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The role of the ketogenic diet in the treatment and prevention of diseases: A literature review

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Abstract
In recent years the ketogenic diet (KD) has become more and more popular. This diet is used not only to reduce weight but also there are an increasingly amount of new researches with multiple positives effects in some diseases, such as prevention in cardiovascular conditions, diabetes mellitus, obstructive sleep apnea syndrome, some types of cancers and psoriasis. This paper offers an overview of these various medical conditions in which ketogenic diet can be used. Furthermore we describe the mechanism and potential efficacy of the KD. The PubMed and Google Scholar databases were searched.

Keywords: Ketogenic diet, Cardiovascular, Cancer, Diabetes, Weight loss

1. INTRODUCTION

Nowadays diets in general with their efficacy and influence on human health are the main topic in TV and social media, health magazines, also in latest medical outcomes. The fact, that KD had more searches on Google than vegan, fish or Mediterranean diet in the whole World proves popularity of this diet. The KD is a high-fat, low-carbohydrate diet that mimics the state of fasting (causing the production of a large amount of ketone bodies from fats) while simultaneously providing a sufficient amount of energy. The KD contrasts sharply with current nutritional recommendations and is not appropriate for most individuals. Nonetheless, there are certain circumstances where this diet can be extremely advantageous for a patient. It should be adhered to for legitimate reasons and under the vigilant, ongoing supervision of healthcare professionals. The physiology of the KD is based on the situation when glycogen stores become depleted (after 10-12 hours) and we still cannot satisfy our hunger, the body begins to produce glucose from the breakdown products of proteins (mainly derived from muscles), fats, and lactates.

After several days of fasting, metabolism adjusts, and ketone bodies become our main fuel. They are the product of fat metabolism in the mitochondria, the cell's energy factories. Therefore, ketone bodies are present in the urine of fasting individuals (and those with diabetes who cannot use glucose due to insulin deficiency. (Pol, 2024) This phenomenon has been very well described in Paoli work. (Paoli, 2014)

2. Methods and materials

This review aims to explore and submit the current literature on efficacy of the ketogenic diet in multiple clinical conditions. This article gathers information from publications available on PubMed and Google Scholar. We used the collected materials to present an outline of basic information about the ketogenic diet and divided them into its possible applications in various diseases and their pathomechanisms as a comprehensive overview of the latest state of knowledge.

The inclusion criteria’s were defined. Scientific papers had to be written in English, with the aim of studying the ketogenic diet for a given clinical condition or comparing its effects with another type of diet. We also considered papers focusing on the mechanism of action of the diet. Review articles, bibliographic studies, and meta-analyses were included. We excluded papers without a specific publication date and those with unclear results that were confounded by external factors not adequately explained by the authors.

About the study duration: Two months for literature review, one month for original draft preparation, one month for revisions.

3. Results

3.1 The first applications

James W. Whelles in his work described the first applications of fasting and the KD (Wheless, 2018). The precursors to the KD were fasting practices. The initial modern application of starvation for treating epilepsy was documented by two Parisian doctors, Gulep and Marie, in 1911. They administered this treatment to 20 individuals, including children and adults, with epilepsy. They observed that seizures were less intense during the treatment period, although they did not provide specific details.

Ten years later, in 1921, Dr. Geyelin presented his findings on using fasting as a therapy for epilepsy at the American Medical Association Convention. Dr. Geyelin was the pioneer in recording the cognitive enhancements that could result from fasting (Geyelin 1921).

The inventor of the „ketogenic diet" term was Dr. Russell Wilder (Wilder, 1921). The research of Dr. Rollin Woodyatt and Dr. Russell Wilder was published around the same time in 1921. The first one observed that during periods of starvation, acetone and beta-hydroxybutyric acid emerged. Woodyatt also found that acetone and beta-hydroxybutyric acid were present in patients following a low-carbohydrate diet (Woodyatt, 1921). Dr. Russell Wilder, a researcher at the Mayo Clinic, proposed that therapeutic ketonemia could be achieved through a low-carb diet rather than through starvation. This approach gained widespread popularity in treating childhood epilepsy. However, when the new medications for epilepsy were found in last years the KD gradually became less prominent as a treatment for epilepsy. The first use of the KD as a weight loss tool was described by Dr. Robert Atkins in his book published in 1972. He initiated a movement and popularized the development of new variations of low-carbohydrate diets as a method for weight loss (Atkins, 1972).

3.2 Types of ketogenic diet

The classic KD follows a 4:1 ratio of fat to carbohydrates plus protein. This classic 4:1 KD provides 90% of its calories from fat, 8% from protein, and only 2% from carbohydrates, similar to the original proposal by the Mayo Clinic group (Weber, 2020). In the years, when this diet was used in treating epilepsy in 1920, KDs were very highly restrictive, which made adherence difficult (Peterman,1925). However, in recent years, new form of this high-fat, low-carbohydrate diet have been developed, making it much easier to follow the diet, because the researchers found that long-term intake has better efficacy. There 3 most popular evaluations : KD rich in medium-chain triglycerides (MCT), Modified Atkins diet (MAD), Low Glycemic Index Treatment (LGIT). The main difference between classic KD and MAD, MCT and LGIT is in proportions fat in grams to carbohydrate and protein with ratio mainly 4:1 in KD to 1:1 or 2:1 in other diets. (Kossoff, et al., 2018)

MCTs (Sills et al., 1986, Shah and Limketkai, 2017, Huttenlocher et al., 1971, Kossof and Dorward, 2008, Auvin, 2012) has two elements that surpass its effectiveness over others, namely smoother entry into the bloodstream and energy production, as well as promoting the production of ketone bodies in the liver. However, this diet is not a choice for many due to numerous unwanted gastrointestinal symptoms.

The MAD (Pfeifer and Thiele, 2005, Crosbie et al., 2022) most significantly differs from the basic version of the KD in the lack of restriction on calorie and protein intake. Compared to the classic Atkins diet, weight loss has ceased to be the primary goal. Additionally, it is recommended to consume a large amount of high-fat foods and impose stricter limits on carbohydrate usage. A review of the MAD for epilepsy in 2012 concluded that it effectively controls seizures and should be the preferred dietary approach for patients in that population (Bueno et al., 2013).

In the LGIT diet, daily carbohydrate intake is capped at 40 to 60 grams from foods with a glycemic index lower than 50 to avoid rapid fluctuations in blood levels of glucose and insulin. The same thing which is common for MAD and LGIT that both of them do not need to calculate daily proteins dose.

3.3 Clinical conditions

Weight loss

Obesity is a continuously growing problem in our civilization, exerting a negative impact on our blood vessels by causing atherosclerotic changes and subsequently developing hypertension. It is also a risk factor for diabetes type 2 and some types of cancer, such as endometrial cancer (Paoli, 2014, Mansoor et al., 2016). Everyone knows that the most important factor to lose some weight is diet, but the question is, which diet is the most effective? Of course, this is a highly individual matter. Let's focus on the effects of the KD. The effectiveness of the KD in combating obesity has been clearly demonstrated in these two meta-analysis of randomized controlled trials (Atkins and McKay, 1972, McGaugh and Barthel, 2022). In Nadia Mansoor work, conclusions were presented in which participants without health disorders exposed to a low-carbohydrate diet experienced greater weight loss compared to those on a low-fat diet. The entire study lasted for half a year (Mansoor et al.2016). The second mentioned study by Bueno leads to similar conclusions, that the KD achieved better results in weight loss than the participants who intake low-fat diet. The difference in the studies lies in the duration of the diets being examined. This study lasted for a minimum of 12 months (Bueno, 2013).

Many researchers have studied the potential mechanisms of the keto diet affecting weight loss. The first theory, that has lost its credibility was proposed by Dr. Atkins, he suggested that weight loss was associated with the energy expenditure involved in the excessive production of ketone bodies (Atkins and McKay, 1972). Nowadays, some main hypotheses with the greatest supporting evidence have been identified (Paoli 2014, McGaugh and Barthel, 2022).

One hypothesis suggests that ketone bodies have an inhibitory effect on hunger and appetite (Johnstone et al. 2008). The study compared hunger, appetite, and weight loss in 17 obese men exposed to a low-carbohydrate KD and a high-protein diet with a normalized carbohydrate content. The patients were not assigned restrictive calorie amounts to consume. The results were clear : Ad libitum energy consuming were lower with the KD than with the medium-carbohydrate one, respectively, also in over the four week period of time the hunger was significantly lower and weight loss was significantly greater with the KD (6.34 kg) than with the comparable diet (4.35 kg).

Another study aimed to investigate how ketosis affects various circulating factors associated with appetite regulation subsequent to weight loss induced by dietary changes, 39 people were exposed to an 8-week ketogenic very-low-energy diet, followed by 2 weeks of reintroduction of foods. The results showed that during ketosis, the rise in ghrelin induced by weight loss was inhibited in participants. Glucose and non-esterified fatty acids levels were elevated, while amylin, leptin, and subjective appetite ratings were lower at week 8 compared to after refeeding (Sumithran et al., 2013).

Another hypothesis is related to the high-energy process of gluconeogenesis, which is stimulated when glucose (our main source of energy) is lacking. This situation occurs precisely when we follow a low-carbohydrate and high-fat diet (Fine and Feinman, 2004).

Decrease in fat production and rise in fat breakdown is the next theory, which could explain the mechanism of weight loss (Cahill, 2006, Feinman and Fine, 2007, Sharman et al., 2004). In these works, the authors present the physiology of insulin secretion in response to glucose intake, which is low in the KD, as well as the action of this hormone. Insulin inhibits the process of lipolysis, so when insulin levels are low, lipolysis is intensified, leading to a decrease in circulating triglyceride levels in the blood.

Diabetes Mellitus type 2

The incidence of diabetes mellitus has increased fourfold over the past 30 years, making it the ninth leading cause of death, the majority of patients with diabetes mellitus type 2 experience at least one complication, with cardiovascular issues being the primary cause of illness and death among these individuals (Zheng et al., 2018). In recent years, the impact of KDs on patients with type 2 diabetes has been intensively studied, with the goal of reducing the use of oral hypoglycemic agents and insulin. Most studies considered not only weight loss, which in patients with this condition is typically significantly excessive, but also changes in the levels of metabolic parameters such as glycated hemoglobin, triglycerides, high-density lipoproteins (Zhou et al., 2022). Most studies indicate that patients following a KD experience greater and more effective improvements in their physical and biochemical health compared to those on a traditional diet. The result from the meta-analysis that summarized some randomized controlled trails (Goday et al., 2016, Tay et al., 2015, Westman et al., 2008, Saslow et al., 2014, Saslow et al., 2017) shows a markedly positive effects on weight loss (SMD, −5.63, $p = 0.008$), the reduction of waist circumference (SMD, −2.32, $p = 0.04$), lowering glycated hemoglobin (SMD, −0.38, $p = 0.0008$) [31]. On the other hand, another study observed not only a decrease in body weight ang Hemoglobin A1c level but also a reduction in the doses of hypoglycemic medications in the majority of study participants, and there were even cases where oral medications were completely discontinued on the KD (Yancy et al., 2005). The positive and rapid effect of the KD appears quite clear, but it raises the question in our minds about its long-term impact. Additionally, strict adherence to a low-carb, high-fat diet is also demanding. The previously mentioned concerns are addressed in Goldenberg's meta-analysis, which indicates that the effectiveness of the diet tends to decline after 12 months compared to its use over a 6-month period (Goldenberg et al., 2021).

Cardiovascular Diseases

By the WHO information : the Cardiovascular diseases (CVDs) are the world's leading cause of death, responsible for approximately 17.9 million fatalities annually. This category includes various heart and blood vessel disorders such as coronary heart disease, cerebrovascular disease, and rheumatic heart disease. Over 80% of CVD-related deaths result from heart attacks and strokes, with one-third of these occurring prematurely in individuals under 70 years old.

It is widely known that preventing diseases is always better than treating them. The main goal in preventing cardiovascular diseases is to mitigate risk factors. Numerous studies have shown how the KD can effectively serve this purpose. It positively impacts weight reduction and glycemic profiles, as described in the previous paragraphs, and also modifies lipid metabolism, exerts anti-inflammatory effects, and influences functioning of the vascular endothelium (Dyńka et al., 2023).

Firstly the KD efficacy on the blood lipid profile will be discussed. Dyslipidemia is a condition in which lipid parameters such as total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides (TG) become abnormal. It is said that high TC, LDL, TG and low level of HDL predispose individuals to cardiovascular risks but in this work (Dyńka et al., 2023) researches summarized recent studies and explain that such a situation does not always occur. Furthermore, authors of this article concluded that reducing LDL cholesterol levels is one of the most common strategies in clinical practice for treating and preventing atherosclerotic cardiovascular disease (Du and Qin, 2023)

The meta-analysis which we already discussed (Zhou et al., 2022) showed us the efficacy of KD as the dietary intervention in overweight patients with type 2 diabetes mellitus, not only weight loss and decreased level of glycated hemoglobin but also influent with deceasing triglycerides, and increasing high-density lipoproteins. Another previously mentioned study by Mansoor (Mansoor, 2016) focused on the comparative impact of the KD on cardiovascular risk factors. They rated 11 randomized controlled trials with 1,369 participants placed into ketogenic versus low-fat diet groups. The outcomes were that patients with low-carbohydrate diet in comparison to the second group had better reduction in body weight and triglycerides, but a greater increase in HDL-cholesterol and LDL-cholesterol. As the conclusion, they suggested that weight loss is more significant than high LDL values as a cardiovascular risk factor.

Another randomized crossover trials the forty participants with pre diabetes or type 2 diabetes mellitus followed the well-formulated ketogenic diet WFKD and the Mediterranean-plus diet (Med-Plus) for 12 weeks each. The results revealed lower effectiveness of the Med-plus diet in terms of the studied factors. The KD showed greater Triglycerides decreased compared with the Med-Plus and LDL cholesterol was higher compared with for the Med-Plus. Weight decreased 8% , compared with 7% and HDL cholesterol increased 11% compared with 7%. However, it should be noted that both diets had a positive impact on risk factors in the studied group of participants.

On the other hand, studies with slightly different results regarding the impact of the KD on lipid metabolism have been described. Twenty middle-aged men with experience in resistance training, who were not in competitive sports, followed a supervised calorie maintenance western diet and resistance training program for 4 weeks. Afterward, they were split into ketogenic and non-ketogenic groups for an 8-week period.

Changes in lipid metabolism and blood glucose levels were among the factors examined, which, as it turned out, did not show significant differences in either group after the study period (Vidić et al., 2021). The second study with different conclusions from the previous one involved 24 young, healthy women with normal weight who consumed a KD for the first 4 weeks and then after the 15 weeks break they were exposed on the control diet recommended by the National Food Agency for the next 4 weeks. The diets were consumed in reverse order by some participants in the study. Surprisingly, there was no weight loss observed in the participants; however, negative effects of the ketogenic diet were reported. They observed increased LDL cholesterol in every female participants. In addition, there were a higher level of small, dense and large LDL cholesterol and Apolipoprotein B-100.

Based on the above studies, it can be concluded that changes in lipid metabolism significantly correlate with weight loss. The effects of the KD are often noticeable after a relatively short period of exposure; however, its longer-term impact on lipid metabolism and its connection with cardiovascular diseases require further investigation. In this systematic review the authors provide conclusions that may question the significance of the cholesterol hypothesis. They researched potential influent LDL cholesterol as a risk factor for all-cause and/or CV mortality in individuals ≥60 years from the general population. The outcomes showed, high levels of LDL cholesterol are inversely correlated with mortality in the majority of individuals over the age of 60. This observation contradicts common knowledge which posits that cholesterol, especially LDL has a significant impact on the development of atherosclerotic changes in blood vessels. Therefore, elderly individuals with elevated LDL cholesterol levels tend to live as long or longer than those with lower LDL cholesterol levels (Ravnskov et al., 2016).

Another aspect of the positive impact of the KD on cardiovascular diseases is its potential anti-inflammatory effect. Based on already conducted studies, the negative influence of inflammation in the body on the acceleration of atherosclerosis development has been confirmed (Fiordelisi et al., 2019, Brigant et al., 2018). The KD exerts an anti-inflammatory effect through various mechanisms, one of which is inducing the body into a state of ketosis and increased production of ketone bodies, among which β-hydroxybutyrate plays a significant role in modifying the inflammatory state. Its effects are diverse, encompassing gene expression modulation, inflammation reduction, and enhancement of mitochondrial function (Dyńka et al., 2023)). Moreover, current ketone bodies in the blood contribute to reducing a significant group of pro-inflammatory cytokines such as IL-1β, IL-6, IFN-γ, MCP-1 and RANTES (Du and Qin, 2023).

The anti-inflammatory properties and positive impact on lipid metabolism of omega-3 fatty acids have been presented in a considerable number of scientific articles as a protective role in cardiovascular diseases. The meta-analysis summarized the associations between omega-3 PUFAs, including α-linolenic acid (ALA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA), with risk of developing cardiovascular diseases taking to the consideration coronary heart disease and mortality. In the results DHA and EPA were associated with a significantly reduced risk of total cardiovascular diseases, coronary heart disease, and total mortality (Jiang et al., 2022). Another work, which confirmed positive impact of omega -3 fatty acids on cardiovascular condition (Yang et al. 2022). Thanks to the nature of the high-fat KD with a high content of omega-3 fatty acids, the mentioned benefits of these fats translate into the favorable effects of this diet on cardiovascular diseases.

Low concentrations of ketone bodies, as achieved through a ketogenic diet, have demonstrated potential for enhancing endothelial and vascular function in metabolic disorders (Nasser et al., 2020).

To summarize the impact of the KD on the cardiovascular system, we can conclude that it acts in a pleiotropic manner. It potentially exerts positive effects on various levels. It has anti-inflammatory effects, may improve endothelial function, lower total cholesterol and triglyceride levels, effectively reduce body weight, and improve the glycemic profile, which undoubtedly enhances cardio protection. However, it is important to remember that it should be applied according to the individual needs of the patient.

Obstructive Sleep Apnea Syndrome

Obstructive sleep apnea syndrome (OSAS) and obesity often coexist with hypertension, dyslipidemia, and insulin resistance. Guidelines advise that patients with obesity and OSAS, who are planned for bariatric surgery, should undergo preoperative continuous positive airway pressure (CPAP) therapy for a minimum of 4 weeks. There is one study, in which they evaluated the clinical benefit of pre-bariatric surgery CPAP along with a KD in patients who suffer from obesity and OSAS. Seventy individuals with obesity and OSAS were randomly divided into groups receiving either CPAP alone or CPAP in combination with a ketogenic diet for a duration of 4 weeks. The apnea–hypopnea index (AHI), weight loss (WL), C-reactive protein (CRP) levels, hypertension, dyslipidemia, and insulin resistance were comparable. AHI scores improved significantly in both groups. No significant advantage was demonstrated for either group with AHI. Moreover, body weight, CRP levels, and blood pressure were significantly reduced in the CPAP+LCKD group after 4 weeks, and CPAP+LCKD had a greater impact on CRP levels than CPAP alone. The CPAP+LCKD group had better reduction in total cholesterol, LDL, and triglyceride levels (Schiavo et al., 2022).

Psoriasis

Psoriasis is an inflammatory condition characterized by significant genetic associations and various autoimmune features, which can also be affected by environmental factors, also nutrition and physical activity have their influent (Duchnik et al., 2023).This research (Castaldo et al., 2021) took 30 patients with psoriasis who underwent a ketogenic dietary plan and were observed for a duration of four weeks. Their clinical data, biochemical and clinical parameters, as well as concentrations of IL-2, IL-1β, TNF-α, IFN-γ, and IL-4, were assessed both before and after the dietary regimen. Research has demonstrated that implementing a low-calorie ketogenic diet among patients with psoriasis led to a reduction in the levels of pro-inflammatory cytokines, such as IL-2 and IL-1β. Additionally, it resulted in a decrease in the PASI index (Psoriasis Area and Severity Index), which assesses the severity of psoriasis. The next study (Barrea et al., 2022) who examine the KD on obese patients with psoriasis. The KD resulted in both weight loss and a decrease in systemic inflammation, potentially mitigating the worsening of clinical symptoms or even preventing the onset of psoriatic disease. This dietary approach could serve as a promising initial treatment for psoriatic patients who are obese.

Cancers

Cancer diseases, their prevention, preventive methods, predisposing factors, new treatment methods, as well as the physical and mental health status during oncological treatment, are currently among the most intensively researched topics in the medical community. Amid all this, there has been room to study the effects of the KD on cancer patients as well as its potential properties for reducing the risk of certain cancers. In one of the previously mentioned studies examining the effects of omega-3 fatty acids, besides the effect of reducing the risk of cardiovascular diseases, a lower risk of colorectal cancer was observed at higher levels of docosapentaenoic acid and docosahexaenoic acid (Jiang et al., 2022).

The authors of one study investigated the effect of the KD on body composition changes in patients with head and neck, breast, and rectal cancer undergoing radiotherapy (Klement et al., 2019). It is worth noting that twenty patients on a KD supplemented with 10 grams of essential amino acids on days of radiotherapy were compared to sixty-one patients consuming a non-ketogenic diet. The results of this study showed, that patients with rectal and breast cancer on KD were associated with a loss of 0.5 and 0.4 kg fat mass per week, with no significant changes in fat free and skeletal muscle mass. In head and neck cancers, where radiotherapy is often combined with chemotherapy, significant decreases in parameters such as muscle mass or free fat were observed, which improved when a ketogenic diet was concurrently used.

In this review (Weber et al., 2020) the authors summarized numerous preclinical and clinical studies that presented the potential beneficial use of the KD as adjunctive therapy in oncology patients. They outlined the possible impact of the diet on gene expression, factors influencing tumor metabolism, elements affecting angiogenesis and vascularization within the tumor microenvironment, as well as improvement in the physical condition of patients during treatment, including the anti-inflammatory component. However, in the conclusions of their work, they emphasized that further detailed studies are required to confirm the potential benefit of the KD in oncology patients.

4. Conclusions

The ketogenic diet is becoming increasingly popular not only due to its positive impact on weight loss but also on other health conditions. Prevention of cardiovascular diseases, certain cancers, impact on carbohydrate metabolism control in patients with type 2 diabetes, and control of exacerbation states in patients with psoriasis are examples of potential benefits resulting from the KD. However, we must always consider the individual characteristics of the patient. The diet and its expected effects must be tailored to the patient. Further research is necessary, particularly on the long-term use of the KD in the mentioned clinical conditions, as well as in other areas not yet covered by studies. Based on current research, the results of the positive effects of the KD are promising and worthy of our attention.

Authors' Contribution

Dawid Barański:: conceptualization, methodology, writing-rough preparation,
Julia Skwara: formal analysis, investigation, resources, data curation
Maciej Nowicki: formal analysis, investigation, resources, data curation
Anna Salińska: visualization, supervision, resources, data curation
Piotr Węgrzyn: writing-review and editing, check, formal analysis
Marcin Wasilewski: writing-review and editing, check, formal analysis
Konstancja Węgrzyn: conceptualization, methodology
Natalia Dąbrowska: conceptualization, investigation, data curation
Agnieszka Góra: software, visualization
Gustaw Laskowski: resources, data curation, writing-review and editing
Dawid Barański: Project administration

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Conflict of interest

The authors declare that there is no conflict of interests.

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Ethical approval

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