to increased protein metabolism, as well as due to increased fatty acids, which undergo peroxide beta oxidation during which much of the energy is lost in the form of heat [*Veech R, 2004*]. A good deal of energy is also spent on enhanced gluconeogenesis activity, which is estimated to be ~ 400-600 *Kcal* per day [*Fine E, Feinman R, 2004*]. As noted earlier, LCKD results in significantly lower insulin and glucose levels. Decreased circulating insulin levels on LCKD increase lipolysis and decrease lipogenesis, thus allowing most of the weight to be lost from fat deposits [*Volek J et al., 2002; 2021; Volek J, Sharman M, 2004*]. However, with the application of resistance training [*Jabekk P et al., 2010; Vargas S et al., 2018, Vidić V et al., 2021*] and with adequate protein intake (1.2-1.7 *g/kg*) [*Phinney S et al., 1991*] muscle mass can be preserved or even slightly increased [*Volek J et al., 2002*]. An increase in some anabolic hormones (testosterone, growth hormone, IGF-1) also contributes to this. Preserving muscle mass will provide a better body composition, increase the value of basal metabolism and thus enable longer-term and healthier weight loss. However, although LCKD achieves greater effects in the initial months (3-6 months) in the long run (12 months) it is not more effective than a standard diet high in carbohydrates and low in fat [*Foster G et al., 2003; Nordmann A et al., 2006; Bueno N et al., 2013*]. In the work of Foster G. and co-authors (2003) it was shown that during the first 3 and 6 months of the study there was a significant difference in weight loss in favor of LCKD, however this difference did not exist after 12 months. Similar data are found in a meta-analysis from 2006 where after 6 months the average difference in weight loss was -3.3 *kg* more in favor of LCKD, whereas after 12 months this difference was only – 1 *kg* [*Nordmann A et al., 2006*]. Bueno N. and colleagues (2013), in their meta-analysis, have found a similar difference that after 12 months was only - 0.91 *kg* in favor of LCKD. The reduction of ketonuria to basal values, which generally occurs after 6 months, is one of the possible reasons why the effects are not so significant in the long run [*Brehm B et al., 2003*]. There is no clear evidence why this phenomenon occurs, but since it is very difficult to ingest a low amount of carbohydrates over a long period of time, it is possible that subjects spontaneously begin to increase their intake.

Effects of low-carbohydrate ketogenic diet on the cardiovascular system and lipid profile

Obese people have a significantly higher risk of developing cardiovascular diseases such as dyslipidemia, atherosclerosis, hypertension, coronary heart disease, myocardial infarction and similar [*Di Angelantonio E et al., 2016*]. It is generally believed that high fat intake, which is a characteristic of LCKD, can negatively affect certain parameters and risk factors for the development of CVD [*Blackburn G et al., 2001*]. However, most studies show positive results, which are reflected in a reduction in systolic and diastolic blood pressure [*Bueno N et al., 2013; Hu T, Bazzano L, 2014; Castellana M et al., 2019*], a reduction in triglyceride levels [*Nordman A et al., 2006; Sumithran P, Proietto J, 2008; Foster G et al., 2003; Bueno N et al., 2013; Hu T, Bazzano L, 2014; Castellana M et al., 2019*] and total cholesterol [*Hu T, Bazzano L, 2014; Castellana M et al., 2019*], and increasing increasing high-density lipoprotein levels [*Foster G et al., 2003; Nordman A et al., 2006; Sumithran P, Proietto J, 2008; Bueno N et al., 2013; Hu T, Bazzano L, 2014*]. Reduction of blood pressure is a logical phenomenon that follows after losing weight and regulating the lipid profile. It is known, and some recent research has confirmed, that large amounts of carbohydrates, if not consumed for work, are converted by insulin into free fatty acids and triglycerides [*Chiu S et al., 2018; Hoffman S et al., 2019*]. Also, insulin activates a key enzyme that enables the synthesis of cholesterol - HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-CoA reductase) [*Paoli A et al., 2013*]. Therefore, decreased triglyceride and total cholesterol levels are most likely associated with decreased circulating insulin levels. However, on the other hand, meta-analysis [*Nordmann A et al., 2006*] shows a greater reduction in total cholesterol on LFD, while [*Foster G et al., 2003*] even noted an increase during the first 6 months. In addition, a large number of studies show an increase in LDL during LCKD [*Foster G et al., 2003; Bueno N et al., 2013*], which is a phenomenon of most concern. However, during weight loss there may be a temporary increase in cholesterol, due to increased mobilization of its adipose stores [*Phinney S et al., 1991*], therefore an increase in LDL on keto diets indicates increased fat metabolism, as well as their utilization as energy substrate, because LDL supplies cells with fat. It was in the work of Foster G. and co-authors (2003) that total cholesterol gradually increased during the first 6 months, then gradually decreased for the next 6 months, while LDL increased sharply during the first 3 months, and then gradually decreased in the following months. In addition, some studies show that on a low-carbohydrate diet, the size of LDL particles increases and the number of LDL particles decreases (which is a positive phenomenon) [*Wood R et al., 2006; Krauss R et al., 2006*]. The diameter and number of LDL particles is a better indicator of the risk of developing CVD compared to the amount of LDL [*Mora S et al., 2010*]. In addition, Gardner C. and colleagues (1996) have shown that small, dense LDL particles and the ratio of triglycerides to high-density lipoprotein are in fact the best predictor of CVD. Since LCKD has a beneficial effect on the value of triglycerides and increasing high-density lipoprotein, it is expected that their relationship will improve. Another concern regarding the LCKD diet is the high intake of saturated fats. However, Siri-Tarino P. and co-authors (2015) in their meta-analysis, which included monitoring 347,747 subjects from 5 to 23 years, show that the use of saturated fats is not associated with an increased risk of cardiovascular and other diseases. However, the use of trans fats is associated with these conditions [*De Souza R et al., 2015*]. Therefore, the increased intake of saturated fats in the keto diet should not be a cause for concern; however, it is desirable to take care of their method of preparation.

Low-carbohydrate ketogenic diet and diabetes

Most scientific studies show that the ketogenic LCKD diet has beneficial effects on people suffering from prediabetes or diabetes by regulating glucose and insulin levels, reducing their fluctuation, improving insulin sensitivity and contributing to weight loss [*Boden G et al., 2005; Arora S, McFarlane S, 2005; Accurso A et al., 2008; Vidić V et al., 2021*]. In addition, it results in a reduction in medication intake, which in turn reduces the possibility of their side effects (Accurso et al., 2008). Such changes further reduce the risk of CVD. In a study by Boden G. and co-authors (2005), administration of LCKD (<20*g* carbohydrate daily) for 2 weeks to patients with DM2 (diabetes mellitus type 2) resulted in a decrease in glucose levels from 7.5 to 6.3 *mmol/L* and HbA1c from 7.3 to 6.8%, as well as an improvement insulin sensitivity by 75%. Also, long-term use of LCKD for 56 weeks resulted in the regulation of glucose levels, as well as a reduction in cholesterol, triglycerides and body weight, in obese people with DM2 [*Dashti H et al., 2007*].

However, certain authors believe that the effects of LCKD are primarily due to weight loss, and not necessarily due to a reduction in carbohydrate intake. Westman E. and colleagues (2007) published a thematic review of the metabolic effects of the LCHF diet and concluded that they lead to a decrease in appetite and consequently to weight loss and thus lead to an improvement in various risk factors for cardiovascular and metabolic diseases. Certainly, the reduction of excess body weight will have a positive effect on the amount of glucose and insulin, but there are also studies that show that the effects of LCKD are independent of weight loss and that they are associated with restriction of carbohydrate intake. In a study where subjects with DM2 administered LCKD and kept their weight stable, there was a significant drop in HbA1c from 8.1 to 7.3%, compared with the group with high carbohydrate intake [*Sheard N et al., 2004*]. In another study, although LCD and HCD (high carb diet) resulted in equal weight loss, in the LCD group lower values of glucose, insulin and HbA1c were recorded (7.6 +/- 0.3 vs 9.8 +/- 0.5%) [*Gannon M et al., 2003*]. These results show that LCKD achieves metabolic effects independent of weight loss, which have a beneficial effect on people with prediabetes or diabetes. This is not a surprising phenomenon assuming that increased ketone levels lead to a proportional drop in glucose and insulin levels [*Paoli A et al., 2013*]. But, although previous studies show positive effects, certain studies still show that these effects are not more significant in the long run than those achieved with a standard low-fat diet (LFD). Stern et al (2004) find that the effects of LCKD are present over a period of 6 months, but that they are not different after 1 year, when compared to LFD. Also, the authors found a significant improvement in insulin sensitivity after 6 months, but not after 1 year [*Forster G et al., 2003*]. In another study, a short-term decrease in HbA1c was observed after 6 months, but this decrease was not maintained after 24 months [*Iqbal N et al., 2010*]. As mentioned earlier, a decrease in ketonuria due to a spontaneous increase in calories and carbohydrates is one of the possible reasons why the effects are not so significant in the long run [*Brehm B et al., 2003*]. Also, in people with diabetes, some negative effects that LCKD can cause have been noticed, such as deficiency of vitamins, minerals, dietary fiber, irregularity in the balance of water and electrolytes, etc. [*Czyzewska-Majchrzak L et al., 2014*]. Also, in people with type 1 diabetes, increased ketone levels can lead to complications and ketoacidosis, which can end in death [*Kanikarla-Marie P, Jain S, 2016*]. What also contradicts the aforementioned findings is the fact that a large number of studies show that a diet high in carbohydrates is also effective in the treatment of diabetes [*Simpson H et al., 1981; Komiyama N et al., 2002; Jung C, Choi K, 2017*]. Positive effects have also been shown in the treatment of type 1 diabetes [*Rosenfalck A et al., 2006*]. Also, a vegan diet, which is rich in carbohydrates per se, showed better results in the serum glucose and lipid profile compared to the standard diet used in the treatment of diabetes [*Barnard N et al., 2009*]. The results of these studies are explained by increased intake of integral and healthy sources of carbohydrates with low values of glycemic index and glycemic load, as well as increased intake of dietary fiber, which are all factors that contribute to insulin and glucose levels [*Brouns F, 2018*].

The quality, not the amount of carbohydrates, seems to be a key aspect to consider, and therefore we cannot generalize the hypothesis that high carbohydrate intake is a major cause of diabetes. We can say that in relation to the standard diet, LCKD is equally effective in the treatment of diabetes, but it is necessary to take into account the negative effects that may occur, especially in people with type 1 diabetes.

Side effects

In addition to the positive effects we mentioned in the paper, the literature often cites some side effects which may be manifested, such as vitamin, mineral, dietary fiber deficiency, electrolyte imbalance and dehydration [*Czyzewska-Majchrzaket L et al., 2014*], hypokalemia, hypomagnesaemia, gout (due to high protein intake) [*Westman E et al., 2003*], metabolic acidosis, cognitive and mental disorders [*Sumithran P, Proietto J, 2008*], ketoacidosis, etc. [*Kanikarla-Marie P, Jain S, 2016*]. Also, certain side effects of LCKD are more common compared to a low-fat diet: constipation (60% vs. 40%), halitosis (38% vs. 8%), muscle cramps (35% vs. 7%), diarrhea (23% vs. 7%), general weakness (25% vs. 8%) and rash (13% vs.0%) as shown in a study which was performed on 119 obese individuals [*Yancy Jr W et al., 2004*]. However, with a proper diet with reduced carbohydrate intake, these effects can be controlled and eliminated in a timely manner, which is why in 2008 the IKDCS (International Consensus on the Use of Ketogenic Diet) was adopted, which states how certain side effects can be treated, prevented or remediated

[*Bergqvist A, 2012*]. Generally high fiber intake through salads and salad vegetables, sufficient fluid intake, increased intake or supplementation of certain vitamins and minerals (potassium, magnesium, sodium) should be procedures that will ensure the safe use of a ketogenic diet.

Conclusion

LCKD is more effective in the short term than other types of diet, and in the long term it is equally effective in the treatment of obesity and associated comorbidities, and its proper implementation can prevent and eliminate potential side effects.

Key items

A diet low in carbohydrates or ketogenic diet compared to a diet high in carbohydrates and low in fat, leads to greater initial effects in weight loss, however, in the long run in most studies there is the same trend of equalization of results;

Most studies show the positive effects of this diet on the cardiovascular and lipid profile, which are reflected in reduced levels of systolic and diastolic blood pressure, triglycerides, cholesterol and increased high-density lipoprotein.

In certain cases there is an increase in LDL cholesterol, but on the other hand, there is also a decrease in small dense LDL particles and an increase in their diameter. Therefore, we believe that without monitoring other parameters, LDL alone cannot be associated with an increased risk of CVD;

LCKD shows significant effects in the treatment of prediabetes or diabetes, but in the long run the effects of this diet are not significantly greater than standard diets.

Increased intake of saturated fatty acids in the keto diet should not cause concern, but it is desirable to take into account the method of food preparation;

By following a proper diet, it is possible to prevent or eliminate side effects that may occur.

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