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POTENTIAL EFFECTS OF KETOGENIC DIETS, A NARRATIVE REVIEW

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ABSTRACT

Background: Ketogenic diets have a long history of therapeutic use and have recently attracted significant attention due to their promising effects on a variety of disorders. However, no definitive links have been identified. This review aims to highlight the possible impacts of ketogenic diets as well as the mechanisms involved in metabolic processes and related non-communicable metabolic diseases. **Methods:** For our analysis, a bibliographic review of articles about ketogenic diets and their therapeutic effect on chronic pathologies was carried out, retrieved from the scientific literature. **Results and discussion:** These studies found both positive and negative outcomes for the effects and implications of ketogenic diets on metabolism. Significant differences in metabolic markers such as weight, glycemia, serum lipids and lipoproteins, anthropometric measures, and hormones such as insulin, leptin, and adiponectin have been reported. In addition to changes in the microbiome that have modest to moderate concurrent effects, changes in metabolism indicate the significance of dietary changes in treating and preventing chronic non-communicable diseases. **Conclusions:** In this review, we present the available scientific evidence on the effects of the ketogenic diet, and thus ketone bodies, on metabolism and related chronic diseases.

Keywords: *Ketogenic diet, ketone bodies, diet, metabolism, chronic non-communicable metabolic diseases.*

1. INTRODUCTION

Following a dietary plan or regimen, commonly known as a diet, is becoming increasingly popular, not only intending to maintain health but also as a non-pharmaceutical option to combat disease. Currently, there are several types of diets, hypocaloric, paleo, protein, alkaline, and regional, such as the Mediterranean diet, others designed explicitly with a dietary approach to hypertension, or those with a minimum percentage of carbohydrates, such as the ketogenic diet (KD), and protocols that diversify eating patterns, such as intermittent fasting, among others.

On the growing list, KD has a long history of clinical use and has recently gained considerable interest due to its promising potential effects on a wide group of pathologies. These diets are high in fat and low in carbohydrates, with adequate protein and caloric content (Weber, 2019). Nutritional ketosis, the desired endpoint of KD, is achieved by restricting carbohydrate intake, moderating protein intake, and increasing the number of calories derived from lipids. Thus, a traditional KD consists of 90% of calories from fat, 8% from protein, and only 2% from carbohydrates, compared to the 45-65% of carbohydrates recommended in a standard diet (Wilder, 1921).

In the 1920s, KD was first used as a dietary adjunct in epilepsy to control seizures in patients who did not respond adequately to antiepileptic drugs (Wilder, 1921); (Ulamek-Koziol,2019); (Wheless, 2008); (Yuen, 2014). In 1921, Russell Wilder first proposed that a ketone-producing diet could be as effective as fasting for the treatment of epilepsy and coined the term 'ketogenic diet' (Wheless, 2008).

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Four main types of KD have been described: classical or long-chain triglycerides (LCT), medium-chain triglycerides (MCT), modified Atkins (MAD), and low glycemic index (LIG) (Kossoff, 2018); (Huttenlocher, 1971). LCT is the most traditional type and is widely used in the clinical setting, with a 4:1 ratio corresponding to a fat/protein or carbohydrate ratio or their combination (Coppola, 2002); (Hassan, 1999). Thus, 90% of calories come from fat; however, when the ratio is 3:1, the caloric contribution from fat is 87%, and the remaining 13% from protein and carbohydrate (Kossoff, 2018); (Seo, 2007).

Due to the severe carbohydrate restriction in this type of KD, Long-chain triglycerides (LCTs) pose an issue due to their unpalatable nature and difficulty in preparation and maintenance. As an alternative, medium chain triglycerides (MCTs) containing octanoic and decanoic acids were devised in 1971, with 60% of the calories they provided. Compared to LCTs, MCTs are more acceptable, ketogenic, and effective, as confirmed by Huttenlocher (1971), Vaisleib (2004), Schwartz (1989), and Neal (2009). However, MCT often leads to gastrointestinal side effects like nausea, vomiting, and sometimes diarrhea (Huttenlocher, 1971); (Liu, 2013). On the other hand, the MAD is based on the Atkins diet, which was popularly used in weight loss. It does not have a strict ketogenic ratio and can usually vary between 1:1 and 1.5:1 and can sometimes reach 4:1. Furthermore, it does not include protein, fluid, or calorie restrictions, carbohydrate intake is restricted to 10-15g/day in the first month and can be increased later to 20g/day (Kossoff, 2003); (Kossoff, 2006); (Foster, 2003); (Kossoff, 2007); (Kang, 2007). Finally, the LIG is also low in carbohydrates, which are restricted to an intake of 40-60g/day, and includes the selection of foods with a low glycemic index and, like the MAD, is easy to implement (Huttenlocher, 1971).

In the initial period of the KD), glucose is primarily produced through gluconeogenesis from amino acids. However, as amino acid consumption decreases, the quantity of glucose acquired from triglyceride (TG) lysis increases due to glycerol liberation (Schutz, 2011); (Dienel, 2019); (Veldhorst, 2009). After a few days of limiting carbohydrate intake, the liver produces ketone bodies (KB) due to the increase in acetyl coenzyme A and fatty acid oxidation. KB is a metabolic state in which the body prefers fat as its primary source of fuel (Owen, 2005); (Bueno, 2013); (Westman, 2007); (McDonald, 2018). This theory emerged from the assessment that a low-carbohydrate, high-fat diet could generate acetone, acetoacetate, and 3-β-hydroxybutyrate (βHB), the primary KB. These KBs have been associated with favorable impacts on the treatment of epilepsy and other disorders (Wilder, 1921); (Woodyatt, 1921); (Paoli, 2014); (Freeman, 2010). When KBs are introduced into the bloodstream, they are utilized by the brain, heart, and muscles to generate cellular energy within the mitochondria (Ulamek-Koziol, 2019; Achanta, 2017; McCue, 2010). Elevated levels of circulating KB can result in the presence of KBs in the urine, known as ketonuria, which is often utilized as an indicator of dietary adherence (Paoli, 2014; Newman, 2017).

Thus, the KD can replicate the metabolic effects of fasting without requiring significant caloric deprivation. This dietary approach has generated considerable interest due to potential therapeutic effects on neurological disorders that are hard to treat using standard medications, as well as on specific metabolic parameters. Several studies have noted such potential benefits (Neal, 2008; Stafstrom, 2012; Rusek, 2019; Westman, 2018; Muscogiuri, 2019; Weber, 2020; Paoli, 2019). (Kong, 2021; Gangitano, 2021) It has been suggested that the KD may play a role in the metabolism of various diseases. Despite this, there is a lack of comprehensive reviews detailing such information. Therefore, this review aims to provide an overview of the potential effects of the KD and the mechanisms involved in metabolic processes and associated non-communicable metabolic diseases.

2. MATERIALS AND METHODS

For this study, it was thoroughly reviewed scientific literature on the KD. Our search included reputable databases such as Scielo, PubMed, Medline, Cochrane Library, and Researchgate. The inclusion criteria involved relevant keywords such as "diet", "ketogenic diet", "metabolic diseases", "obesity", "dyslipidemia", "microbiota", and "metabolic effects".

All authors evaluated the relevance of the retrieved records to the inclusion and exclusion criteria and their alignment with the consulted databases by assessing their titles, abstracts, and keywords.

Within the inclusion criteria, we included articles that were accessible in full text and published either in English or Spanish. Our selection incorporates both animal and human studies. For the human studies, we specifically

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considered articles that featured adult male and female participants, with endpoints focusing on changes in body weight, lipid profile, or biomarkers of metabolic disease risk. Excluded from the analysis were studies conducted *in vitro*, studies conducted in animal models different from the established one, qualitative studies, and studies that examined the effect on acute diseases or in the absence of metabolic alterations. The search was conducted between March and September 2022. Additionally, while following the established criteria for study inclusion, we conducted manual searches of bibliographic references from the records to identify any pertinent documents that may have been overlooked in the bibliographic search strategies.

3. RESULTS AND DISCUSSION

3.1. Ketogenic diet and its metabolic implication

Non-communicable metabolic disorders (NMDs) are a major cause of mortality worldwide. This term describes a group of conditions that are not primarily caused by acute infections but instead have enduring implications for overall health. Consequently, these pathologies often necessitate ongoing treatment and support (World Health Organization, 2002). Examples of NMDs include diabetes mellitus (DM), obesity, cardiovascular disease, and cancer. These conditions can be prevented by reducing or eliminating common risk factors as a preventive therapeutic objective. The impact of KD implementation has been subject to investigation. Adopting preventive, therapeutic goals to reduce common risk factors to prevent these conditions is recommended. Additionally, the potential impact of implementing the KD requires further study. (Zhang, 2021).

3.1.1 Diabetes Mellitus

The global incidence of diagnosed DM in adults has risen, with undiagnosed cases and individuals at risk of developing the disease (Abuyassin, 2016) also needing to be acknowledged. Type 2 DM is a widely studied disease characterized by chronic hyperglycemia and elevated HbA1c concentrations. As dietary carbohydrates primarily increase these levels, it is logical to assume that reducing carbohydrate intake could be a valuable tool for managing the disease (American Diabetes Association, 2008; Hallberg, 2018), with potential benefits for glycaemic control, HbA1c levels and body weight (Michalczyk, 2020; Ahmed, 2020). In diabetics, a 24-week study indicated that a very low-carbohydrate diet led to a greater reduction in blood glucose levels than a low-calorie diet (Rafiullah, 2021). Furthermore, a 12-month study found that people with type 2 DM experienced greater weight loss with a high-fat diet than with a high-carbohydrate diet. Similarly, Nanri's (2015) five-year prospective study found an association between low-carbohydrate diets and a lower risk of DM in women, as well as a significant decrease in postprandial glucose concentrations and HbA1c, which was also reported in studies by Dashti (2007), Gannon (2010), Rizza (2010), Hussain (2012), and Nuttall (2008). Consequently, these diets hold promise in aiding patient weight loss and reversing metabolic syndrome manifestations in individuals with type 2 DM (Hallberg, 2018).

In addition, the observed improvement in clinical trials could potentially result in reduced or eliminated insulin requirements. This can be attributed to the strong correlation between insulin resistance and the main ketosis pathways. Glucose transporter type 4, a protein regulated by insulin, has been found to have a direct correlation with proteins involved in DC induced pathways such as 3-hydroxyacyl-coenzyme A dehydrogenase and acyl-coenzyme A oxidase 1 (Farrés, 2010). Furthermore, research conducted on mice suffering from type 2 DM exhibited that KD reduced the expression of type 2 glucose transporter mRNA in the liver, implying a decrease in insulin levels (Zhang, 2018).

On the other hand, both positive and negative outcomes have been noted in individuals with type 1 DM. While KD may enhance glycemic control, they can also potentially cause dyslipidemia, which is a particular worry for those with diabetes who already have an elevated risk of cardiovascular events. Likewise, metabolic irregularities and sustained ketosis are associated with this pathology in individuals with type 1 DM, which may heighten the likelihood of complications (Kanikarla-Marie, 2016; McClean, 2019; Leow, 2018).

The advantages of the KD have predominantly been linked to type 2 diabetes studies. Its efficacy relates to decreased blood glucose levels, HbA1c, and significant weight loss. However, the benefits of KD appear to decrease over time (Brouns, 2018). Short-term studies have reported only a few adverse effects (Ellenbroek,

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2014; Westman, 2008; Colica, 2017). However, it should be noted that the use of this diet is not recommended for individuals with type 1 diabetes mellitus, as it may increase the risk of dyslipidemia, even though it may improve glycemic control.

3.1.2 Obesity

In recent years, researchers have noted the advantages of KD in treating patients with obesity. It has been previously stated that in patients with DM, KD can result in weight loss (Foster, 2003); (Westman, 2008); (Dashti, 2004); (Dashti; 2006). A meta-analysis of randomized controlled trials indicated that, compared to low-fat diets, KD was more effective in enhancing metabolic parameters linked to blood glucose, weight, and lipids in obese individuals, chiefly those with pre-existing diabetes (Choi, 2020). In the short term, the KD has significantly reduced body mass index (BMI), body weight, body fat percentage, waist circumference, hip circumference, blood pressure, and insulin resistance significantly. Furthermore, it has substantially decreased serum levels of inflammatory markers like C-reactive protein, proinflammatory cytokines, leptin, and adiponectin (Michalczyk, 2020; Castaldo, 2016; Kong, 2020; Walton, 2019; Monda, 2020). Therefore, the KD would impact hormonal levels, as evidenced in a 12-week dietary intervention study with sedentary obese adults. The study detected a noteworthy decrease in insulin and leptin levels and an increase in adiponectin (Mohorko, 2019).

On the other hand, in the long run, a KD notably lowered weight, body mass index (BMI), glucose levels (Dashti, 2007), and overall serum cholesterol (TC) in obese patients with high cholesterol, mitigating the risks of various chronic illnesses linked to obesity (Dashti, 2004). Similarly, a study conducted over two years compared the efficacy of a low-calorie diet with a very low-calorie KD in treating obesity. The findings indicated that KD led to higher weight loss percentages despite side effects such as fatigue, headache, constipation, and nausea, which did not cause patients to withdraw from the trial (Moreno, 2016). Thus, evidence highlights KD's potential in enhancing biochemical, hormonal, and anthropometric markers in obese patients.

3.1.3 Cardiovascular diseases

Cardiovascular diseases (CVD) encompass various conditions adversely affecting cardiac and vascular function (Virani, 2020). The heart is a constantly functioning pump, demanding a lot of energy. Fatty acids serve as the primary fuel for mitochondrial ATP production in the adult heart, while glucose is also a significant energy substrate, enabling adaptive changes in utilization during development and in response to nutritional conditions (Dorn, 2015). Drawing from the evidence that the malfunctioning heart enhances the utilization of KB as a protective mechanism against metabolic stress, a down-regulation of heart failure (HF) was observed in the absence of βHB oxidation, compared to controls, indicating the potential efficacy of ketone supplementation for treating HF (McMurray, 2019). CVD has been linked to chronic HF (CHF), indicating that providing ketones exogenously could enhance cardiovascular function and prevent CHF development (Nielsen, 2019; Horton, 2019). Although no recent studies have directly addressed new paradigms, KD has been associated indirectly with atherogenic risk due to observed lipid and lipoprotein profile modifications.

3.1.4 Lipoprotein metabolism

KD is enriched in lipid content, and there is natural concern regarding the resulting elevated serum lipid levels. On the one hand, Ozdemir et al. point out that prescribing to patients with at least 12 months of KD could significantly elevate TC and low-density lipoprotein (LDL-C) and TG without affecting the high-density lipoprotein (HDL-C) level. In addition, another investigation (Zamani, 2016) found that a 6-month KD could markedly increase median triglycerides, TC, LDL-C and HDL-C. Another study revealed that a KD rich in fat significantly elevated lipoproteins containing apolipoprotein B (apoB) and decreased HDL-C, the anti-atherogenic par excellence, inferring that the diet impairs endothelial function and facilitates inflammation and the formation of atherosclerotic lesions. (Kwiterovich, 2003) Regarding LDL-C with a very low carbohydrate diet, in a 6-month study, 29% of the participants had an average increase of 18mg/dL of this lipoprotein (Westman, 2002). In a similar study of the same duration, 30% of participants had increased LDL-C, which is related to an atherogenic effect (Yancy, 2004). However, recent

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studies have provided evidence that reducing dietary carbohydrates can reduce serum concentrations of TC, TG and increase HDL-C, data that are considered beneficial to health (Tragni, 2021); (Alarim, 2020). In relation to the LDL-C particles, it is known that KD can increase the size and volume (Volek, 2021), which is thought to reduce the risk of cardiovascular disease, since smaller and denser LDL particles have greater atherogenic activity. Furthermore, depending on the model, it has been observed that KD affects the levels of HDL-C, LDL-C and TG in rodents (Ellenbroek, 2014); (Bielohuby, 2013); (Douris, 2015), while in humans it does the opposite (Tay, 2018). All this leaves conflicting results depending on the study model and the fact that this could be due to the different composition of the diets, considering that animal studies generally use diets that are higher not only in total fat, but also in saturated fat (Kosinski, 2017).

3.1.5 Gut microbiota

It is interesting to describe how the gut microbiota and diet interact and how this interaction relates to overall health to determine whether changes in dietary habits, such as a low-calorie diet, have a positive or negative effect on overall diversity. The microbiota consists of more than eight thousand different species of bacteria, viruses, and fungi living in a complex ecosystem in the human gastrointestinal tract (Wallace, 2018). Its composition plays a fundamental role in human health, which is mainly determined by factors such as diet (David, 2014). According to one study, the average heritability of gut microbiota taxa is only 1.9%, while more than 20% of the variability is associated with diet and lifestyle (Rothschild, 2018). This composition is important because an alteration can lead to intestinal dysbiosis, which has been linked to a wide range of chronic metabolic disorders (Turnbaugh, 2009); (Le Chatelier, 2013); (Qin, 2012); (Karlsson, 2013) such as obesity (Tremaroli, 2015) and weight loss after bariatric surgery (Ridaura, 2013), in addition to findings in mice suggesting specific bacteria that could cause insulin resistance (Pedersen, 2016). This highlights the importance of the state of the microbiota in influencing overall health. Based on the analysis of popular diets, low carbohydrate diets have a higher risk of being nutritionally inadequate due to the lack of fiber, vitamins, minerals, and iron (Adam-Perrot, 2006); (Kennedy, 2001). Thus, positive changes in the gut microbiota and general health have been observed depending on the food group, e.g. energy-restricted diets or diets rich in fiber and vegetables (Claesson, 2012), (Lynch, 2016). In contrast, KD alters the intestinal microbiota, causing changes in the intestinal microbiota due to the production of KB, as in the case of βHB, which selectively inhibits the growth of Bifidobacterium, a protective barrier bacteria against inflammation (Turroni, 2008); (Ang, 2020). Furthermore, compared to high-fat diets, KD reduces the levels of proinflammatory intestinal Th17 cells, which supports the role of KD in reducing mucosal protective mechanisms, which could generate uncertainty about its implementation (Ang, 2020); (Aguilar-Jimenez, 2011).

3.2 Adverse effects of implementation

Important factors to consider are directly related to the implementation of KD in adults. On the one hand, KD is often low in thiamine, folate, vitamin A, vitamin E, vitamin B6, calcium, magnesium, iron, and potassium (Freedman, 2001). Without multivitamin supplementation, people on low-carbohydrate diets risk significant nutritional deficiencies (Bilsborough, 2003). And very low carbohydrate diets may also lack fiber and phytochemicals (Liu, 2013); (Patterson, 2020); (Slavin, 2012). Thus, extreme carbohydrate restriction can have a profound effect on diet quality.

Dietary adherence remains a major challenge in KD. Inefficacy, side effects, food restriction, and unpleasant taste can reduce patient motivation and lead to discontinuation and subsequent treatment failure (Howrie, 1998); (Zarnowska, 2020). The ability to control hunger is also a key component of success, and low carbohydrate diets are more effective in controlling hunger (McClernon, 2007); (Martin, 2011); (Castro, 2018). In addition, there is a measurable biomarker, βHB, when a person is in ketosis, the body begins to produce ketones, and βHB levels increase, indicating adherence to the diet (Mohorko, 2019).

Various adverse effects have been reported, depending on the type of restriction. Short-term effects such as fatigue, irritability, headache, nausea, hypoglycemia, diarrhea, and refusal to eat are common in the first few weeks of the diet, as are reactions to the metabolic changes induced by the diet, which are generally predictable and preventable. One of the most common is mild to moderate dehydration due to reduced fluid intake, acidosis, reduced renal tubular reabsorption, and increased urinary

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excretion. There are also adverse effects that can last for the duration of the diet, often including gastrointestinal disturbances such as constipation, abdominal pain, vomiting, and gastroesophageal reflux disease.

On the other hand, most studies have not been long-term due to the difficulty of adhering to the diet, as food choices are limited and not sustainable over time. In addition, KD has been described to reduce bone mineral density, nephrolithiasis, cardiomyopathy, and anemia (Zarnowska, 2020); (Furth, 2000); (Crosby, 2021); (Włodarek, 2019).

4. CONCLUSIONS

KB is involved in several metabolic pathways. The protective effects of KB and the implementation of KD may lead to improved health status.

Regarding chronic metabolic disorders, KD was positively associated with type 2 DM by reducing blood glucose levels, HbA1c, and greater weight loss. However, it was not recommended in type 1 DM, where it improved blood glucose levels but favored the development of dyslipidemia. In addition, KD reduced BMI, body weight, anthropometric measures, and inflammatory markers, demonstrating its benefits in improving obesity-related factors.

Moreover, KD has been shown to reduce serum concentrations of TC, TG, and LDL-C and increase HDL-C, which could be related to an anti-atherogenic pattern, although studies have been reported that show the opposite, increasing these parameters. Another factor to consider is the effect of dietary composition and how it affects the microbiota, where KD has been negatively associated because KB inhibits the growth of bifidobacterium, bacteria that protect against inflammation.

Although KD has promising therapeutic potential, its clinical implementation remains uncertain. Therefore, further studies are necessary to deliver high-quality clinical evidence regarding its efficacy and safety. It is crucial to modify treatment plans to minimize adverse effects and enhance tolerability while comprehensively understanding the mechanisms involved, guiding personalized application for individuals with pre-existing diseases.

5. DECLARATIONS

5.1. Study Limitations

This research is limited to the references consulted during the study.

5.2. Acknowledgements

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5.3. Funding source

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5.4. Competing Interests

The authors declare no conflict of interest.

5.5. Open Access

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