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REVIEW ARTICLE

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Clinical approaches to the ketogenic diet in the treatment of obesity and other chronic diseases: a systematic review

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Abstract

Introduction: The ketogenic diet, a restrictive diet, is mainly characterized by high fat content, low or absent carbohydrate content, and low or normal amounts of protein. **Objective:** It was to present the important role of the ketogenic diet in the treatment of obesity and other chronic diseases. **Methods:** The PRISMA Platform systematic review rules were followed. The research was carried out from September to October 2023 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 111 articles were found, and 44 articles were evaluated, and 22 were included in this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 19 studies with a high risk of bias and 32 studies that did not meet GRADE. Most studies showed homogeneity in their results, with X^2=65.7%>50%. It was concluded that the therapeutic use of the ketogenic diet is relevant in the treatment of obesity and metabolic syndrome. Furthermore, this work also showed the benefits of the metabolism of ketone bodies in the adjuvant treatment of cancer, diabetes, and obesity, thus contributing to updating knowledge about the use of the ketogenic diet in the therapy of diseases of great clinical and epidemiological importance. When it comes to obese and diabetic people, it is important to highlight that due to the lower consumption of fiber, and an increased consumption of proteins (mainly of animal origin) and fat, the risk of heart disease, colon cancer, and intestinal constipation increases.

Keywords: Ketogenic diet. Obesity. Diabetes. Comorbidities.

Introduction

Despite continued advances in the world of medicine, obesity continues to be a major danger to global health, with adult mortality rates of up to 2.8 million per year. Most chronic diseases such as diabetes, hypertension and heart disease are largely related to obesity, which is often a product of an unhealthy lifestyle and poor eating habits. Appropriately tailored diet regimens for weight reduction can help control the obesity epidemic to some extent. One diet regimen that has proven to be very effective for rapid weight loss is a very low-carb, high-fat ketogenic diet (KD) **[1-3]**.

The use of the KD was introduced into clinical practice in the 1920s, although there are reports of ketogenic medicine dating back to ancient Greece. KD consists of high-fat content, low or absent carbohydrate content, and a low or normal amount of protein **[4]**. Despite being a special and therapeutic diet, it must comply with the general principles of nutrition and provide the body with energy, proteins, minerals, and vitamins, even though supplements, aim at the development and maintenance of the patient's physiological conditions **[5]**.

Classic KD is typically comprised of a 4:1 macronutrient ratio (4 g of fat for every 1 g of protein plus carbohydrates combined), thus changing the predominant caloric source from carbohydrate to fat. Lower fat ratios (3:1, 2:1, 1:1), referred to as modified KD, may be used depending on the patient's age, tolerance, level of ketosis, and protein needs. To increase flexibility and adaptability, "easier" variants have been developed, including the modified Atkins diet, the low-glycemic index diet, and the KD combined with medium-chain triglyceride (MCT) oil **[6]**.

Chronic intake of high amounts of low-carbohydrate fats causes changes in hepatic metabolism similar to what happens during periods of fasting, with increased lipolysis, gluconeogenesis and synthesis of ketone bodies **[6]**. Due to the reduction of carbohydrates in the body, energy in KD is derived mainly from the oxidation processes of fatty acids in the mitochondria, which generates large amounts of acetyl-CoA and leads 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 **[4]**. The ketone bodies generated, 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, as it is volatile, is quickly eliminated through the lungs and urine **[6]**.

The use of this type of diet for weight loss and its effect on long-term mortality is controversial, as recently shown by Seidelmann et al., (2018) **[7]**, and may depend on the source of replacing dietary carbohydrate with fat and plant or animal-based protein. As for therapeutic use, KD has been used successfully to control drug-resistant epileptic seizures, and several epileptic syndromes and other anomalies are currently described in the literature in which KD can be particularly beneficial **[8]**.

Thus, this systematic review presented the important role of the ketogenic diet in the treatment of obesity and other chronic diseases.

Methods

Study Design

The present study followed a concise systematic review model, following the systematic review rules - PRISMA (Transparent reporting of systematic review and meta-analysis: //www.prisma-statement.org/).

Search Strategy and Search Sources

The literary search process was carried out from September to October 2023 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, covering scientific articles from various eras to the present. The descriptors (MeSH Terms) were used: *"Ketogenic diet. Obesity. Diabetes. Comorbidities"*, and using the Boolean "and" between the *MeSH terms* and "or" between historical discoveries.

Study Quality and Risk of Bias

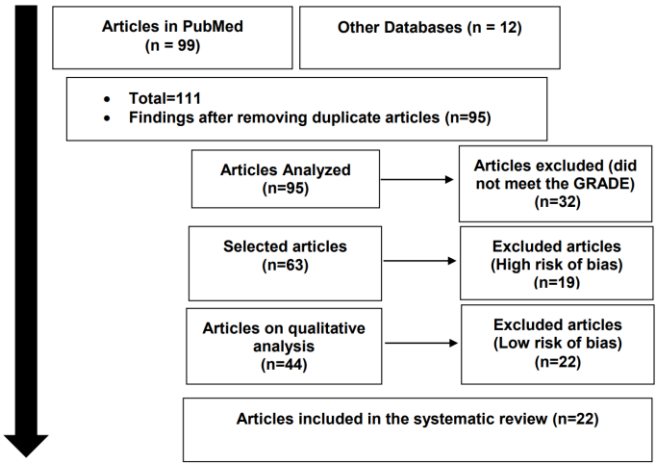
Quality was classified as high, moderate, low, or very low in terms of risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using the Cohen test (d).

Results and Discussion

Summary of Findings

As a corollary of the literary search system, a total of 111 articles were found that were subjected to eligibility analysis and, subsequently, 22 of the 44 final studies were selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering in the first instance the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with X^2=65.7%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 19 studies with a high risk of bias and 32 studies that did not meet GRADE.

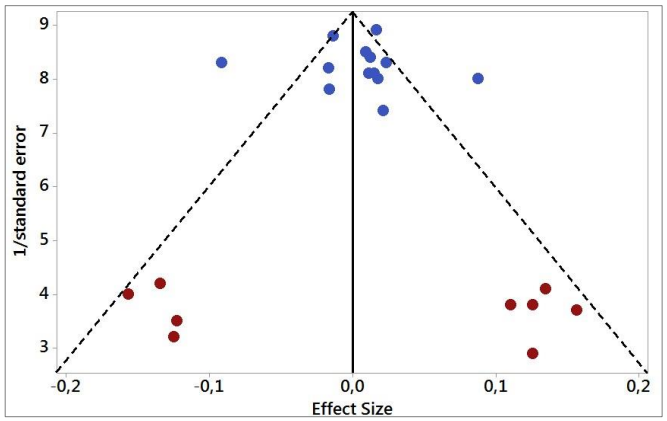
Figure 1. Flowchart showing the article selection process.



Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with a small sample size (lower precision) that are shown at the bottom of the graph and in studies with a large sample size that are presented at the top.

Figure 2. The symmetric funnel plot suggests no risk of bias among the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (n=22 studies).



Source: Own authorship

Main Clinical Findings

Dietary restriction, arising from KD, reduces plasma glucose levels and limits the energy source to a few cells while increasing ketone levels in the circulating blood **[4]**. The KD also imposes on cells to rely on fat oxidation and mitochondrial respiration as compared to glycolysis for energy production since there is an unavailability of carbohydrates. Regarding these characteristics of metabolism arising from KD, it can be expected that these dietary modifications reduce tumor size and growth rate that depend on glucose as an energy source during anaerobic glycolysis **[9-14]**. Furthermore, other metabolic modifications found in malignant cells are related to the inability to metabolize ketone bodies due to various deficiencies in mitochondrial enzymes **[15,16]**. Thus, due to the state of ketosis combined with the absence of glucose provided by KC and in addition to discoveries on the metabolism of malignant cells, the prospects for the therapeutic use of DC against tumors have increased considerably **[3]**.

Also, a systematic review was carried out to evaluate the effects of KC on the growth and survival time of tumor cells in animal studies. All research included in this review indicated that KC exhibited an inhibitory effect on tumor growth and nine research indicated that KC could increase survival time. Tumor types included tumors in the pancreas, stomach, colon, neuroblastoma, prostate, and lung cancer. 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 **[17]**.

About recent advances in nutritional aspects in cancer therapy, a review was carried out focusing on the effects of dietary interventions, such as KD or fasting itself, on metabolic pathways within cancer cells and the tumor environment (such as microbiota, system immune system, and tumor microenvironment) involved in cancer progression and resistance as well as cancer cell death. 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 cancer immune surveillance. Finally, based on literature data analysis, this study designed a nutritional intervention consisting of a moderate KD that may be beneficial and also explored for future preclinical research in cancer therapy. Nutritional therapy does not replace any conventional treatment **[18]**.

Before the discovery of insulin, KD was used as a way to avoid high blood sugar levels, which were 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 [19].

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 elements 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 [20]. Furthermore, KD is beneficial in improving glycemic control (glycated hemoglobin), reducing diabetic medications, increasing HDL cholesterol, and promoting weight loss in overweight and obese individuals with type 2 diabetes and protein limitation. and carbohydrates in KD can improve diabetic nephropathy [21].

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 [20]. It 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 solely to the calorie deficit imposed by the diet. Previously, a study done by Dashti et al., (2004) [22] observed that KD can significantly reduce serum levels of cholesterol, and glucose and also decrease body weight, and body mass index (BMI) and therefore reduce the risk factors for several chronic diseases in obese hypercholesterolemic patients, if replacing carbohydrates with predominantly vegetable proteins and fats, it can be considered a long-term approach.

Furthermore, one study suggested a long-term negative association between life expectancy and both low- and high-carbohydrate diets when food sources are not taken into account. These data provide additional evidence that animal-based low-carbohydrate diets should be discouraged [7].

Conclusion

It was concluded that the therapeutic use of the ketogenic diet is relevant in the treatment of obesity and metabolic syndrome. Furthermore, this work also showed the benefits of the metabolism of ketone bodies in the adjuvant treatment of cancer, diabetes, and obesity, thus contributing to updating knowledge about the use of the ketogenic diet in the therapy of diseases of great clinical and epidemiological importance. When it comes to obese and diabetic people, it is important to highlight that due to the lower consumption of fiber, and an increased consumption of proteins (mainly of animal origin) and fat, the risk of heart disease, colon cancer, and intestinal constipation increases.

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Ethical Approval

Not applicable.

Informed consent

Not applicable.

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

It was applied by Ithenticate@.

Peer review process

It was applied.

References

1. Masood W, Annamaraju P, Uppaluri KR. Ketogenic Diet. 2022 Jun 11. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan.
2. Zhu H, Bi D, Zhang Y, Kong C, Du J, Wu X, Wei Q, Qin H. Ketogenic diet for human diseases: the underlying mechanisms and potential for clinical implementations. Signal Transduct Target Ther. 2022 Jan 17;7(1):11. doi: 10.1038/s41392-021-00831-w.
3. Ilyas Z, Perna S, A Alalwan T, Zahid MN, Spadaccini D, Gasparri C, Peroni G, Faragli A, Alogna A, La Porta E, Ali Redha A, Negro M, Cerullo G, D'Antona G, Rondanelli M. The Ketogenic Diet: Is It an Answer for Sarcopenic

Obesity? Nutrients. 2022 Jan 30;14(3):620. doi: 10.3390/nu14030620.

4. Hartman AL, Gasior M, Vining EP, Rogawski MA. The neuropharmacology of the ketogenic diet. Pediatr Neurol. 2007; 36: 281-92.
5. Nonito-Borges CB, Bustamante VCT, Rabito EI, Inuzuka LM, Sakamoto AC, Marchini JS. Dieta cetogênica no tratamento de epilepsias farmacorresistentes. Rev Nutr. 2004; 17: 515- 21.
6. McDonald TJW e Cervenka MC. The expanding role of ketogenic diets in adults neurological disorders. Brain Sci. 2018; 8: 1-35.
7. Seidelmann SB, Claggett B, Cheng S, Henglin M, Shah A, Steffen LM et al. Dietary carbohydrate intake and mortality: a prospective cohort study and meta-analysis. Lancet 2018, 3: 419-28.
8. Rola M e Vasconcelos C. Dieta Cetogênica - Abordagem Nutricional. Nutrícias. 2014; 22: 169.
9. Reming VM. Medical nutrition therapy for neurologic disorders. Krause's Food & Nutrition Therapy. 12º ed. Philadelphia W.B. Saunders 2008; 1067-101.
10. Vasconcelos MM, Azevedo PM, Esteves L, Brito AR, Olivaes MC, Herdy GV. Ketogenic diet for intractable epilepsy in children and adolescents: report of six cases. Rev Assoc Med Bras. 2004; 50:380-5.
11. Wheless JW, Baumgartner J, Ghanbari C. Vagus nerve stimulation and the ketogenic diet. Neurol Clin 2001;19: 371-407.
12. Pereira E, Alves M, Sacramento T, Rocha VL. Dieta cetogênica: como o uso de uma dieta pode interferir em mecanismos neuropatológicos. R. Ci. méd. biol. 2010; 9: 78-82.
13. Sharma S, Jain P. The ketogenic diet and other dietary treatments for refractory epilepsy in children. Ann Indian Acad Neurol 2014; 17: 253-8.
14. Liu H, Yang Y, Wang Y, Tang H, Zhang F, Zhang Y, et al. Ketogenic diet for treatment of intractable epilepsy in adults: A meta-analysis of observational studies. Epilepsia Open 2018; 3: 9-17.
15. van Berkel AA, Ijff DM, Verkuyl JM. Cognitive benefits of the ketogenic diet in patients with epilepsy: A systematic overview. Epilepsy Behav 2018; 87: 69-77.
16. Allen BG, Bhatia SK, Buatti JM, Brandt KE, Lindholm KE, Button AM, et al. Ketogenic diets enhance oxidative stress and radio-chemo-therapy responses in lung cancer xenografts. Clin Cancer Res. 2013; 19: 3905-13.
17. Khodadadi S, Sobhani N, Mirshekar S, Ghiasvand R, Pourmasoumi M, Miraghajani M. Tumor Cells Growth and Survival Time with the Ketogenic Diet in Animal Models: A Systematic Review. J Prev Med 2017; 25: 8:35.
18. Lettieri-Barbato D e Aquilano K. Pushing the limits of câncer therapy: the nutriente game. Front. Oncol. 2018; 8: 148.
19. Alberti KG, Johnston DG, Gill A, Barnes AJ, Orskov H. Hormonal regulation of ketone- body metabolism in man. Biochem Soc Symp. 1978; 43: 163–82.
20. Gupta L, Khandelwal D, Kalra S, Gupta P, Dutta D, Aggarwal S. Ketogenic diet in endocrine disorders: Current perspectives. J Postgrad Med. 2017; 63: 242-251.
21. Hussain TA, Mathew TC, Dashti AA, Asfar S, Al-Zaid N, Dashti HM. Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes. Nutrition. 2012; 28:1016-21.
22. Dashti HM, Mathew TC, Hussein T, Asfar SK, Behbahani A, Khoursheed MA, et al. Long- term effects of a ketogenic diet in obese patients. Exp Clin Cardiol. 2004; 9: 200-5.

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