



Therapeutic Indications of the Ketogenic Diet: A Integrative Review

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Abstract: The ketogenic diet (KD), a restrictive diet, is mainly characterized by high-fat content, low or no carbohydrate content, and low or normal protein content. This review aimed to address the main syndromes or diseases in which the therapeutic use of KD can be beneficial. One of the main clinical indications of KD has been, for some time, in the treatment of epilepsy refractory to the use of medications, with satisfactory results in the control of seizures. Recently, studies have addressed the metabolism of ketone bodies caused by KD, in the adjuvant treatment of tumors and endocrine disorders, such as diabetes and obesity, with promising results. In this work, the therapeutic aspect of KD was analyzed, as an aid in the control of pre-existing diseases, and that being a very restrictive diet with controversial effects, its use may be limited and it is not advisable to maintain it for long periods or without the proper follow-up.

Keywords: Ketogenic diet, Epilepsy, Cancer, Obesity, Diabetes

Introduction

The use of the ketogenic diet (KD) was introduced into clinical practice in the 1920s, although there are reports of ketogenic medicine since ancient Greece. KD consists of high-fat content, low or no carbohydrate content, and low or normal protein content [1]. Despite being a special and therapeutic diet, it must meet the general principles of nutrition and provide the body with energy, proteins, minerals, and vitamins, even though supplements, aiming at the development and maintenance of the patient's physiological conditions [2].

Classic DC is typically composed of a 4:1 macronutrient ratio (4 g fat for every 1 g protein plus carbohydrate combined), thus shifting the predominant caloric source from carbohydrate to fat. Lower fat ratios (3:1; 2:1; 1:1), termed modified DC, can be used depending on the patient's age, tolerance, ketosis level, and protein requirement. To increase flexibility and adaptability, "easier" variants have been developed, including the modified Atkins diet, the low glycemic index diet, and the ketogenic diet combined with oil of medium-chain triglycerides (MCT) [3-5].

Chronic ingestion of high amounts of fats with low carbohydrate content causes changes in liver metabolism similar to what happens during periods of fasting, with increased lipolysis, gluconeogenesis, and

synthesis of ketone bodies [3]. Due to the decrease of carbohydrates in the body, the energy in KD is mainly derived from the oxidation processes of fatty acids in the mitochondria, which generate large amounts of acetyl-CoA and lead to a reduction in the metabolic efficiency of the Krebs cycle and the diversion of excess of acetyl-CoA for the production of ketone bodies [1]. The generated ketone bodies, acetoacetate, and β -hydroxybutyrate enter the bloodstream and reach the organs, including the central nervous system (CNS), where they are used as a source of energy, and the acetone produced by the decarboxylation of acetoacetate, being volatile, is rapidly eliminated through the lungs and urine [3].

The use of this type of diet for weight loss and its effect on long-term mortality is controversial, as recently shown [6], and may depend on the source of replacement of dietary carbohydrate with fat and plant-based or animal-based protein. As for its therapeutic use, the KD has been successfully used to control drug-resistant epileptic seizures, and currently, several epileptic syndromes and other anomalies in which KD can be particularly beneficial are described in the literature [7].

Thus, this review aimed to address the main therapeutic indications in which the use of KD has shown satisfactory results.

Methods

Study Design

The present study followed an integrative review model, following the rules of systematic review - PRISMA (Transparent reporting of systematic reviews and meta-analysis-HTTP: [//www.prisma-statement.org/](http://www.prisma-statement.org/)) [8].

Search Strategy and Information Sources

The search strategy was carried out in the PubMed, Cochrane Library and Scopus databases, as well as Google Scholar in the search for doctoral and master's theses, using scientific articles from 1978 to 2021, using the descriptors ***Ketogenic diet. Epilepsy. Cancer. Obesity. Diabetes***, and use of the Booleans "and" between MeSH Terms and "or" among historical findings.

Study Quality and Bias Risk

Quality was classified as high, moderate, low, or very low to the risk of bias, clarity of comparisons, precision, and consistency of the analyzes. The most evident highlight was for systematic review articles or meta-analysis of randomized clinical trials, followed by randomized controlled trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument [9]. The risk of bias was analyzed according to the Cochrane instrument [10].

Results

As a corollary to the literary search system, a total of 105 studies were compared that were submitted to the eligibility analysis and, after that, 28 studies of high to medium quality were selected, considering in the first instance the level of scientific evidence of studies in type of study as meta-analysis, randomized, prospective and observational. The biases risk not compromising the scientific basis of the studies.

The Ketogenic Diet in Epilepsy

Epilepsy is a neurological disorder characterized by recurrent epileptic seizures that often lead to cognitive deficits. It is characterized by disturbances in the functioning of the neuronal circuitry, resulting from excessive and sudden neuronal discharges with heterogeneous clinical manifestations and with various etiologies [11]. Epilepsy affects a large number of

individuals, being one of the most serious and frequent neurological disorders in the pediatric age [12]. Approximately one-third of epileptic patients progress to a more severe condition with intractable epilepsy from a drug point of view, crises that are not controlled by maximum tolerated doses of 2 or 3 antiepileptic drugs, requiring the use of more invasive alternative treatments, such as a surgical procedure [2,7]. Refractory epileptic seizures represent a threat to the child, due to the increased risk of accidents and mortality, secondary malnutrition, with consequent damage and delay in physical and cognitive development, resulting from the disease and therapy, whose effectiveness is not as achieved [7,13].

Parallel to and regardless of the medication used, it was observed that epileptic patients had better seizure control when fasting or in the presence of metabolic acidosis resulting from prolonged fasting, and thus, the KD has been increasingly used in the treatment of epilepsy refractory to use of medications [14]. Glucose is normally the only fuel for the human CNS since the blood-brain barrier prevents the passage of fatty acids and makes its use as an energy source impossible. In contrast, ketone bodies enter the brain in proportion to the increase in serum ketosis levels, although under normal metabolic conditions ketone bodies are not utilized by nerve cells. During the use of KD, however, ketone bodies partially replace glucose as fuel for the brain [1,15].

The mechanism of action by which KD leads to the reduction of epileptic seizures is still unclear. It is suggested that the excessive supply of fat together with the reduction in the supply of carbohydrates can maintain the metabolic mechanism of starvation, a situation in which lipids are used as an energy source, maintaining a state of ketosis. The sedative effect of ketone bodies, their concentration in plasma, the degree of acidosis, partial dehydration, marked changes in lipid concentration and the metabolic adaptation of the brain resulting from ketosis would be the main factors responsible for controlling the attacks [2]. It is further suggested that a fundamental shift from glycolysis to DC-induced intermediary metabolism is necessary and sufficient for clinical efficacy. This hypothesis is supported by an exponential number of studies indicating that together, polyunsaturated fatty acids, ketone bodies, and glucose restriction may play mechanistic roles possibly by increasing ATP production, mitochondrial respiration, and decreasing reactive oxygen production. Another anticonvulsant mechanism triggered by KD involves an increased synthesis of gamma-aminobutyric acid (GABA). Metabolism via

ketosis would provide an increase in this neurotransmitter, decreasing the rate of epileptic seizures [16].

In recent years, the effectiveness of KD has been evaluated using the original research and evaluation system, which showed that diet was an effective and well-tolerated treatment for refractory childhood epilepsy [17]. These results have boosted interest in KD as a treatment for intractable epilepsy for adults as well. Recently, a meta-analysis study analyzed findings from published studies relevant to identifying the efficacy of KD for the treatment of intractable epilepsy in adults. A study of more than 402 articles was performed and the results of this meta-analysis showed the effectiveness of KD in the complete absence of seizures, in reducing seizures by 50% or more, and reducing seizures by less than 50% in adults with drug-intractable epilepsy were 13%, 53%, and 27%, respectively [18].

This same study also evaluated the adverse reactions arising from the use of KD in patients with difficult-to-control epilepsy. The results showed that the adverse reactions of classic KD were mild, while the glycemic index diet and diet with low fish oil content may have even fewer adverse effects, including weight loss, high level of low-density lipoprotein and high total cholesterol were the most frequent. In the child population, one should be aware of possible micronutrient deficiencies and the growth curve due to food restriction.

Thus, this meta-analysis study [18] indicated that the use of KD for refractory epilepsy in adults can be a well-tolerated treatment and that its side effects are acceptable, showing that the therapeutic use of KD is a promising treatment. in intractable epilepsy also in adults.

Patients with epilepsy may present, among other impairments, cognitive deficits. Cognition deficiencies are likely caused due to complex interactions between epileptic seizures, brain damage, and harmful effects of drug treatment. The severity of cognitive problems depends on the age of onset of epilepsy, etiology, type of epileptic seizure, and use of medication.

Thus, patients with frequent and chronic seizures with drug overuse are particularly affected by cognitive problems. Recently, a review study with a systematic approach [19] was carried out to evaluate the effects on cognition after the treatment of KD in adults and children with frequent epileptic seizures. This

study showed that using subjective assessments of patient experience, cognitive improvements were frequently reported during KD treatment in the domains of attention, attention, and global cognition; in addition, neuropsychological tests confirmed dietary benefits on alertness but found no improvement in global cognition. There was also evidence that these improvements are caused by both the reduction in seizures and the direct effects of KD on cognition.

Thus, the use of KD in the control of drug-resistant epilepsy proved to be beneficial by reducing the number of seizures, tolerable adverse effects, and with good results on the cognitive aspects of pediatric and adult patients with epilepsy [15].

Ketogenic Diet and Cancer

Dietary restriction from KD reduces plasma glucose levels and limits the energy supply to some cells while increasing circulating blood ketone levels [1]. KD also imposes on cells that they depend on fat oxidation and mitochondrial respiration, compared to glycolysis for energy production, since carbohydrates are unavailable. Regarding these characteristics of KD-derived metabolism, these dietary modifications can be expected to decrease tumor size and growth rate that depend on glucose as an energy source during anaerobic glycolysis. Furthermore, other metabolic changes found in malignant cells are related to the inability to metabolize ketone bodies due to various deficiencies in mitochondrial enzymes [20]. Thus, due to the state of ketosis combined with the absence of glucose provided by KD and in addition to the discoveries of malignant cell metabolism, the perspectives for the therapeutic use of anti-tumor KD have increased considerably [21].

Recently, a systematic review was carried out to evaluate the effects of KD on the growth and survival time of tumor cells in animal studies [22]. All studies included in this review indicated that KD exhibited an inhibitory effect on tumor growth and nine studies indicated that KD could increase survival time. Tumor types included pancreas, stomach, colon, neuroblastoma, prostate, and lung cancer tumors. The authors of this study, therefore, concluded that although studies in this field are rare and inconsistent, recent findings have demonstrated that KD can potentially inhibit the growth of malignant cells and increase survival time and also that due to physiological differences between humans and animals, studies in humans they are necessary [22].

Regarding recent advances in nutritional aspects of cancer therapy, a review was carried out focusing on the effects of dietary interventions, such as KD or fasting itself, on the metabolic pathways within cancer cells and the tumor environment (such as microbiota, system immune, and tumor microenvironment) involved in cancer progression and resistance, as well as cancer cell death [23]. This review demonstrated that a growing body of evidence has shown that nutrients can selectively sensitize malignant cells while protecting normal cells from their side effects. This modulation of nutrient supply through the diet may also improve immune cancer surveillance. Finally, based on the analysis of literature data, this study designed a nutritional intervention that consisted of a moderate ketogenic diet that could be beneficial and also explored for future preclinical research in cancer therapy [23]. Nutritional therapy does not replace any conventional treatment.

Ketogenic Diet and Endocrine Disorders

Before the discovery of insulin, the KD was used as a way to avoid high blood sugar levels, which was inevitably fatal for type 1 diabetics. The favorable and beneficial effects of the therapeutic use of KD on caloric intake, body weight, lipid parameters, glycemic indexes, and insulin sensitivity make this dietary profile a therapeutic option in metabolic syndrome, obesity, and type 2 diabetes. In addition, several hormones such as insulin, glucagon, cortisol, catecholamines, and growth hormone also affect significantly the metabolism of ketone bodies. Based on this evidence, a review study was recently published regarding current perspectives on the use of KD in endocrine disorders [24].

The analysis of studies on the perspective of the therapeutic use of KD in diabetes identified a strong relationship between the insulin resistance pathway and the metabolic state of ketosis. This study highlighted that element of lipid metabolism can facilitate the proper cellular localization of glucose transporters and their respective recycling, and KD can also alleviate certain inflammatory processes by blocking specific cytokines [25]. In addition, the KD is beneficial in improving glycemic control (glycated hemoglobin), reducing diabetic medications, increasing HDL cholesterol, and can promote weight loss in overweight and obese individuals with type 2 diabetes, as well as protein limitation and carbohydrates in KD may improve diabetic nephropathy [26].

In obese patients, this same review study showed that the therapeutic use of KD can result in

greater weight loss compared to other balanced diets [25]. He also highlighted that the possible mechanisms for greater weight loss may be due to the control of hunger and the greater satiety effect caused by KD. However, weight loss can also be linked only to the caloric deficit imposed by the diet. Previously, a study [27] observed that KD can significantly reduce serum levels of cholesterol, glucose and also decrease body weight, body mass index (BMI) and therefore reduce risk factors for various chronic diseases in obese hypercholesterolemic patients, if the replacement of carbohydrates is predominantly vegetable proteins and fats, it can be considered a long-term approach. A recent study suggests a long-term negative association between life expectancy and both low and high carbohydrate diets when dietary sources are not taken into account. These data provide further evidence that animal-based low-carbohydrate diets should be discouraged [6].

In this context, therefore, the use of a ketogenic diet (KD) is recommended in the treatment of obesity and diabetes, as it has benefits in metabolic disorders, epileptic seizures, autosomal dominant polycystic disease of the kidney, cancers, peripheral neuropathy, and skeletal muscle atrophy. Many high-profile pathways are available for KD action, including sustaining metabolic actions on glucose sugar, suppressing insulin-like growth factor-1 (IGF1), and phosphoinositide 3-kinase (PI3K) / protein kinase B (AKT) / mammal target of rapamycin pathways (mTOR). Thus, KD regulates the glucose and insulin sugar level and therefore can be considered an effective approach to diabetes [28].

Conclusion

This review study summarized the main and current clinical indications for the use of the ketogenic diet. The therapeutic use of this special type of diet has an important and known relevance in the treatment of epilepsies that are difficult to control with medication. In addition, this work showed the benefits of the metabolism of ketone bodies also in the supportive treatment of cancer, diabetes, and obesity, thus contributing to the updating of knowledge about the use of ketogenic diet in the therapy of diseases of great clinical and epidemiological importance. In the case of obese and diabetic patients, it is important to point out that due to lower consumption of fiber, and increased consumption of proteins (mainly of animal origin) and fat, the risk of heart disease, colon cancer, constipation is increased. In this work, the therapeutic aspect of the

diet was analyzed, as an aid in the control of pre-existing diseases, and that being a very restrictive diet with controversial effects, its use may be limited and it is not advisable to maintain it for long periods or without the proper follow-up. As for its use for weight control, it can be said that the loss of body fat improves several risk factors (decrease in visceral fat, decrease in blood pressure, improvement in cholesterol and blood sugar levels), having been proven in several interventions' studies. The important thing is to have a diet that allows the control of body fat and muscle mass and is by each patient's lifestyle.

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No additional data are available

Ethics Approval

Approval was sought and granted by the Departmental Ethics Committee.

Informed consent

Informed written consent obtained from the participant

Conflict of interest

The authors declare no conflict of interest.

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