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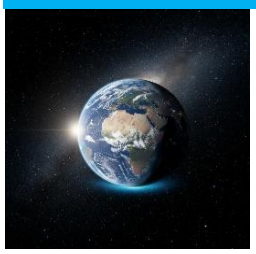

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Ketogenic Diet Overview: Downsides May Outweigh Benefits

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ABSTRACT

Introduction: Due to the growing problem of high mortality and incidence of civilization diseases, including metabolic syndrome and obesity, there is an urgent need to find effective ways to prevent it. The purpose of this study was to review the effects of a ketogenic diet on particular systems and organs, as well as to analyze possible associated risks.

Methods: Systematic review and current research about the impact of Ketogenic Diet to different systems was made. Authors wanted to highlight pros and cons of conveying this type of nourishment.

Results: Consequently, there has been an increased focus on a healthy diet. Mass media allow access to abundant information on the purported beneficial effects of various diets, whether it is a weight loss diet, a cleansing diet, or a diet aimed at supporting the functioning of individual organs. The Ketogenic Diet is one of the most frequently used nowadays. It significantly reduces carbohydrate intake to just 5-10% of the total calorie consumption in favor of approximately 55% to 60% fat intake. According to previous research, we should emphasize the fact that conducting this type of diet can reveal many side effects.

Conclusion: Despite the advantages of the diet for people suffering from obesity and diabetes mellitus type 2, for most individuals it results only in temporary improvements and an increase of unfavorable effects. Overall, according to our research, the risks of the ketogenic diet might outweigh its benefits. The Ketogenic Diet is an example of a nutrition trend that should not be used on such a large scale.

KEY WORDS

ketogenic diet, low-carbohydrate ketogenic diet, metabolic diseases, diabetes mellitus, insulin resistance, obesity,

Introduction

In 1921 Russel Wilder coined the term “ketogenic diet” (KD) and started to use it as epilepsy therapy, especially among the pediatric population. The medical world has accepted this method of treatment and for almost ten years it has been used to treat children [1]. Before this discovery a pair of Parisian physicians treated epilepsy using starvation – it was the first time that somebody connected diet with disease [2]. Nowadays such methods are not popularly applied as the main treatment because of the introduction of efficient antiepileptic agents [3]. After a few decades the topic of the ketogenic diet caught scientists’ attention again and started to be an object of research. In 1972 Dr. Atkins released a book which promoted a ketogenic diet for weight loss and popularized it widely [4]. Since then, public interest in this diet has been growing for 50 years. We should be aware of the fact that the ketogenic diet is considered fashionable and is promoted by bloggers and nonscientists. This group of people may not be aware of the adverse effects, nutritional deficiencies and metabolic changes caused by this way of nutrition [5].

Aim

The aim of this study is to demonstrate the advantages and disadvantages of the ketogenic diet among patients either with or without metabolic diseases. Many previously published studies were short-term only, and longer studies are needed to show potential side effects.

Definition

A ketogenic diet (KD), also called a low carbohydrate ketogenic diet (LCKD), essentially involves consuming high fats, moderate proteins, and very low carbohydrates – below 50 g per day. Thanks to the advantages of fats, nutritional ketosis is achieved. Urinary ketone levels are often used as an indicator of dietary adherence. In the KD dietary macronutrients are usually divided into approximately 55% to 60% fat, 30% to 35% protein, and 5% to 10% carbohydrates. The ketogenic diet is a reversal of the current food pyramid supported by the

dietary guidelines [6]. This diet is mainly composed of animal fats and proteins along with very small quantities of carbohydrates from plant foods. Typically, when implemented in scientific studies, the KD restricts consumption of carbohydrates to <50 g per day with varying amounts of fat and protein [7]. Restriction in carbohydrate intake below the recommended 130 g/day, named a low-carbohydrate diet (LCD), is not sufficient to change the main fuel of the body from carbohydrates to fats and cannot cause nutritional ketosis [8]. Ketogenic diets have proved to be effective in promoting weight loss, improving glucose metabolism and insulin action, and reducing cardiovascular disease, but patients should be aware of the potential risk and long-term effects, which are not fully known [9].

Metabolic changes

Due to lower intake of carbohydrates in the KD there are many metabolic changes such as lower blood glucose level and a shift in insulin level. For this reason there is a turnabout from a state of storing fat to a state of fat oxidation. The organism changes the primary source of energy from glucose to fatty acids – beginning the production of ketone bodies in the liver in a process called ketogenesis [10]. There are three main ketone bodies produced and utilized as the source of energy during ketosis: acetone, acetoacetate and β-hydroxybutyrate. Furthermore, research has shown that β-hydroxybutyrate plays a role as a signal molecule and may function as a suppressor of appetite [11]. All cells which have mitochondria, including the brain and muscle, can leverage energy from ketone bodies [12]. A large side effect at the beginning of KD, named “keto flu,” takes place when the organism changes its main source of energy from carbohydrates to fats. The commonest symptoms, including fatigue, headache, nausea, dizziness, "brain fog", gastrointestinal discomfort, decreased energy, feeling faint and heart beat alterations, may continue for 4 weeks [13]. It is important to emphasize that consumption of processed and high fat meat contributes to obesity and insulin resistance and increases the risk of colorectal cancer [14]. Increasing morbidity is influenced not only by dietary patterns which can cause obesity but also lifestyle [15]. Furthermore, a ketogenic diet is a type of diet in which patients are suggested to restrict carbohydrate intake; hence they consume low amounts of fruits and vegetables, which are rich in fiber. Apart from fiber intake, fruits and vegetables supply a huge number of bioactive compounds, such as vitamins, minerals, folate, plant sterols and protease inhibitors. Many of them have potential antioxidant and anti-inflammatory effects, which could counteract DNA and cellular damage [16].

Therefore, the lack of these ingredients may result in negative consequences.

Diabetes and obesity – pros and cons of the ketogenic diet

Patients with type 2 diabetes mellitus (DM2) demonstrate metabolic abnormalities such as these in glucose level, lipid profile and glycation of proteins. In the course of DM the levels of low-density lipoproteins (LDLs) and very low-density lipoproteins (VLDLs) grow and the level of high-density lipoproteins (HDLs) decreases. These changes can lead to higher risk of heart attack and stroke [17]. Another problem which can cause complications is glycation of proteins. A measurable parameter of this process, HbA1c, is a significant indicator of glycemic control and the level of oxidative stress. Research has revealed convincingly that dietary carbohydrate restriction may improve HbA1c and be conducive to reduced development of diabetic complications [12]. There is a tendency in DM2 to coexist with obesity, and we should investigate these problems together. Thanks to other surveys we know that dietary choices have a major impact on both diabetes and obesity. Some authors have suggested that the most appropriate and effective way of dealing with DM is glycemic and weight control using a ketogenic diet (KD) [18]. Ketone bodies, which are produced from fats in the liver in a process called fat oxidation, have appetite suppressive and diuretic effects. A high level of fats in the organism retards the digestive processes, which can have an appetite suppressive effect. Furthermore, under the KD patients can lose weight thanks to the alteration in the main fuel for cells from carbohydrates to fats, which promotes fat loss [19]. On the other hand, guidelines of the Polish Diabetes Society from 2022 presented other recommendations concerning the most advised proportions of macronutrients. They claim that reduction of weight can be achieved through diets with a reduced caloric value and various proportions of macronutrients, but long-term diets with significantly reduced carbohydrate intake are not recommended. The percentage share of fat should be the same as in the diet applied by people without diabetes and may range from 25% to 40% of the energy value of the diet [20].

Benefits of the ketogenic diet in cardiology

The beneficial effects of the KD on cardiovascular parameters have been emphasized for many years. Factors such as body weight, HDL, LDL, triglyceride levels, and blood pressure are frequently analyzed. Santos et al. observed that KD has a positive effect on these

parameters, but the study was conducted for a short period of time, which limits its applicability [9], [21]. In studies on various types of diets, the positive effect of a carbohydrate restricted diet on decreasing triglyceride levels and increasing HDL cholesterol levels is often accentuated. An analysis by Nordmann et al. showed a reduction in triglycerides and an increase in HDL cholesterol in subjects following a low carbohydrate diet (LCD) for six months compared to those following a low fat diet (LFD) [22].

Hypertension (high blood pressure), found in approximately 40% of the world's population, is a component of the metabolic syndrome and a risk factor for heart disease, chronic kidney disease, and stroke. For this reason, it is still of interest to clinicians [23]. In addition to pharmacological treatment, dietary recommendations such as increasing the proportion of fruits and vegetables in the daily diet and limiting the intake of sodium, red meat and sugary drinks, also play an important role. Until now, no randomized trial has been conducted that has unequivocally demonstrated a relationship between KD and lowering blood pressure values. The available studies included people in specific categories such as morbidly obese, which makes it difficult to analyze for people not struggling with excessive obesity. It is undeniable that fat mass reduction and body weight control have a positive effect on BP values. In an analysis of 13 randomized trials conducted in 2009 by Hession et al. data on LCD and LFD were compared. There were differences in favor of LFD in parameters such as systolic blood pressure (SBP) (mean difference in SBP was 2.19 mmHg ($p = 0.05$)) and diastolic blood pressure (DBP) (mean difference DBP was 0.76 mmHg ($p = 0.37$)) [19]. In another analysis conducted in 2012, including 17 studies (6 papers followed the principles of the ketogenic diet and the remaining 11 papers were based on other diets with limited carbohydrate supply) involving 1141 patients struggling with obesity, a positive effect of a LCD on blood pressure was observed. They reported lower values for systolic blood pressure by 4.81 mmHg and for diastolic blood pressure by 3.10 mmHg. At the same time, an improvement in lipid indices with an increase in HDL concentration was obtained [21]. Ketone bodies take part in a number of metabolic reactions and are also used by the heart muscle, which is their biggest consumer per unit mass [24]. It has been demonstrated that β-hydroxybutyrate reduces heart rate, sympathetic nervous system activation and total energy expenditure (TEE). In addition, it has anti-inflammatory effects by blocking the NLRP3 inflammasome [13]. An interesting observation is the increased oxidation of ketone bodies by the failing heart, which may suggest

that this is how the heart deals with reduced energy production in order to provide itself with sufficient energy to maintain efficient functioning. These observations may provide an opportunity to use ketone bodies in supporting the failing heart, but for this to be possible, further research on this issue is needed in the future [3],[25].

Disadvantages of the ketogenic diet in cardiology

In a study conducted by Nordman et al., in addition to the increase in HDL and decrease in triglycerides, an increase in total cholesterol and LDL was observed simultaneously in subjects on the KD. This may raise the suspicion that restricting carbohydrate intake promotes the development of atherosclerosis [22]. It is believed that this process is influenced by the inhibition of insulin production in response to reduced carbohydrate supply, which leads to the activation of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and HMG-CoA lyase involved in the production of ketone bodies. These findings, together with the possible negative influence of diet on endothelial function, make experts cautious in formulating opinions about the long-term effects of diet on cardiovascular function [26]. It is worth mentioning that the overall health effects are influenced not only by the amount and type of carbohydrates consumed, but also by the source of provided proteins and fats. Fung et al. demonstrated that an LFD with plant-based fats compared with a KD based on animal fats may be associated with a reduced risk of cardiovascular mortality. It is important to consider, therefore, that the increase in LDL concentrations during the KD may also be related to the type of fat consumed [3]. Despite numerous positive reports on the effects of β hydroxybutyrate (β-OHB), there are also negative opinions regarding its safety for the cardiovascular system. Increased levels of this ketone body in cardiac tissues have been observed in patients with atrial fibrillation [27]. Additionally, an association between high β OHB concentrations and adverse cardiovascular events has been found in hemodialysis patients [28]. A study conducted by Xu et al. in rats showed that long-term KD use can negatively affect the cardiovascular system by exacerbating cardiac fibrosis. High concentrations of ketone bodies contribute to the reduction of mitochondria, which in cardiac cells account for up to 30% of total cellular content. Although the possibility of cardiac fibrosis in rats due to elevated β-OHB concentrations has been demonstrated, the authors of this study point out that there are many additional issues that still need to be clarified before definite conclusions can be drawn [2]. These reports should prompt clinicians and patients to consider the appropriateness of long-

term KD use. Experts from the American College of Cardiology emphasize that based on the results of randomized trials, long-term use of KD should be approached with caution, as this diet promotes consumption of animal protein and dairy products while limiting consumption of fiber and fruits containing polyphenols, which have a protective effect on the heart [29]. Data regarding an association between dietary carbohydrate restriction and premature death from any cause and from ischemic heart disease, cancer and cerebrovascular disease were presented in 2018. The study included 24,825 participants in the U.S. National Health and Nutrition Examination Survey (NHANES) trial from 1999 to 2010. It showed that those who consumed the lowest amount of carbohydrates had a 32% higher risk of death from all causes over 6 years of follow-up, compared with those who consumed the highest amount of carbohydrates. In addition, the risk of death from coronary heart disease, cerebrovascular disease, and cancer was significantly higher (by 51%, 50%, and 35%, respectively). Admittedly, patients analyzed in the trial consumed more carbohydrates than allowed by the KD (on average about 200 g/day for more than 6 years), but the results suggest that restrictive diets used for a long time may have serious health consequences [30].

Ketogenic diet – impact on kidneys

The impact of the KD on the kidneys is not entirely unequivocal. Although there were high hopes associated with high-protein diets, including the KD, the research is inconclusive [31],[32]. It is essential to analyze the patient's condition and kidney function, and afterwards select the appropriate caloric content of the KD, or consider its complete exclusion.

In healthy patients, generally very-low-calorie diets do not seem to affect the kidneys negatively. Even in patients with mild stage CKD (glomerular filtration rate [GFR]>60) the improvement of markers of glomerular filtration has been noted[33]. Friedman et al. conducted a small clinical study on six obese patients with advanced diabetic nephropathy (GFR<40) and urinary albumin excretion >30 mg/day. Patients were subjected to a 12-week-long ketogenic weight reduction diet, which led to a reduction of the albumin excretion rate (by 36%) and filtration markers: serum creatinine (3.54 vs 3.13 mg/dl) and cystatin C (2.79 vs 2.46 mg/l). These results, in such a short-term clinical trial, showed a decrease in kidney disease progression, especially in advanced diabetic nephropathy [34]. Likewise, A. Bruci et

al., following a clinical trial, reported normalization of glomerular filtrate in 27.7% of obese patients with mild renal failure after a KD [35]. Considering the diabetic nephropathy, the research on diabetic mice conducted by I. Tomita et al. showed that a diet rich in 1,3-butanediol reduced albuminuria, apoptosis and interstitial fibrosis. Interestingly, 1,3-butanediol is converted to β hydroxybutyrate, one of the ketone bodies, which suggests that a KD can effectively reverse diabetic kidney disease [16], although these findings require further research.

Nonetheless, patients in the advanced stage of kidney disease may develop disease progression on a KD [36],[37]. There are studies demonstrating that animal protein, the basis of many ketogenic diets, could increase the risk of developing chronic kidney disease (CKD) [36], [38]. Considering the high animal (saturated) fat consumption in the KD, of equal concern is an increased risk of albuminuria and GFR decline. Worth attention is also the fact that the KD causes hypercalciuria and hypocitraturia. Low urinary citrate excretion (less than 320 mg/day), which inhibits crystal growth and aggregation, leads to urolithiasis and metabolic acidosis [39], [40]. Ketone production in the KD has a close association with the absence of alkali found in foods often excluded from the diet, such as fruits, vegetables, and whole grains. These can also contribute to development of metabolic acidosis, which can have a negative impact on cellular function and contribute to increased morbidity and mortality [36]. In patients suffering from CKD, high acid load has been considered as a risk factor of end stage kidney disease [41], and accordingly, N. Goraya et al. reported that alkaline food consumption is related to delayed progression of CKD [42].

Brain effects of ketogenic diet

It has been demonstrated that the KD, which is a simple and affordable diet, has several advantageous effects on the central nervous system (CNS). These are neuroprotective, antioxidant and anti-inflammatory properties. The brain is known to require a high amount of energy to maintain its functions. In healthy brain tissue glucose is a fundamental substrate to produce usable ATP in the mitochondria. The KD changes the energy balance in the human brain, resulting in the use of ketone bodies as the main source of energy. Interestingly, compared to glucose, ketone bodies (especially beta-hydroxybutyrate) have higher efficiency in energy production (ATP) per gram of oxygen [43]. The impact of the KD on neurotransmitter changes has also been noted. The increase in GABAergic transmission that

causes anxiolytic effects is the primary reason why the KD has been recommended in epilepsy treatment, increasing the sensitivity to anticonvulsant medications. Several studies and meta-analyses proved that nearly 50% of patients with epilepsy on the KD experienced a decrease in seizures, and the effects remained after discontinuing the diet [43]. Dietary patterns also have a huge impact when it comes to modulation of the immune system. The regulation of neuroinflammatory processes is important in the pathogenesis of Alzheimer's disease (AD) and progression of neurodegeneration[43]. The survey showed that AD, diabetes, obesity, insulin resistance, and cardiovascular disease are powerfully interconnected pathologies. Low intake of saturated fats, proteins derived from animals and refined sugars can decrease the risk of neurocognitive impairments such as AD [20]. Unfortunately, in the KD intake of nutrients and saturated fats of animal origin constitutes a significant part of daily food intake [5] and may have potential long-term side effects.

Conclusions

As history shows, the KD has been a focus of interest for researchers in various medical fields for many years. As studies have demonstrated, the KD, due to its low carbohydrate content, can help control and treat diabetes. At the same time, weight loss results in more favorable cardiovascular parameters such as lowering blood pressure and improving lipid profile. Like any diet, the KD with strong carbohydrate restriction has its drawbacks. In addition to unpleasant initial symptoms such as headaches, dizziness, and gastrointestinal upset, the shortage of fiber and vitamins from fruits and vegetables is also a concern. In animal studies it has been shown that chronic use of the KD can increase myocardial fibrosis and its effect on the endothelium is not negligible. Increased levels of total and LDL have been observed in patients following a KD, which is important in the context of the development of atherosclerosis. High protein intake and exclusion of fruits and vegetables from the KD may lead to hypercalciuria and hypocitraturia. They also increase the formation of kidney stones and cause metabolic acidosis. Low citrate levels and decreased urinary excretion of citrate additionally facilitate crystal formation and the development of urolithiasis. On the other hand, the suggested beneficial effects of the KD on central nervous system function are an area to explore in treatment of epilepsy and Alzheimer's disease. Based on the above arguments, clinicians should always consider each patient individually when thinking about starting a KD and take into account the patient's comorbidities as well as the duration of the diet to limit

possible side effects.

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Conflict of interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.