

A Review of the Uses of the Ketogenic Diet

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Abstract

The use of the ketogenic diet is a safe and effective process to reduce the health complications of obesity, thus losing weight while preventing weight regain at the same time. Humans have metabolic flexibility and the potential to utilize ketones as an energy source by reducing carbohydrate intake in the diet, this reduces insulin levels, and ketogenesis occurs. These conditions promote the release of excess stored fat, avoid muscle weakness, and improve insulin sensitivity. Losing weight by diet causes appetite feeling and a rise in ghrelin release, that raises the likelihood of regaining weight and is thus counterproductive to goals for weight reduction. The study's aim is to review evidence on a ketogenic diet for weight loss and metabolic illnesses like insulin resistance, lipid disorders, cardiovascular disease, fatty liver disease development, and Polycystic Ovarian Syndrome and exercise and delay aging, in addition to addressing the side effects of the ketogenic diet, and thus we provide basic information about nutritional ketones and the mechanism of their generation.

1. Introduction:

The BMI (body mass index) is used to classify obesity (BMI). A BMI between 18.4 and 25 $km.(m)^{-1}$ is thought to be ordinary, however a BMI between 24.9-30 is considered weight gain, and a BMI of 30 is regarded to be obesity (it is also defined as Type 1 obesity when the BMI is between 30.0 and 34.9, Type 2 when the BMI is between 35.0 and 39.9, and Type 3 when the BMI is more than 40.0) [1]. Over 1.9 billion adult humans are overweight, with over 650 million being obese [2]. Type 2 diabetes, high blood pressure, heart problems, malignancy, apnea (sleep deprivation), and hypoventilation Syndrome in Obese People are only a few of the comorbidities linked with obesity. Over the last few years, the success of various kinds of meals supported on limitations for different macronutrients has already been a point of contention. Some researchers advocate for carbohydrate restriction, while others advocate for protein or fat reduction [3]. Weight loss treatments through safe and effective diets are among the most crucial methods to reduce Obesity's consequences on results relating to health [4].

To induce ketosis, the ketogenic diet (KD) should consist of a diet that is low in carbohydrates, moderate in protein,

and high in fat ketosis [5]. The KD concept was initially developed in 1921 for the management of intractable epilepsy in pediatric patients [6]. Typically, the diet primarily consists of lipid, with carbs and protein accounting for only %20 to %80 of the total calories consumed. More than 90% of calories are obtained from lipid [7]. All variations of this diet are based on a severe restriction of carbohydrates to get them below 50 gram per day. In a well-designed KD, protein should be less than 2 gram per pound of body weight. Furthermore, the regimen does not limit fat consumption and suppresses hunger, actually results weight reduction that occurs quickly shortly after beginning the program [8].

KD has been demonstrated to help people lose weight, lower their insulin levels, and enhance their insulin sensitivity. Patients with diabetes, on the contrary, hypoglycemia may be severe if their medication regimen is not carefully maintained during the start of KD therapy, KD is also not recommended for people who have liver failure, pancreatitis, or inborn fat metabolism abnormalities [8]. The 'keto flu,' which includes symptoms such as fatigue, headache, dizziness, nausea, vomiting, constipation, and low exercise tolerance, is a frequent short-term side effect of initiating treatment with KD [9]. As the body adapts to a low-carb ketogenic state, symptoms normally fade after several days or even weeks. Symptoms usually disappear within several days or even weeks as the body responds to a low-carb ketogenic condition. The benefits

of adhering to a KD have long been proven [10].

2. History and origin:

The ketogenic diet was first studied in the early twentieth century as a strategy to minimize seizure occurrence and manage epilepsy. Treatments showed less seizure occurrence and improved mental performance after being put into ketosis, demonstrating ketones' potential to deliver energy to the brain [11]. It is a treatment system that was invented to replace the old traditional system in the treatment of epilepsy, and despite its popularity in the twenties and thirties of the last century, it was banned and withheld to allow new epilepsy drugs to enter the market. Most individuals can control their epileptic seizures with medications, but about 20 – 30% fail to control them with many medications [12]. Therefore, for this percentage, especially for children, the diet was able to find a role for itself once again in the treatment of epilepsy.

3. Dietary ketosis as an alternative source of energy release:

Humans have flexibility in their ability to metabolize alternative sources of energy release. Instead of relying on external sources of glucose for optimal function, Depending on the availability of different fuel sources, our bodies have developed to use ketosis [13]. The body can go into ketosis, in which ketones derived from fats made by the liver are used to supply energy to nearly all of the body's cells instead of glucose. When blood glucose and glycogen stored in the liver are reduced, the liver produces ketone molecules (acetone, acetoacetate, and β -hydroxybutyrate). Ketones are compounds that are soluble in water created from lipids by the hepatic. Glycogen exhaustion occurs, and ketosis levels rise during starvation, low-carbohydrate eating, severe exercise, malnutrition, or in type I diabetes due to a lack of insulin.

Fatty acid metabolism is the breakdown of lipid and ketosis (synthesis of ketone) are triggered by the epinephrine and glucagon hormones, which are blocked by insulin. Insulin secretion stabilizes at low levels on a reduced carbohydrate diet, but glucagon secretion rises. When you have a low insulin amount, hormone-sensitive lipase breaks down lipids stored in adipose tissue. Glucagon also accelerates glycogen breakdown in the liver while activating fat breakdown to liberate lipids that have been stored from fat deposits in the body [14]. Fatty acids that are not bound together undergo β -oxidation in the mitochondria in the liver to produce acetyl-CoA and ketone, which are the middle materials between both oxidation of fatty acids and catabolism of glucose. After then, acetyl CoA might join the Krebs acid cycle to produce the necessary compounds for oxidative phosphorylation to generate ATP. When blood glucose levels rise (as they do after a carbohydrate-heavy diet), The amount of insulin in your body increases as well, and Ketogenesis is stopped to support fat metabolism. As a result, ketogenesis is defined as a change

from a condition in which glucose is needed regulated by insulin to a higher possibility to use stored lipid and intake fat as power generation. Ketones are a type of organic compound are created in the hepatic and subsequently distributed all around the body to provide the brain's energy, cortex of the kidneys, circulatory system, and muscle fibers of the skeletal through this mechanism [15].

4. Dietary ketosis as a medical treatment:

Since the 1960s, Ketogenic diets have proven to have therapeutic potential in a variety of conditions, including hyperglycemia, polycystic ovaries syndrome, skin problems, nervous system diseases, seizure disorders, amnesia, stroke, malignancies, respiratory improvement, and risk factors for cardiovascular disease, in recent studies [11]. Eating potentially reduces or eliminates the need for medication, but can have significant side effects, so this regimen requires further studies. The formation of ketogenesis and the maintenance of insulin amount, which is a marker of biomarkers for metabolic syndrome, are crucial features of ketogenic diets. Ketosis can be utilized as a lipolysis indication by lowering insulin levels and increasing the release and oxidation of stored fats [16].

4.1 Dietary ketosis to weight lose:

Nutrition ketogenic is described as a reduction in carbohydrate consumption in order to increase ketone generation and create a metabolic response that lowers blood sugar and insulin release. Several studies have found that raising insulin causes an increase in food consumption, whilst lowering insulin causes weight reduction. The ketogenic diet consists of (20 to 50 gram per day) carbohydrates, (1 to 1.5 $gram.kg^{-1}$ per day) protein, and fats till you've had enough. An indicator of nutritional ketosis is blood ketone values between 0.5 and 3 $mg.dL^{-1}$ [17]. Adaptation occurs several weeks after adherence to a ketogenic diet, which indicates the body's response to using ketones derived primarily from fat as fuel to release energy. One possible reason for the system's adaptation is gene transcription on a regular basis, which encodes the metabolic pathway required for ketogenesis, as a result, the density of mitochondria in oxygenated tissues including the brain and muscle rises. This could be attributed to accelerated division or reduced mitochondrial damage, according to studies in mice [18].

4.2 Dietary ketosis for metabolic syndrome:

Even with an increased intake of saturated fats, reducing carbohydrates can lead to significant improvements in blood lipid markers, Among the important modifications in fatty indicators are significantly reduced in triglyceride values in serum, substantial benefits in terms of decreasing blood cholesterol levels, and rise cholesterol high-density lipoprotein, the change in the amount and volume of LDL particles [19]. In an 84-day study, reduced carbohydrate nutrition consisting of

12% carbohydrate, 59% fat and 28% protein or , reduced lipid nutrition consisting of 56% carbohydrate, 24% fat, and 20% protein were tested on 40 people with overweight and lipid disorders caused by atherosclerosis . After eating saturated fat while fasting, the participants on reduced carbohydrate nutrition had decrease triglyceride amount, and HDL values that are increased . The goal was to find out how it affects indicators of metabolic syndrome and cardiovascular disease risk. The carbohydrate-restricted group had a reduction in obesity, sugar, insulin, and triglycerides, as well as a rise in High - density lipoprotein , but an effect on LDL most intriguing was, after reducing carbohydrate intake, they noticed a shift from smaller, denser, more LDL size to larger LDL size [20]. A study [21] confirmed that high levels of LDL-c and VLDL-c and low levels of HDL-c are associated with high levels of ALT, AST, ALP and GGT, which indicates damage to liver cells and leakage of enzymes into the blood serum.

Many researchers have found a link among carbohydrate consumption and LDL particle size and density, with the link appearing to be stronger among diabetics . It is known that smaller and denser LDL particles are directly associated with an increased risk of cardiovascular disease. The positive effects of a low-carbohydrate diet on lipids are explained by the turnover of lipoproteins. Increased levels of plasma triglycerides are associated with cholesterol esterification of VLDL particles, leading to the formation of small, dense LDL particles [22]. Persistent elevation of blood sugar leads to hyperinsulinemia, liver insulin resistance arises as a result of this and VLDL size rich in triglycerides have risen that cause atherosclerosis by lowering HDL and increasing small and dense LDL particles [23]. High levels of LDL-c and VLDL-c are directly correlated with the level of MDA and inversely with the levels of GSH, CAT and TAC, which leads to high levels of free radicals and a decrease in the level of antioxidants, thus causing tissue damage and metabolic disorders [24]. And the high levels of LDL-c and VLDL-c in the blood serum or liver extract lead to histological disorders, imbalance in sex hormones, an increase in the level of free radicals and a decrease in the level of antioxidants [25],[26],[27].

4.3 Dietary Ketosis for Glycemic Control and Insulin Sensitivity:

In treating diabetes and avoiding comorbidities, such as systemic microvascular problems, plasma glucose should be controlled and the effects of insulin on lipid metabolism modified because insulin resistance leads to increased liver fat accumulation, VLDL synthesis, and endogenous glucose formation [22]. Insulin resistance also causes fat deposits in non-fatty organs such as skeletal muscle, heart, and pancreas [28]. Ketogenic diet on a nutritional level is possible enhance drug lowering and blood glucose control use, in addition to its weight-loss benefits . In a study (Saslow et al.,2017), 34 overweight and obese people were randomly assigned to a low-carb ketogenic diet or a low-fat, moderate-carbohydrate

diet for 12 months, subjects on the ketogenic diet showed a more significant decline in hemoglobin glycosylated in comparison to persons who consume a reduced lipid diet , moderate-carbohydrate diet , and the ketogenic diet was able to reduce anti-diabetic medications [29].

The ketogenic diet in patients with type 2 diabetes is associated with a reduced need for insulin that is produced outside of the body. Increased ketone levels decrease glucose production in the liver, which means that higher ketogenic concentrations are associated with better blood sugar control. The use of the ketogenic diet in patients with type 2 diabetes compared to the high-carbohydrate diet reduced the amount of insulin secretion in answer to a diet and reduced the need for insulin to maintain a normal blood sugar level, and more than in this study, 50% of patients were capable to halt or reduce diabetes drugs after changing to the ketogenic diet , which indicates that the ketogenic diet improves insulin sensitivity and glycemic control and reduces the need for less insulin to reach target glucose [30]. In a study (McKenzie et al.,2017) 262 people with diabetes were tested on a ketogenic diet and administered medication with the assistance of a physician. Reassessment after 70 days revealed a consistent decrease in carbohydrates as indicated by mean levels of beta-hydroxybutyrate, decrease in glycosylated hemoglobin, and use of diabetes medications [31]. Diabetic individuals who followed a ketogenic diet for a year compared to the standard diet experienced improvement in indicators of cardiovascular disease, such as lipid level, LDL particle size, blood pressure, and inflammation [32]. The results in the study (Hallberg et al., 2018) showed that participants who depended on the ketogenic diet decreased glycosylated hemoglobin, while halving the use of diabetes medications, and at the same time, 40% of the subjects were able to stop using exogenous insulin, Additionally 60% of users cut their daily insulin dose in half [33].

Although the majority of studies have been in patients with type 2 diabetes, there are no contraindications to therapy with a low carb diet of type 1 diabetes. Results in a study (Leow et al.,2018) of adults with type 1 diabetes showed results Those who adhered to the keto diet for 30 months had an excellent reduction in glycosylated hemoglobin levels while maintaining a normal blood glucose level [34]. Most studies examining both ketogenic and non-ketogenic diets in individuals with type 2 diabetes found lower glycosylated hemoglobin, which measures the value of blood sugar, and improved response to insulin in response to less carbohydrate consumption [35].

4.4 Polycystic Ovarian Syndrome:

KD favorably affects women with polycystic ovarian syndrome (PCOS). PCOS causes disorder or menstrual is not present , sterility, fatness , and other hyperandrogenism symptoms such as hirsutism in women . PCOS is neatly related to other endocrine and metabolic disorders, Resistance of Insulin , high blood insulin , diabetes mellitus of the type 2 , dyslipi-

demia, and excessive androgen are some of the conditions that can occur [36]. (Mavropoulos et al., 2005) applied KD to women aged 18 to 45 years with PCOS, with a body mass index higher than $27 \text{ km} \cdot (\text{m})^{-1}$, without other disease states. For 180 days, the participants adhered to a ketogenic diet that contained less than 20 grams of carbohydrates per day, while consuming fat until fullness. After 168 days, the results of the study showed a significant decrease in the insulin value, the rate of luteinizing hormone to follicle-stimulating hormone and testosterone. Additionally, the study participants had a reduction in average body mass index and overweight [36]. Patients with PCOS were assigned randomly to either a regular or a KD diet in this study. The outcomes showed that KD is capable of managing to a decrease in sugar and reduce insulin resistance [37]. Similar results were obtained in another study with major decreases in body weight, glycemic index, low-density lipoprotein, triglyceride, luteinizing hormone, and testosterone [38].

5. Ketogenic diet and appetite:

On a ketogenic diet, induction of ketosis occurs when lipids in the hepatic are converted to ketones (referred to as HB levels in the blood) because of low levels of glycogen in tissues [39]. That ketosis can prevent increased appetite after weight loss, persons have mentioned starting to feel less starvation in the fasting state and, in some cases, feeling satiety after a repast. This is critical in clinical practice, as persistent rises in sense of hunger are an usual grumble in people who have slimmed down through energy-restricted diets [40]. It could lead to a decrease in long-term adherence to diets that are low in calories. Thus, heightened emotions of hunger can also guide to reduce aims for weight loss and even weight recovery in the long term. A study (Lyngstad et al., 2019) showed that when weight loss is stimulated using the ketogenic diet, the feeling of hunger does not increase and ghrelin secretion remains at normal levels [41]. A study (Sumithran et al., 2013) on women and men in equal numbers (35 of them) suffering from overweight and obesity, no changes in the release of active postprandial GLP-1 with 13% weight loss and a significant decrease in total postprandial PYY release, and no decrease in CCK secretion after eating, as with weight loss when in ketosis [42].

A study (Deemer et al., 2020) indicated that there is a relationship between ketogenic body concentrations in the serum and markers of appetites in volunteers who are directly exposed to the ketogenic diet, evidence of the role of ketones in suppressing appetite. It was confirmed that there was a decrease in ghrelin secretion and a higher perception of satiety with an increase HB in plasma under nutritionally induced ketogenic conditions. This indicates that ketones, measured here as β -hydroxybutyric acid, may influence the release of appetite-related hormones directly or indirectly, particularly ghrelin, whose release is inversely related to the

magnitude of ketosis [43]. β -HB appears to raise circulating levels of adiponectin, brain -aminobutyric acid, and phosphorylation of AMP-activated protein kinase. However, in feeding-related parts of the hypothalamus, β -HB increases postprandial free fatty acid secretion and decreases neuropeptide Y and agouti-related protein expression. It also increases postprandial cholecystokinin secretion, decreases ghrelin secretion, and decreases AMP-activated protein kinase expression [44].

6. Ketogenic diet and exercise:

Studies have shown that ketogenic body supplementation is a way to induce ketosis and provide sustainable sources of fuel for energy generation and enhanced exercise performance [45]. In addition to the use of the ketogenic diet for weight loss, the ketogenic diet is also prominent within the athletic community as a superior source of energy [46]. The contribution of lipids to oxidation metabolic changes depending on the duration and strengthening exercises. [47]. Fatty acid oxidation during exercise of low and medium intensity is an important source of energy, as the involvement of lipid to oxidation metabolic during gym of moderate severity with increases the period of exercise. Thus the KD may be beneficial by encouraging the use of fats rather than carbohydrates as an energy source. The fat stored in adipocytes is a constant source of fuel, whereas intracellular glucose reserves of stored energy in muscle fibres and the hepatic are restricted. The high ketones produced by the ketogenic diet may provide an alternative energy source for humans to maintain good exercise performance. [48],[49]. A study (Phinney et al., 1980) reported significant loss of body weight and fat mass by obese individuals, especially women, on a sugar-restricted diet coupled with moderate-intensity exercise [50]. This indicates that exercise increases the efficiency of the ketogenic diet in weight loss.

7. ketogenic diet and aging:

A decrease in amount of muscle fibers and operate effectively occurs as one grows older. This is called as Sarcopenia, which occurs in the rate of 14% in people aged 65 to 69 years, and ratio 50% in people aged up to 80 years. Sarcopenia the capacity to administer actions of everyday life and involvement to absence of movement and flexibility, in addition an elevation in the danger of weakness, disease and death. The setback of muscle weight as a result of aging leads in a reduction in the number of muscle fibers and a decrease in their thickness [51],[52]. Calorie restriction is one of the much more effective anti-aging treatments that inhibits the initiation and progression of sarcopenia in skeletal muscle, and adherence to the ketogenic diet is one mechanism that underlies the benefits of caloric restriction for muscle mass retention with age [53],[54].

Adherence to the ketogenic diet (KD) increases life expectancy, improves health, acts as a neuroprotectant, improves mitochondrial function, activates autophagy, has anti-inflammatory effects, and increases expression of antioxidants and anabolic signals in aged mice [55],[56],[57]. A study (Wallace et al., 2021) compared the muscles of mice fed a ketogenic diet for 14 months. Skeletal muscle mass significantly increased in the leg muscle and increased regulation of gene expression of mitochondria, metabolic oxidation and capability for antioxidants, whereas reducing stress on the endoplasmic reticulum and production of proteins compared to the normal control group [58]. These modifications may create a healthy cellular environment, reduce oxidative stress resulting in improved protection of amount of muscle fibers and operate effectively and suppress aging as one grows older.

8. Possible side effects of the ketogenic diet:

Despite the benefits of the ketogenic diet, there are still various concerns. Studies indicate that adherence to the ketogenic diet leads to the deposition of fat in the liver and thus the occurrence of hepatic steatosis, as well as affecting the balance of glucose levels in the blood [59]. Recent evidence raises potential concerns about the impact of a ketogenic diet on bone health, as several studies of a ketogenic diet in rodents have shown a reduction in bone mineral content and bone density [60],[61]. The study (Simm et al., 2017) when using a ketogenic diet by children with epilepsy showed a decrease in metal composition of bones and bones deterioration [62]. The use of a ketogenic diet accelerated the neurodegeneration process in a neurodegenerative models in a transgene mice and prompted mitochondrial dysfunction, despite its role in promoting mitochondrial biogenesis [63]. In addition, the ketogenic diet caused the formation of stones in the renal in 6% of babies have uncontrollable epilepsy but it could be reduced by administering potassium citrate [64]. Surprisingly, latest research have noticed considerable reductions in the hormone ghrelin in children with epilepsy when adhered to the ketogenic diet, and thus reduced growth rates [65]. As a result, future research should concentrate on characterizing the hormonal shifts that may occur as a result of consuming of the ketogenic diet in adults, and conducting additional long-term studies to address the issue of safety and effectiveness of adhering to the ketogenic diet in both normal and pathological conditions.

9. Conclusions:

We can take advantage of the antagonistic link between rise glucagon and decrease insulin values, which stimulates fat burning for energy while inhibiting muscle glycogenogenesis, according to our assessment of alternative fuel sources of ketones. It leads to a decrease in blood pressure, triglycerides and glycosylated hemoglobin, reduced blood sugar, increased

insulin sensitivity and reduced effects of PCOS in addition to an increase in HDL and weight loss. Ketogenic diets (KDs) have been shown to prevent the increase in ghrelin secretion, which can be seen with weight loss, as well as reduce hunger and/or inhibit hunger. However, the above effects should be pursued for a longer period, because the changes reported in the studies we reviewed were for short periods. More research is needed to determine the long-term consequences of the ketogenic diet. Although the positive effect of ketogenic nutrition on HDL, the persistence of the KD too long and severely may lead to rise risk of heart disease. In addition, it can be difficult to adhere to the dietary restrictions necessary to stay in ketosis. Most of the available studies lack generalization because of the low number and short research times. Given the scarcity of well-designed research and strong evidence assessing the diet's possible dangers, suggestions should be made to users of the KD system who do not suffer from comorbidities or cardiovascular and endocrine diseases, and those who suffer from the above-mentioned diseases should avoid the KD system.

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مراجعة حول استخدامات النظام الغذائي الكيتوني

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الخلاصة

يعد استخدام النظام الغذائي الكيتوني من العلاجات الآمنة والعمليات الفعالة لتقليل المضاعفات الصحية للسمنة، وبالتالي فقدان الوزن مع منع استعادة الوزن في نفس الوقت. ان الانسان يمتلك القدرة على المرونة الأيضية والقدرة على استخدام الكيتونات كمصدر للطاقة عن طريق انخفاض تناول الكربوهيدرات في النظام الغذائي، وبهذا ينخفض مستويات الأنسولين ويحدث تكوين الكيتون. هذه الحالات تعزز تحرر الدهون المخزونة الزائدة، و تجنب ضعف العضلات، وتحسن حساسية الأنسولين. يؤدي فقدان الوزن بواسطة الحمية الغذائية الى زيادة في إفراز هرمون الجريلين والشعور بالجوع ، مما يزيد من خطر استعادة الوزن وبالتالي يضر بأهداف فقدان الوزن. الهدف من هذه الدراسة هو مراجعة المعلومات عن النظام الغذائي الكيتوني لغرض إدارة الوزن و الاضطرابات الأيضية، أي تخفيف مقاومة الأنسولين ،واضطرابات الدهون ، والإصابة بأمراض القلب والأوعية الدموية، وتطور مرض الكبد الدهني ومتلازمة تكيس المبايض وممارسة الرياضة وتأخير الشيخوخة، بالإضافة الى التطرق للأثار الجانبية للحمية الكيتونية، وبهذا نقدم معلومات أساسية عن الكيتونات الغذائية والية تولديها.

الكلمات الدالة: النظام الغذائي الكيتوني، مصدر الطاقة، إنقاص الوزن، متلازمة الايض، حساسية الأنسولين.

التمويل: لا يوجد.

بيان توفر البيانات: جميع البيانات الداعمة لنتائج الدراسة المقدمة يمكن طلبها من المؤلف المسؤول.

اقرارات:

تضارب المصالح: يقر المؤلفون أنه ليس لديهم تضارب في المصالح.

الموافقة الأخلاقية: لم يتم نشر المخطوط أو تقديمها لمجلة أخرى، كما أنها ليس قيد المراجعة.