REVIEW

KETOGENIC DIET: BENEFITS VS UNWANTED EFFECTS - A SHORT REVIEW

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ABSTRACT

Since the introduction of ketogenic diet as a successful epilepsy treatment in the 1920s, researchers showed a continously elevating interest in the therapeutic use of this alimentary regimen even for other non-neurological conditions. Almost a century later, it is known that the ketogenic diet has many other beneficial effects, so that it can surely be used as either stand-alone or adjuvant therapy in several illnesses. We found that there is a long list of benefits regarding the ketogenic diet, both in neurological diseases such as epilepsy and Parkinson's disease, as well as in non-neurological conditions such as type 2 diabetes mellitus. We discussed about each potential therapeutic use of the alimentary regimen, also considering whether there is sufficient evidence or further studies are needed.More beneficial effects of the ketogenic diet were found during our research than adverse reactions. However, even the low likelihood of an unwanted effect to appear makes the risk assessment for each individual patient reasonable. Our aim was to identify what therapeutic uses the ketogenic diet has and also the adverse effects that can diminish the adherence and compliance of the patients related to this alternative treatment. Thus, our study consists of a literature review.

KEYWORDS: *ketogenic diet, therapeutic use, adverse effects*

INTRODUCTION

Ketogenic diet is an alimentary regimen that has been first introduced for almost a hundred years in the therapy of pediatric epilepsy, as an alternative treatment regarding the manangement of refractory epileptic patients [1]. A century later, as it still is a successful option in treating this neurological disease, there is a constant elevation in the number of studies that involve not only the benefits, including the non-neurological ones, but also the unwanted effects of this still mysterious diet.

Despite the important elevation in terms of worldwide consumption of proteins [2] and in protein-based diets, too, the ketogenic diet is defined as a high-fat and low-carbohydrate intake, which aims for inducing system ketosis, which is an increase in the levels of ketone bodies in the blood [3]. Therefore, it is defined as a radical change in diet, meaning that one must ingest only a tiny amount of carbohydrates, with a 4:1 ratio of fats to carbohydrates and proteins [4].

The principle of inducing ketosis is based on the ability of one's organism to adapt to glucose deprivation. Central Nervous System (CNS) utilizes glucose as its main energy source, which mostly originates from the dietary intake of carbohydrates. After several days of fasting, CNS will only be able to properly function if it finds an alternative energy source. Giving the

fact that fatty acids are unable to cross the blood-brain barrier (BBB), and therefore cannot be used instead, the actual available option will be the use of ketone bodies, a group of three compounds: beta-hydroxybutyric acid, acetoacetic acid and acetone [5].

It has been proven that elevation of ketone bodies levels in blood and therefore in brain, correlated with a low glucose usage can reduce neuronal excitability, which explains the benefits regarding epileptic seizure control [4]. This is only an example regarding the usability of ketogenic diet as a stand-alone or adjuvant therapy and opens a great interest in finding the other effects that could increase its therapeutic potential.

Considering the fact that in the last decades there was a continously elevated curiosity related to the ketogenic diet, we aim to identify which the beneficial effects of this regimen are and also the unwanted outcomes that could, at least theoretically, reduce the use of it.

MATERIAL AND METHODS

Our study was conducted as a literature review. We used several electronic databases: PubMed, Elsevier ClinicalKey, Cochrane Database of Systematic Reviews and Elsevier Scopus. The articles were searched using MeSH (Medical Search Heading) indexed term combinations of the keywords ("ketogenic diet") AND ("therapeutic use") AND ("adverse effects"). All papers were published between 2008 and 2016, with the exception of one study that was published in 2005. After searching using this search formula and filtering the results, we obtained 24 papers.

RESULTS

1. Benefits

Epileptic seizures. The first therapeutical use of the ketogenic diet was the treatment of epilepsy in pediatric patients and dates for almost a century [1]. Meanwhile, the use of this high fat regimen has been extended for all ages, hence new studies also include adolescents and adults [6].

Regardless of age, the ketogenic diet has good impact on seizure control. A systematic review found that in children, there are short to medium term benefits, which is comparable to the efficacy of modern antiepileptic drugs [7]. Another study revealed that the ketogenic diet is proven to be efficient in pharmacoresistant childhood epilepsy, which accounts for more than 30% of the patients. Even if neurosurgical techniques come in help for these patients, there will always be a number of patients that lack control of their symptoms, regardless of surgical treatment and this is where the ketogenic diet is introduced for its therapeutic effects [8]. There is an explanation for the beneficial effect of the ketogenic diet on epilepsy: ketone bodies and more importantly glucose reduction can lower neuronal hyperexcitability [4]. However, many patients found the diet difficult to initiate, compared to the Atkins diet, which has similar benefits in treating epilepsy and it is also less restrictive [7].

Weight reduction. Another application of the ketogenic diet is as a weight-loss therapy. It has been proven that a well-formulated ketogenic diet is correlated to a significant improvement not only in weight loss, but also in some metabolic parameters [9]. A meta-analysis of randomized controlled trials confirms that the use of ketogenic diet decrease body weight. Moreover, individuals that use this regimen achieve a greater reduction in weight than those who use a conventional low-fat diet [10] or a hypocaloric regimen [11].

Type 2 Diabetes Mellitus. As the pathophysiology of type 2 diabetes (D2) is centered on insulin resistance and the signs and symptoms of this pathology are an outcome of this "carbohydrate intolerance", the use of a ketogenic diet, which means a low-carbohydrate intake, make the clinical aspects of D2 to improve or often disappear [9]. In addition, patients that suffer from D2 and use a ketogenic diet experience beneficial effects on many parameters related to this pathology, such as blood glucose level, glycosylated hemoglobin, triglycerids, uric acid, body mass index and waist circumference. The results are even more significant than for D2 patients who use a low-calorie diet [12]. Laboratory studies on animal models assessed a reverse in some diabetic complications such as diabetic nephropathy and also a remarkable reduce in blood glucose both in type 1 and type 2 diabetes [13].

Acne. There could also be a potential therapeutic use of ketogenic diet on acne [14]. Considering multiple studies that involve this dermatological condition, there is a hypothesis that it is also linked to certain food types, mostly the ones with a high glycaemic load. As the ketogenic diet is a low-carbohydrate regimen, there could be an influence in skin quality, as well as in progression and severity of acne. Though, randomized clinical trials are needed to confirm this theory, as the actual results are not yet conclusive [9].

Pain. As previously mentioned, ketogenic diet can reduce neuron excitability. The mechanism of chronic pain is also based on hyperexcitability of neurons and this is the basis of another theory regarding therapeutic use of ketogenic diet: as a hypoalgic treatment [15]. Results from studies conducted on laboratory rats show that the use of ketogenic diet is correlated with a decrease in thermal hypoalgesia [16]. However, there are articles that also infirm the results of the above mentioned studies, hence some rats experienced a hypernociceptive state while being fed with a ketogenic diet [17]. This is the reason why the use of ketogenic diet as a hypoalgic therapy remains uncertain, unless randomized clinical trials will be published.

Amyotrophic lateral sclerosis. Mitochondrial function impairment is a characteristic of many neurological diseases, which is also the case of amyotrophic lateral sclerosis (ALS). In laboratory studies, it seems that addition of ketone bodies to mitochondria isolated from the spinal cord of ALS-affected mice increased ATP production, which could be associated to an enhance in neuronal survival. This effect was confirmed by the improved motor function of the animal models treated with ketogenic diet [18]. Though, this outcome must also be confirmed for humans in further randomized clinical trials.

Brain trauma. It seems that the ketogenic diet can also have beneficial effects on brain traumatized patients, as there is strong evidence regarding the seizure control of this regimen. Reducing the incidence of seizures, which are considered long-term complications of traumatic brain injuries could increase the quality of life of these patients. At least hypothetically, this effect is possible, but there is still no consensus on the real effect of ketogenic diet specifically on a traumatized brain. Thus, further studies must be conducted in this direction, so that the above-mentioned theory could be confirmed [9].

Parkinson's disease. As the main event in the pathogenesis of Parkinson's disease is the degeneration of dopaminergic neurons in pars compacta of the substantia nigra, the underlying mechanism is also considered to be a mitochondrial function impairment, as above-mentioned for ALS. Thus, the ketogenic diet induced-elevation of ketone bodies is associated with an increase in the activity of a complex inside the mitochondria, which correlates with enhanced levels of dopamine in the affected neurons. Hence, patients treated with ketogenic diet may experience attenuation of motor deficits, as some studies show [18].

Cognitive function. A systematic review involving the effects of ketogenic diet on behavior and cognition found that this kind of regimen has neuroprotective effects in children, also associated with better cognitive functioning, increased alertness and improvement in behavior [19]. The results are similar to those of another study, which concluded that patients with glucose transporter protein 1 deficiency syndrome (GLUT1-DS) experience considerable improvement in different neuropsychological aspects. Thus, the youngest children had the greatest progress, with success in preventing developmental delay. In adults, the outcome was an improvement in alertness and also in learning capacity [20].

Cancer. There is evidence that there may be a link between carcinogenesis and blood levels of insulin and glucose. It has been shown that cancer cells express insulin and IGF-1 receptors and also that insulin is capable of stimulating mitogenesis and protecting cancer cells from apoptotic stimuli. The IGF-1/insulin pathway can also stimulate angiogenesis, which is a mandatory step in tumor growth. As there is a strong correlation between insulin and glycemia, and also between glycemia and carbohydrates intake, another theory can be postulated: ketogenic diet may reduce tumor growth progress, through reducing insulin effects on cancer cells. This outcome may also be obtained through glucose "starvation", which

is a characteristic in this low-carbohydrate diet [9].

2. Unwanted effects

Considering the multiple above-mentioned benefits of the ketogenic diet, it is hard to believe that it may still have harmful effects. Though, it seems that there are some unwanted consequences mentioned in several studies, but some of them still need to be confirmed by randomized clinical trials.

Cardiac complications. Ketogenic diet could have some adverse effects on the cardiac electrical activity. In a few cases, this effects were described as prolonged QT interval and also arrhythmias such as torsades de pointes. Yet, there is no evidence that these effects could be directly linked to the ketogenic diet, as a study made on 27 patients could not confirm that there is a statistically significant correlation between these electrocardiogram consequences and the low-carbohydrate regimen [21]. Another study also concluded that there are no significant effects on the electrocardiogram parameters of the included patients [22].

Hyperlipidemia. A stronger evidence exists on the adverse effects of the ketogenic diet on the lipid profile. It seems that over 60% of the children treated with ketogenic diet experienced elevation in the levels of triglycerides, total cholesterol, LDL and VLDL. Additionally, the HDL level decreased, which means a higher risk for atherosclerotic plaques to form. Even though genetics seem to influence this negative outcome, it is also relevant which the proportion of saturated fats in the regimen is. A higher level of saturated fats makes a patient more susceptible for this lipid profile alteration. Conversely, elevations in the uptake of polyunsaturated fats tend to reduce the cardiovascular risk of the ketogenic diet [23].

Bone demineralization. There is a 15 months long study that obtained a progressive loss of bone mineral content in pediatric patients treated with ketogenic diet for intractable epilepsy. Though, they could not explain the mechanism of these results, therefore concluding that further studies would be needed [24]. Conversely, a later published case series, which observed the patients for more than 5 years, resulted in no statistically significant data on the negative effects of the ketogenic diet on bone health [25]. This is why the topic on these adverse effect may still be open, as larger studies may be needed to establish whether this low-carbohydrate regimen could affect or not bone mineral content.

Nephrolithiasis. There are studies that observed an elevated risk for the patients treated with ketogenic diet to form kidney stones. This effect can be explained by the elevated levels of uric acid and ketone bodies in the blood, and also by the hypercalciuria and low urine citrates. However, these effects are preventable, while good hydration and use of exogenous citrates reduce the risk for developing nephrolithiasis [23].

CONCLUSIONS

Even if there is a long list of beneficial effects that can be assigned to the ketogenic diet, there are also several adverse reactions described in the literature. However, the number of these unfortunate outcomes is significantly low, compared to that of the benefits, and the evidence for these effects is poor. Still, we consider that physicians may use this type of alternative therapy only by assessing the potential benefits and risks for each individual patient, hence there still is a low chance for the patient to develop several adverse reactions. After almost a century since the introduction of the ketogenic diet as a therapy, further studies may still be needed in order to establish the medical uses that are currently not discovered and to confirm or refute the uncertain hypotheses that are postulated at the moment about this still surprising regimen.

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