Health Benefits of Ketogenic Diet

Subjects: Nutrition & Dietetics

Contributor: Simran Banga

Considering the lack of a comprehensive, multi-faceted overview of the ketogenic diet (KD) in relation to health issues, we compiled the evidence related to the use of the ketogenic diet in relation to its impact on the microbiome, the epigenome, diabetes, weight loss, cardiovascular health, and cancer. The KD diet could potentially increase genetic diversity of the microbiome and increase the ratio of Bacteroidetes to Firmicutes. The epigenome might be positively affected by the KD since it creates a signaling molecule known as β-hydroxybutyrate (BHB). KD has helped patients with diabetes reduce their HbA1c and reduce the need for insulin. There is evidence to suggest that a KD can help with weight loss, visceral adiposity, and appetite control. The evidence also suggests that eating a high-fat diet improves lipid profiles by lowering low-density lipoprotein (LDL), increasing high-density lipoprotein (HDL), and lowering triglycerides (TG). Due to the Warburg effect, the KD is used as an adjuvant treatment to starve cancer cells, making them more vulnerable to chemotherapy and radiation.

Keywords: β-hydroxybutyrate (BHB) ; body mass index (BMI) ; type 1 diabetes ; type 2 diabetes (T2D) ; hemoglobin A1c (HbA1c) ; visceral adipose tissue (VAT) ; cardiovascular disease (CVD) ; high-density lipoprotein (HDL) ; low-density lipoprotein (LDL) ; Apolipoprotein B (ApoB)

1. Introduction

Ketogenic diets have started to increase in popularity as doctors and researchers investigate the potential benefits. Nutritional ketosis, the aspirational endpoint of ketogenic diets, is achieved by restricting carbohydrate intake, moderating protein consumption, and increasing the number of calories obtained from fat [1]. Theoretically, this restriction of carbohydrates causes the body to switch from glucose metabolism as a primary means of energy production. This results in the use of ketone bodies from fat metabolism, a metabolic state where the body prefers to utilize fat as its primary fuel source. Recent studies utilizing Low-carbohydrate, High-fat (LCHF) diets, such as the ketogenic diet, show promise in helping patients lose weight, reverse the signs of metabolic syndrome, reduce, or eliminate insulin requirements for type II diabetics [2], reduce inflammation, improve epigenetic profiles, alter the microbiome, improve lipid profiles, supplement cancer treatments, and potentially increase longevity [3] and brain function.

The number of Americans suffering from obesity, diabetes, and metabolic syndrome is on the rise. The markers of metabolic syndrome include an increase in abdominal adiposity, insulin resistance, elevated triglycerides, and hypertension [4][5]. All of these negative health markers increase the risk of cardiovascular disease, diabetes, stroke, and Alzheimer's disease. According to WebMD, there are currently 27 million people with Type 2 diabetes and 86 million with pre-diabetes. In addition, the Centers of Disease Control and Prevention (CDC) also estimates that almost 40% of adults and around 20% of American children are obese [6][7]. Many researchers believe these diseases are a result of carbohydrate intolerance and insulin resistance. Thus, a diet that reduces the exposure to carbohydrates, including whole grains, might become a more logical recommendation for improving health [8]. In line with this, two dietary regimens, the standard ketogenic diet, and the therapeutic ketogenic diet (Figure 1), which restrict carbohydrate consumption to varying degrees are being studied for their health impacts. The therapeutic ketogenic diet, which severely restricts both carbohydrates and protein, is typically used in the treatment of epilepsy and cancer. However, the Dietary Guidelines for Americans suggests that between 45 and 65% of caloric intake should come from carbohydrates (Figure 1). If a person consumed 2000 calories per day that would equate to an average of 225–325 g of carbohydrates each day [9].

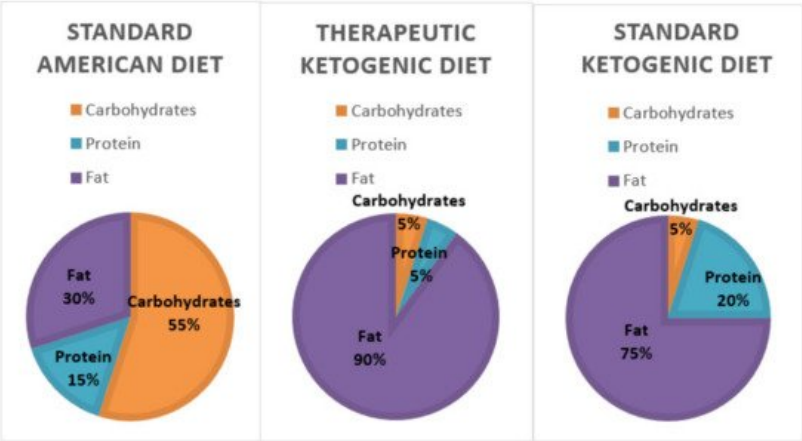

Figure 1. A comparison between the macronutrient breakdown of the standard American diet, therapeutic ketogenic diet, and the typical ketogenic diet. The therapeutic ketogenic diet is typically used in epilepsy and cancer treatments.

One emerging diet that is becoming mainstream is a low-carb/high-fat diet. However, there is a difference between a low-carb and a low-carb ketogenic diet (LCKD). Ketosis is normally achieved through either fasting or carbohydrate restriction. It is important to clarify that a low-carb diet typically refers to a diet with an intake of 50 to 150 g of carbohydrate per day. However, although this is a lower amount of carbohydrates than the standard American diet, it is not low enough to enter nutritional ketosis. Only when a patient restricts carbohydrates to less than 50 g/day will the body be incapable of fueling the body by glucose and will switch to burning fat [10]. The ketogenic diet is a reversal of the current food pyramid supported by the dietary guidelines. Thus, instead of a diet rich in carbohydrates, it is high in fat (Figure 2). The resulting carbohydrate restriction lowers blood glucose levels, and the subsequent insulin changes will instruct the body to change from a state of storing fat to a state of fat oxidation [10]. Once fats are utilized as the primary fuel source in the liver, the production of ketone bodies begins, a process known as ketogenesis. During ketosis, three major ketone bodies are formed and utilized by the body for energy: acetone, acetoacetate, and β-hydroxybutyrate [11]. All cells that contain mitochondria can meet their energy demands with ketone bodies, including the brain and muscle. In addition, research suggests that β-hydroxybutyrate acts as a signal molecule and may play a role in suppressing appetite [12].

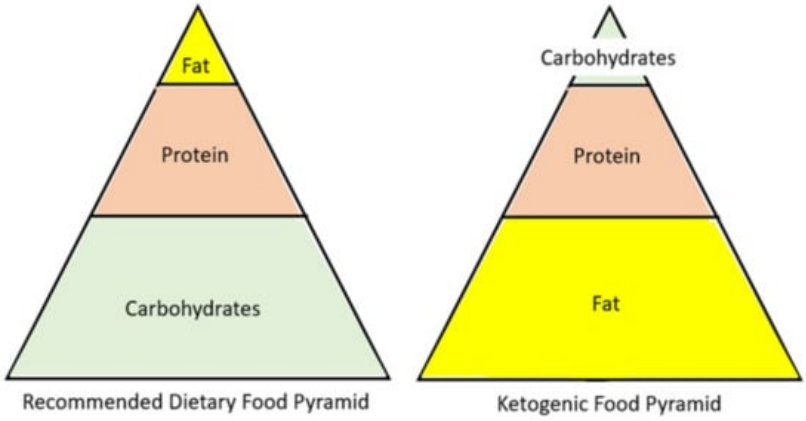

Figure 2. A visual comparison of the recommended dietary food pyramid, including major macromolecule components, to the ketogenic diet food pyramid.

However, there is some heterogeneity in the available data. Thus, the aim of this review is to highlight the role the ketogenic diet has in altering the microbiome, epigenetics, weight loss, diabetes, cardiovascular disease, and cancer as summarized below (Figure 3).

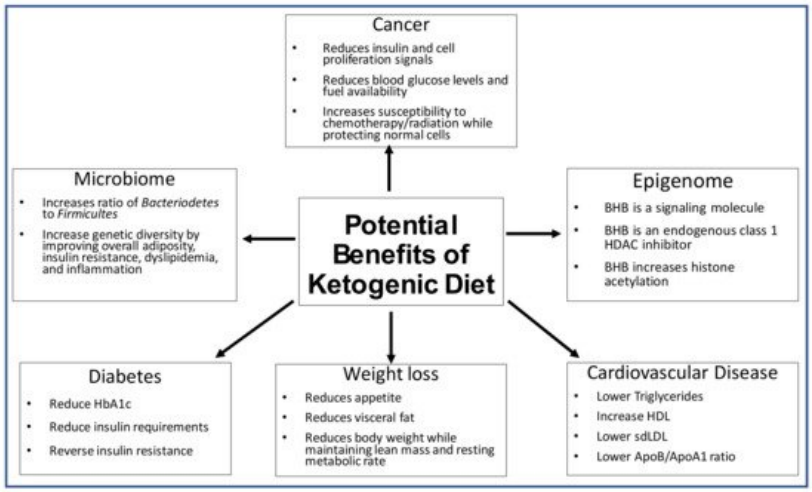

Figure 3. The potential therapeutic impacts of the ketogenic diet on the microbiome, epigenome, diabetes, weight loss and cardiovascular disease.

2. The Effect of the Ketogenic Diet on the Microbiome

The microbiome consists of trillions of microscopic organisms in the human gastrointestinal tract. It comprises over 8000 different types of bacteria, viruses, and fungi living in a complex ecosystem [13]. Recent research suggests that the genetic make-up of a microbiome can be affected by lifestyle factors which include but are not limited to sleep, exercise, antibiotic use, and even diet. These bacteria can alter our response to different food sources because they differ in their ability to harvest energy from food, affecting the postprandial glucose response (PPGR) [13]. Since the controlling of glucose levels in the blood seems to reduce the risk of metabolic disease, diabetes, and obesity, this might be an innovative way to help reduce disease risk. A study conducted at the Weizmann Institute demonstrated that a mathematical algorithm could be used to determine an individual's microbiome profile and predict their glycemic response to different types of foods [14]. Thus, the patients were able to change from stable blood glucose to unstable levels by simply eating the foods that the program predicted as good or bad based on their microbiome. Their initial results were confirmed by a repeat study at the Mayo Clinic with a different population [13]. It is important to note that the composition of the microbiome, which is believed to have a fundamental role in human health, is shaped predominantly by environmental factors. According to a study conducted by Rothschild et al. [15], the average heritability of the gut microbiome taxa is only 1.9%, while over 20% of variability was associated with diet and lifestyle.

Thus, research into the complex interactions that exist between diet, the microbiome, and host metabolic rates have increased. A study exploring the benefits of prebiotic foods, such as inulin and oligosaccharides, observed an increase in the number of *Bifidobacteria* in the colon and the presence of other critical butyrate-producing bacteria [16]. Another study determined that the diversity of the gut microbiota was influenced more by a Westernized diet than by the body mass index of the subjects [17]. The patients who followed the Westernized diet showed an increase in *Firmicutes* and a decrease in *Bacteroidetes* in their microbiome, which are negative changes. A review article also reported positive changes in the gut microbiome and overall health in energy-restrictive diets or diets rich in fiber and vegetables [18]. Thus, people eating processed and bland food had reduced diversity of their microbiota, while people eating a diet rich in fruit and vegetables had increased diversity in their gut microbiota [19]. Moreover, gut biomes that lacked genetic diversity were related to overall adiposity, insulin resistance, dyslipidemia, and an inflammatory phenotype [20].

Discovering how the gut microbiota and diet interact and how this interaction is connected to overall health, is critical. It is important to determine whether new dietary changes, such as a ketogenic diet, will positively or negatively affect overall microbiome diversity and species make-up. Some research has found that whole grains play an important role in the development of a healthy microbiome and are necessary for good health [21]. Thus, a person consuming a ketogenic diet might not consume enough whole grains to maintain a healthy microbiome [12]. According to Adam-Perrot et al. [12] low-carb diets are at greater risk of being nutritionally inadequate by lacking in fiber, necessary vitamins, minerals, and iron. This idea is based on analysis of popular diets and food surveys conducted to determine nutrient intake while consuming varying levels of carbohydrates [22]. Thus, it is even more critical that people on a LCKD choose desirable low carbohydrate foods that are rich in fiber. In addition, a ketogenic diet should maintain moderate protein intake of around 1.5 g/day per kg of respective body weight [23]. If people consume red meat and organ meats, then they should be able to obtain adequate amounts of iron as well. Additionally, the consumption of small amounts of leafy greens, nuts, berries, and resistant starchy vegetables, all of which are optional ketogenic foods, could potentially maintain healthy gut microbiota [23].

Currently, scientists do not have any data on the long-term effects of the ketogenic diet on the gut microbiome. Based on various studies, many predict that the diet will positively affect the microbiome by increasing the *Bacteroidetes* and *Bifidobacteria* species associated with improved health and decreasing microbial species known to increase health risks. In fact, a study found that the disrupted gut microbiota of epileptic infants was improved with a one-week ketogenic diet, which managed to increase their *Bacteroides* amount by ~24% [24]. Another 6-month study on children with refractory epilepsy found a significant decrease in *Firmicutes* and an increase in *Bacteroides* although the overall diversity decreased [25].

Studies have shown that a low ratio of *Firmicutes* to *Bacteroidetes* is an indicator of a healthy microbiome [26]. A few studies found that obese patients were more likely to have a higher *Firmicutes* to *Bacteroidetes* ratio [26][27][28] and higher levels of short chain fatty acids (SCFAs) in their stool [5]. However, another study found that obese patients showed an increase in *Bacteroidetes*, while *Firmicutes* remained the same [29]. Therefore, it appears that reducing obesity with the KD may result in positive changes in the microbiome. A study by Basciani et al. [30] recently analyzed the changes in the gut microbiota in obese, insulin-resistant patients who followed isocaloric ketogenic diets which varied in their source of proteins. The very low-calorie ketogenic diets (VLCKDs) contained either whey, vegetable, or animal proteins. The data indicated all groups had a decrease in relative abundance of *Firmicutes* and an increase in *Bacteroidetes* after 45 days. However, the positive changes were less pronounced in the group that consumed animal protein sources.

Recently, a few short-term studies tested the impact of the KD on patient microbiomes. A study by Nagpal et al. [31] analyzed the effect of a modified Mediterranean Ketogenic Diet (MMKD) vs. the American Heart Association Diet (AHAD) on the microbiome of patients with normal cognition or mild cognitive impairment. They found that the MMKD did not show significant changes in the *Firmicutes* or *Bacteroides* phyla at 6 weeks. However, they did see a decrease in the family *Bifidobacteriaceae* and an increase in family *Verrucomicrobiaceae*, which was considered a positive change. Furthermore, the beneficial SCFA, butyrate, increased in the MMKD. The presence of butyrate has been known to increase gut health [31].

3. The Effect of the Ketogenic Diet on the Epigenome

Epigenetics refers specifically to changes “on top” of the genome that can modify and alter levels of gene expression. These epigenetic markers are heritable, yet recent research suggests that some changes can be reversed or occur through environmental changes [20]. The modifications of the genome involve DNA methylation, changes to chromatin structure, histone modification, and noncoding RNAs. Most notable are histone modifications. For example, the N-terminal of histone tails can be acetylated, methylated, phosphorylated, ubiquitinated, or SUMOylated. Histone deacetylases (HDACs) are enzymes that can remove acetyl groups and condense the chromatin. Similarly, sirtuins (SIRTs) are also capable of deacetylating histones. Histone lysine methylation can either activate or repress a gene’s activity based on the exact location and number of methyl groups added to the histone tail [32]. Research has found that most epigenetic modification occur during early embryogenesis, but the genome can acquire changes later in life. Some of the later epigenetic modifications are caused or modified because of diet [32].

Some ketogenic food sources that positively regulate epigenetic activity are cruciferous vegetables, dietary fiber, foods rich in long-chain fatty acids, and berries, such as raspberries [20]. The benefits of some of these food sources have a multitude of positive effects. For instance, black raspberries not only positively affect methylation patterns in the WNT-signaling pathway, but they also profoundly impact the microbiome make-up (increased *Lactobacillus*, *Bacteroidaceae*, and anti-inflammatory bacterial species), and increased production of butyrate by fermentation in the gut [20]. Thus, it appears that diets rich in certain foods can positively modify genes that increase overall cell health.

The benefits of the ketogenic diet might also go beyond treating existing disease, and instead help prevent chronic and degenerative disease [23]. A literature review by Miller et al. [23] argued that a state of nutritional ketosis will positively affect mitochondrial function and enhance resistance to oxidative stress and noted that the ketones directly up-regulate bioenergetic proteins that influence antioxidant defenses [23]. According to Boison [33], “Ketone bodies, such as β-hydroxybutyrate (BHB), and their derivatives have received the most attention as mediators of the anti-seizure, neuroprotective, and anti-inflammatory effects of KD therapy” [34][35][36]. The ketogenic diet’s mechanism of action might be due to increased levels of adenosine [37][38], which blocks DNA methylation and, thus, exerts an epigenetic change. A study in epileptic rats subjected to the KD therapy found ameliorated DNA methylation mediated changes in gene expression by increasing adenosine [39], which blocks DNA methylation [40]. It is also being studied for its role in the aging process since it is linked to the positive regulation of epigenetic modifications, such as nuclear lamin architecture [41], reduced telomere length [42][43], DNA methylation, and chromatin structure [44].

The effect of the ketogenic diet on brain health appears to be well supported and is due specifically to the production of BHB [23]. They found that BHB is more than a fuel molecule; it plays important roles in cell signaling. The signaling functions of BHB link the effects of environmental factors on epigenetic regulation and cellular processes since it is an endogenous class 1 HDAC inhibitor [45]. Thus, a ketogenic diet has been linked to increased global histone acetylation, with a specific increase in the expression of protective genes, such as Foxo3a [46].

Evidence also suggests that BHB can have a direct epigenetic effect via a novel histone modification known as β-hydroxybutyrlation of H3K9, which results in improved gene regulation in the hypothalamus and improved overall aging [47]. Furthermore, the energy carrier molecule, nicotinamide adenine dinucleotide (NAD) is important in oxidative respiration. In its oxidative state (NAD+), NAD also acts as a cofactor for sirtuin enzymes and poly-ADP-ribose polymerase (PARP). Sirtuins and PARP play roles in gene expression, DNA damage repair, and fatty acid metabolism [46]. The energy available to a cell is measured by the NAD+/NADH ratio, which is modified by the utilization of glucose versus BHB as a fuel source [48]. During a ketogenic state, more NAD is found in the oxidative state which allows sirtuins and PARP to be more active. Additionally, catabolism of BHB into acetyl-CoA, another energy carrier molecule, raises acetyl-CoA levels. It has been found that the production of two moles of acetyl-CoA using BHB as the precursor reduces only one mole of NAD+ to NADH. However, four moles of NAD+ are produced by glucose metabolism. Thus, the ketogenic diet creates excess NAD+ for the cell and has a positive impact on the redox state of the cell [48]. This might have positive impacts on the activity of NAD+ dependent enzymes, such as sirtuins. Newman et al. [49] found that increased acetyl-CoA favors both enzymatic and nonenzymatic protein acetylation, specifically in the mitochondria, which improves overall mitochondrial function.

BHB produced by a ketogenic diet may also increase the efficiency of ATP production in the mitochondria and reduce the number of free radicals. As a result of the positive impacts of BHB, one study found that BHB precursor molecules improved cognition and disease progression in an Alzheimer's mouse model [50]. Additionally, the presence of BHB showed improvement in a case study of a patient with Alzheimer's disease [51]. The presence of D-β-hydroxybutyrate protect neurons from oxidative damage by reducing the cytosolic NAD+/NADPH ratio, resulting in an increase in the antioxidant agent known as reduced glutathione [52]. BHB also inhibits NF-kB, which is known to regulate the expression of multiple pro-inflammatory genes. This results in a diminished pro-inflammatory response [52]. Similarly, the BHB precursor, 1,3 butanediol, also modulates the expression of the inflammasome via histone β-hydroxybutyrlation. Thus, it reduces the expression of caspase-1, IL-1B, and IL-18 [53], which are inflammation markers. A study in *C. elegans* found that BHB alone could extend their life span [3]. Thus, the endogenous effects of BHB produced by a ketogenic diet might enhance health and increase longevity.

4. The Effect of the Ketogenic Diet on Weight Loss

According to recent Harvard models, 50% of the children today are likely to be obese by the age of 35 years [9]. As scientists try to determine the most effective strategies to combat the obesity epidemic, many studies have emerged that compare the health outcomes of different diets. A recent meta-analysis of seven random-controlled trials using diazoxide or octreotide for suppressing insulin secretion in obese patients found that it led to reduced body weight, fat mass, while maintaining lean mass [54]. However, the cost of artificially reducing insulin levels was an increase in blood glucose levels. While these studies seem promising as an indicator of biomarkers that can stimulate weight loss, it seems more logical to help patients achieve lower insulin levels via changes to their diet. The reduction of carbohydrate intake naturally reduces blood glucose levels, thus reducing insulin as a result. Many studies have now demonstrated that the ketogenic diet reduces both blood glucose and insulin levels [55][56][57]

A study conducted by Fumagalli et al. [58] analyzed the genetic profiles of patients and looked at the impacts on metabolism. They specifically looked at human CHC22 clathrin, which plays a central role in intracellular traffic of insulin-responsive glucose transporter 4 (GLUT4). The GLUT4 pathway is the dominant mechanism used by humans to remove glucose from the circulating blood after a meal. They found two major gene variants, one which is more frequent in farming populations than in hunter-gatherers. Hunter-gatherers have the gene that allows GLUT4 to be sequestered more effectively and thus have an inherent increased risk of insulin resistance. It is hypothesized that as humans became farmers and increased glucose in the diet, it was beneficial for the blood sugar to be lowered more easily with the newer form of CHC22. Thus, people with different forms of CHC22 are likely to differ in their ability to clear blood sugar after a meal. The people with the form that allows blood sugar levels to remain elevated could eventually lead to diabetes in the face of a high-carbohydrate load in the diet. This new finding might explain why some patients are successful on a high-carbohydrate low-fat diet, while others prefer to maintain weight with a low-carbohydrate, high-fat diet [58].

The importance of dietary adherence is of great concern for the success of any diet study. The study conducted by Shai et al. [59] that was able to control for the feeding of at least one meal a day (cafeteria meal), might better reveal the true effects of a sustained ketogenic diet. The Shai study [59] compared a low-fat, restricted-calorie diet (LFD), a Mediterranean, restricted-calorie diet (MD), and a low-carbohydrate, non-restricted calorie diet (LC) on 322 moderately obese subjects over a period of two years. The dietary adherence was >85% at the end of two years. This study instructed the LC group to be ketogenic for the first 2 months (<20 g/day) and gradually increase to 120 g/day of carbohydrates. The results found that the greatest weight loss occurred in the low-carb group and both the LC and MD were more effective than the LFD. Although, the weight loss during the first 3 months in the LC group was significantly greater than either of the other two groups, as carbohydrates were added back into their diet, their weight rebounded back to a level close to the MD group. Shai et al. [59] found that one of the benefits of the LC group was the similar calorie deficit achieved even though it was not a calorie-restricted diet. The researchers propose that a LC diet may be the optimal choice for individuals that cannot follow a calorie restricted diet since these subjects will be permitted to eat until satiated but will still most likely end up lowering their total caloric intake.

A similar long-term (56 week) ketogenic study was conducted on 66 obese people with a BMI >30 [60]. All patients were instructed to eat <20 g of carbohydrates in the form of green vegetables and salads for 12 weeks and then they could increase the carbohydrates to 40 g/day for the remainder of the study. The weight and body mass index of all patients decreased significantly. More interestingly, the patients were advised to maintain a state of nutritional ketosis and they were able to show continued decreases in both BW and BMI throughout the study. Consequently, this study did not show the plateau and gradual increases seen in the Shai study [59] which allowed the reintroduction of carbohydrates after the initial weight loss period. A similar study by Samaha et al. [61] also found that patients lost significantly more weight on a 30 g/carbohydrate per day diet for six months compared to a LFD. Another possible benefit from the ketogenic diet is that there is a measurable biomarker that signifies dietary adherence, which is β-hydroxybutyrate (BHB). When an individual is in ketosis, the body will begin ketone production and the level of BHB in the blood will be over 0.5 mmol. Studies that include this measurement can therefore confirm dietary adherence and determine the true effects of the diet on health outcomes, like weight loss. Mohorko et al. [57] conducted a 12-week ketogenic diet study on obese patients who were calorie restricted (1200–1500 kcal) for the first two weeks and then were instructed to eat ad-libitum for hunger for the remaining weeks while eating the macronutrient composition necessary to remain in a state of nutritional ketosis. BHB was measured throughout the study and patients maintained levels above 0.5 mmol throughout the 12 weeks. Patients showed significant weight loss in both the men and women groups (average of (-)18 kg for men and (-)11 kg for women). Interestingly, as the diet progressed, the patients Fat Mass (FM) became the largest component of weight loss and it significantly correlated with BHB. Another valuable outcome in this study was the reduction of the hunger hormone, leptin, as well as a slight increase in energy expenditure, even while weight decreased throughout all 12 weeks. Another long-term study was done by Hallberg et al. [2] which followed diabetic patients on a ketogenic diet for one year. At the beginning of this study, 92% of the patients in the ketogenic group were obese. These patients were instructed to eat less than 30 g of total carbohydrates per day and the goal was to maintain BHB blood levels of 0.5–3.0 mmol/L. These patients had an average of 12% decrease in body weight, with some patients achieving as high as ~40% change. The patients who were in the standard care diet group (American Diabetic Association recommended diet) did not see any significant change in body weight [2].

A short-term, 4-week ketogenic diet (KD) on 20 obese Chinese females had profound outcomes [62]. In this study, compliance to the diet was measured with urinary ketone strips. These participants were given a monitored 4-week normal diet which was followed up with a 4-week KD with the same daily caloric intake but a drastic reduction in carbohydrates to <10% of calories. The effect was a significant decrease in body weight, body mass index, waist circumference, hip circumference, body fat %, and decreased fasting leptin levels. Similar positive outcomes were seen in other KD diet studies [56][63][64]. Similarly, a recent meta-analysis concluded that very low-calorie ketogenic diets are a very effective strategy for treating obesity [65]. An 8-week study conducted by Goss et al. [66] compared the very low carbohydrate diet (VLCD) (<10% carbohydrates) to a low-fat diet in older obese adults with BMI between 30 and 40. This study precisely measured fat loss with DXA and MRI measurements. Both groups exhibited decrease in total fat, but the VLCD experienced ~3 fold greater decrease in visceral adipose tissue and a significant decrease in intermuscular adipose tissue with a 5-fold greater reduction in total body fat mass.

Another long-term study monitored weight loss as well as changes in visceral fat mass using DEXA. The study by Moreno et al. [67] compared a very low-calorie ketogenic diet (VLCK) to a low-calorie (LC) diet as a treatment for obesity over two years. Participants in the active stage consumed 600–800 kcal/day and <50 g of carbohydrates per day until they were 80% of target weight loss goals (stage 1). Urinary ketone strips were used during stage 1 to confirm a state of ketosis. Then they used a standard low-calorie diet (10% below total metabolic expenditure) during stage 2 until they achieved another 20% weight loss, followed by long-term maintenance of weight loss in stage 3. The comparison control group

used the low-calorie diet throughout the study to achieve weight loss. The weight loss in kilograms in the VLCK diet was double that of the LC diet throughout most of the study and remained significant. The amount of visceral fat loss in the VLCK diet group was 3X greater than the control group while preserving lean body and skeletal bone mass. The main side effects recorded in the VLCK were fatigue, headache, constipation, and nausea. However, none of these side effects were severe enough to cause the patients to drop out of the study and most subsided within the first month [67].

A meta-analysis conducted by Bueno et al. [68] compared randomized controlled trials of very low carb ketogenic diets (VLCKD) with low fat diets for 1 year. This study found a significant difference in decreased body weight for the VLCKD group. Another study compared a KD (<30 g carbohydrates/day) with two control groups (standard American diet (SAD) without exercise and SAD with 3-5 days of exercise for 30 minutes) over ten weeks [69]. The KD outperformed the other control groups in all variables tested, with 5 out of 7 being statistically significant. The patients showed significant decreases in body mass index (BMI), body fat mass (BFM), and weight while their resting metabolic rate (RMR) increased. The RMR in the experimental group produced a positive, sizeable change with a magnitude of slope that was more than 10X the two control SAD groups. These results reveal that diet plays a more significant role in outcomes than exercise [69].

The ability to control hunger is also a key component to weight loss success. Castro et al. [70] evaluated patients from the very low-calorie ketogenic diet (VLCK) study and found a negative correlation between BHB levels and the urge to eat and feelings of hunger during the phase of maximum ketosis, even though there was no significant change in ghrelin hormone. This result is supported by other large investigations in overweight and obese adults which also found that low-carbohydrate diets were more effective in controlling hunger than low-fat diets [71][72]. A 2-week study conducted by Choi et al. [73] compared varying nutrition drinks on weight loss in obese adults. There were three groups: 4:1 fat to protein and carbohydrate ratio, 1.7:1 ratio with increased protein, and a balanced nutrition drink with similar carbohydrates to recommended dietary advice. All groups decreased body weight and body fat mass, but only the 1.7:1 KD-group maintained protein mass. Furthermore, only the KD groups improved blood lipid levels with appetite reduction. Since this was a nutritional drink feeding study, all the groups had similar caloric reduction; thus, results were due to macronutrient composition. In addition, levels of ketosis were strongly related to positive differences in food cravings, alcohol cravings, physical activity, sleep patterns, and sexual activity [73]. This outcome might also be supported by a recent finding that postprandial glycemic dips were the best predictor of appetite and energy intake following a meal and large glycemic dips are usually associated with high carbohydrate consumption [74]. Furthermore, a study showed that high carbohydrate meals had a greater impact on brain reward and homeostatic activity in ways that could impede weight loss maintenance [75]. Interestingly, the increased brain activity findings were partially associated with higher insulin levels, too. Thus, the ability of the KD to reduce hunger, lower glycemic fluctuations, and reduce influences on areas of the brain associated with addiction are all positive signs that a ketogenic diet should be considered as a treatment option for obesity.

One of the major concerns for rapid weight loss is the lowering of the resting metabolic rate (RMR). This bodily change can lead to weight regain, which is known as adaptive thermogenesis. Thus, it is typical for hunger to increase and energy expenditure to decrease during weight loss, which is a hindrance to long-term weight loss maintenance. Gomez-Arbelaez et al. [76] tested this outcome in subjects on the very low-calorie ketogenic (VLCK) diet study and followed them for 2 years. In this study, twenty obese patients lost 20.2 kg of body weight after four months and sustained this weight loss without the expected reduction in RMR. Authors of the study hypothesize that RMR did not drop because the subjects maintained their lean body mass. DEXA scans revealed that although they lost ~20 kg of fat mass, they only lost 1 kg of muscle mass. This conclusion was also supported by normal renal activity and positive nitrogen balance while subjects maintained their fat loss upon follow-up [76].

A study by Hall et al. [77] hypothesized that the development of obesity is “a consequence of the insulin-driven shift in fat partitioning toward storage and away from oxidation resulting from an increased proportion of dietary carbohydrates.” To test this hypothesis, they tested seventeen obese men in metabolic wards with a four-week high-carbohydrate diet followed by a four week, isocaloric ketogenic diet. The results showed that a state of ketosis increased energy expenditure (~100 kcal/d), most likely due to beta oxidation and the partitioning of fuel towards ATP production rather than fat storage [77]. However, this level of energy expenditure change due to a ketogenic diet is not as high as measured in another study. In the study by Ebbeling et al. [78], it was noted that short-term feeding studies do not consider the body’s process of fat adaptation, which takes at least 2–3 weeks, if not longer. Thus, the Framingham study by Ebbeling et al. [78] conducted a randomized trial on 164 patients where they lost weight and were then placed on varying diets of carbohydrate content for twenty weeks to measure changes in energy expenditure. The difference in total energy expenditure was 209–278 kcal/d or around 60 kcal/d increase for every 10% decrease in the carbohydrate percentage of total energy intake. This study concluded that dietary quality could affect energy expenditure independently of body weight. In accordance, Mobbs et al. [79] has suggested that ketogenic diets “reverse obesity by preventing the inhibitory

effects of lipids on glycolysis, thus maintaining relatively elevated post-prandial thermogenesis.” Further studies will need to be conducted to evaluate and confirm the exact mechanisms of action.

More recent studies on the KD are analyzing the outcomes of the diet in conjunction with other comorbidities related to obesity. A small study was conducted by Carmen et al. [80] that followed three obese participants on a 10% carbohydrate KD for 6–7 months that exhibitied comorbid binge eating and food addiction symptoms. No adverse effects were found, and participants had reductions in binge eating episodes and food addiction symptoms. All three lost 10–24% BW and maintained treatment outcomes 9–17 months after initiating the diet and continued adherence to the diet [80]. Another study looked at the outcomes for male and female severely obese patients who also suffered from non-alcoholic fatty liver syndrome (NAFLD) [81]. They used a very low-calorie ketogenic diet of <50 g of carbohydrates and <800 kcal/day. Both males and females showed significant losses in body weight. However, males lost significantly more weight and had greater reductions in waist circumference. The patients also improved their biomarker for NAFLD, which was a reduction in gamma-glutamyl transferase [81]. To determine if the ketogenic diet negatively affects kidney function, Bruci et al. [82] conducted a 3-month very low-calorie ketogenic diet (VLCKD) study for weight loss in obese patients with and without mild kidney failure. All patients were advised to consume <20 g carbohydrates and 500–800 calories per day. The average mean weight loss from initial weight was nearly 20%, participants had significant reduction in fat mass, and 27.7% of the patients with mild kidney failure acquired normalized glomerular filtrate rate. It was, therefore, concluded that a KD not only leads to weight loss but also improvement in kidney function.

References

1. Moore, J.; Westman, E.C. Keto Clarity: Your Definitive Guide to the Benefits of a Low-Carb, High-Fat Diet; Victory Belt Publishing Inc.: Las Vegas, NV, USA, 2020.
2. Hallberg, S.J.; McKenzie, A.L.; Williams, P.T.; Bhanpuri, N.H.; Peters, A.L.; Campbell, W.W.; Hazbun, T.L.; Volk, B.M.; McCarter, J.P.; Phinney, S.D.; et al. Effectiveness and Safety of a Novel Care Model for the Management of Type 2 Diabetes at 1 Year: An Open-Label, Non-Randomized, Controlled Study. Diabetes Ther. 2018, 9, 583–612.
3. Edwards, C.; Canfield, J.; Copes, N.; Rehan, M.; Lipps, D.; Bradshaw, P.C. D-beta-hydroxybutyrate extends lifespan in C. elegans. Aging 2014, 6, 621–644.
4. Longo, V.D.; Mattson, M.P. Fasting: Molecular Mechanisms and Clinical Applications. Cell Metab. 2014, 19, 181–192.
5. Den Besten, G.; van Eunen, K.; Groen, A.K.; Venema, K.; Reijngoud, D.J.; Bakker, B.M. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J. Lipid Res. 2013, 54, 2325–2340.
6. Fryar, C.D.; Carroll, M.D.; Afful, J. Prevalence of Overweight, Obesity, and Severe Obesity among Adults Aged 20 and over: United States, 1960–1962 through 2017–2018; E-Stats; NCHS Health: Hyattsville, MD, USA, 2020. Available online: (accessed on 12 May 2021).
7. Fryar, C.D.; Carroll, M.D.; Afful, J. Prevalence of Overweight, Obesity, and Severe Obesity among Children and Adolescents Aged 2–19 Years: United States, 1963–1965 through 2015–2016; E-Stats; NCHS Health: Hyattsville, MD, USA, 2020. Available online: (accessed on 12 May 2021).
8. Westman, E.C.; Yancy, W.S.; Mavropoulos, J.C.; Marquart, M.; McDuffie, J.R. The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus. Nutr. Metab. 2008, 5, 36.
9. Abbasi, J. Interest in the Ketogenic Diet Grows for Weight Loss and Type 2 Diabetes. JAMA 2018, 319, 215–217.
10. Westman, E.C.; Feinman, R.D.; Mavropoulos, J.C.; Vernon, M.C.; Volek, J.S.; Wortman, J.A.; Yancy, W.S.; Phinney, S.D. Low-carbohydrate nutrition and metabolism. Am. J. Clin. Nutr. 2007, 86, 276–284.
11. Paoli, A. Ketogenic Diet for Obesity: Friend or Foe? Int. J. Environ. Res. Public Health 2014, 11, 2092–2107.
12. Adam-Perrot, A.; Clifton, P.; Brouns, F. Low-carbohydrate diets: Nutritional and physiological aspects. Obes. Rev. 2006, 7, 49–58.
13. Wallace, C. Dietary advice based on the bacteria in your gut. 2018 February 25. Wall Street Journal. Available online: (accessed on 12 May 2021).
14. Zeevi, D.; Korem, T.; Zmora, N.; Israeli, D.; Rothschild, D.; Weinberger, A.; Ben-Yacov, O.; Lador, D.; Avnit-Sagi, T.; Lotan-Pompan, M.; et al. Personalized Nutrition by Prediction of Glycemic Responses. Cell 2015, 163, 1079–1094.
15. Rothschild, D.; Weissbrod, O.; Barkan, E.; Kurilshikov, A.; Korem, T.; Zeevi, D.; Costea, P.I.; Godneva, A.; Kalka, I.N.; Bar, N.; et al. Environment dominates over host genetics in shaping human gut microbiota. Nature 2018, 555, 210–215.

16. Rivière, A.; Selak, M.; Lantin, D.; Leroy, F.; De Vuyst, L. Bifidobacteria and Butyrate-Producing Colon Bacteria: Importance and Strategies for Their Stimulation in the Human Gut. Front. Microbiol. 2016, 7, 979.

17. Davis, S.C.; Yadav, J.S.; Barrow, S.D.; Robertson, B.K. Gut microbiome diversity influenced more by the Westernized dietary regime than the body mass index as assessed using effect size statistic. Microbiologyopen 2017, 6, e00476.

18. Lynch, S.V.; Pedersen, O. The Human Intestinal Microbiome in Health and Disease. N. Engl. J. Med. 2016, 375, 2369–2379.

19. Claesson, M.J.; Jeffery, I.B.; Conde, S.; Power, S.E.; O'Connor, E.M.; Cusack, S.; Harris, H.M.B.; Coakley, M.; Lakshminarayanan, B.; O'Sullivan, O.; et al. Gut microbiota composition correlates with diet and health in the elderly. Nature 2012, 488, 178–184.

20. Gerhauser, C. Impact of dietary gut microbial metabolites on the epigenome. Philos. Trans. R. Soc. B Biol. Sci. 2018, 373, 20170359.

21. Gong, L.; Cao, W.; Chi, H.; Wang, J.; Zhang, H.; Liu, J.; Sun, B. Whole cereal grains and potential health effects: Involvement of the gut microbiota. Food Res. Int. 2018, 103, 84–102.

22. Kennedy, E.T.; A Bowman, S.; Spence, J.T.; Freedman, M.; King, J. Popular Diets. J. Am. Diet. Assoc. 2001, 101, 411–420.

23. Miller, V.J.; Villamena, F.A.; Volek, J.S. Nutritional Ketosis and Mitohormesis: Potential Implications for Mitochondrial Function and Human Health. J. Nutr. Metab. 2018, 2018, 5157645.

24. Xie, G.; Zhou, Q.; Qiu, C.-Z.; Dai, W.-K.; Wang, H.-P.; Li, Y.-H.; Liao, J.-X.; Lu, X.-G.; Lin, S.-F.; Ye, J.-H.; et al. Ketogenic diet poses a significant effect on imbalanced gut microbiota in infants with refractory epilepsy. World J. Gastroenterol. 2017, 23, 6164–6171.

25. Zhang, Y.; Zhou, S.; Zhou, Y.; Yu, L.; Zhang, L.; Wang, Y. Altered gut microbiome composition in children with refractory epilepsy after ketogenic diet. Epilepsy Res. 2018, 145, 163–168.

26. Ley, R.E.; Turnbaugh, P.J.; Klein, S.; Gordon, J.I. Microbial ecology: human gut microbes associated with obesity. Nature 2006, 444, 1022–1023.

27. Turnbaugh, P.J.; Ley, R.E.; Mahowald, M.A.; Magrini, V.; Mardis, E.R.; Gordon, J.I. An obesity-associated gut microbiome with increased capacity for energy harvest. Nat. Cell Biol. 2006, 444, 1027–1031.

28. Ley, R.E.; Bäckhed, F.; Turnbaugh, P.; Lozupone, C.A.; Knight, R.D.; Gordon, J.I. Obesity alters gut microbial ecology. Proc. Natl. Acad. Sci. USA 2005, 102, 11070–11075.

29. Schwiertz, A.; Taras, D.; Schaefer, K.; Beijer, S.; Bos, N.A.; Donus, C.; Hardt, P.D. Microbiota and SCFA in Lean and Overweight Healthy Subjects. Obesity 2010, 18, 190–195.

30. Basciani, S.; Camajani, E.; Contini, S.; Persichetti, A.; Risi, R.; Bertoldi, L.; Strigari, L.; Prossomariti, G.; Watanabe, M.; Mariani, S.; et al. Very-Low-Calorie Ketogenic Diets with Whey, Vegetable, or Animal Protein in Patients With Obesity: A Randomized Pilot Study. J. Clin. Endocrinol. Metab. 2020, 105, 2939–2949.

31. Nagpal, R.; Neth, B.J.; Wang, S.; Craft, S.; Yadav, H. Modified Mediterranean-ketogenic diet modulates gut microbiome and short-chain fatty acids in association with Alzheimer's disease markers in subjects with mild cognitive impairment. EBioMedicine 2019, 47, 529–542.

32. Bishop, K.S.; Ferguson, L.R. The Interaction between Epigenetics, Nutrition and the Development of Cancer. Nutrients 2015, 7, 922–947.

33. Boison, D. New insights into the mechanisms of the ketogenic diet. Curr. Opin. Neurol. 2017, 30, 187–192.

34. Freeman, J.M.; Kossoff, E.H. Ketosis and the Ketogenic Diet, 2010: Advances in Treating Epilepsy and Other Disorders. Adv. Pediatr. 2010, 57, 315–329.

35. Youm, Y.-H.; Nguyen, K.Y.; Grant, R.W.; Goldberg, E.L.; Bodogai, M.; Kim, D.; D'Agostino, D.; Planavsky, N.J.; Lupfer, C.; Kanneganti, T.D.; et al. The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome–mediated inflammatory disease. Nat. Med. 2015, 21, 263–269.

36. Rahman, M.; Muhammad, S.; Khan, M.A.; Chen, H.; Ridder, D.A.; Müller-Fielitz, H.; Pokorná, B.; Vollbrandt, T.; Stölting, I.; Nadrowitz, R.; et al. The β-hydroxybutyrate receptor HCA2 activates a neuroprotective subset of macrophages. Nat. Commun. 2014, 5, 3944.

37. Lusardi, T.A.; Akula, K.K.; Coffman, S.Q.; Ruskin, D.N.; Masino, S.A.; Boison, D. Ketogenic diet prevents epileptogenesis and disease progression in adult mice and rats. Neuropharmacology 2015, 99, 500–509.

38. Masino, S.A.; Li, T.; Theofilas, P.; Sandau, U.S.; Ruskin, D.N.; Fredholm, B.B.; Geiger, J.D.; Aronica, E.; Boison, D. A ketogenic diet suppresses seizures in mice through adenosine A1 receptors. J. Clin. Investig. 2011, 121, 2679–2683.

39. Kobow, K.; Kaspi, A.; Harikrishnan, K.N.; Kiese, K.; Ziemann, M.; Khurana, I.; Fritzsche, I.; Hauke, J.; Hahnen, E.; Coras, R.; et al. Deep sequencing reveals increased DNA methylation in chronic rat epilepsy. Acta Neuropathol. 2013, 126, 741–756.

40. Williams-Karnesky, R.L.; Sandau, U.S.; Lusardi, T.A.; Lytle, N.K.; Farrell, J.M.; Pritchard, E.M.; Kaplan, D.L.; Boison, D. Epigenetic changes induced by adenosine augmentation therapy prevent epileptogenesis. J. Clin. Investig. 2013, 123, 3552–3563.

41. Dechat, T.; Pfleghaar, K.; Sengupta, K.; Shimi, T.; Shumaker, D.K.; Solimando, L.; Goldman, R.D. Nuclear lamins: Major factors in the structural organization and function of the nucleus and chromatin. Genes Dev. 2008, 22, 832–853.

42. Armanios, M.; Alder, J.K.; Parry, E.M.; Karim, B.; Strong, M.A.; Greider, C.W. Short Telomeres are Sufficient to Cause the Degenerative Defects Associated with Aging. Am. J. Hum. Genet. 2009, 85, 823–832.

43. Hewitt, G.M.; Jurk, D.; Marques, F.D.; Correia-Melo, C.; Hardy, T.L.D.; Gackowska, A.; Anderson, R.; Taschuk, M.T.; Mann, J.; Passos, J.F. Telomeres are favoured targets of a persistent DNA damage response in ageing and stress-induced senescence. Nat. Commun. 2012, 3, 708.

44. Sun, D.; Yi, S.V. Impacts of Chromatin States and Long-Range Genomic Segments on Aging and DNA Methylation. PLoS ONE 2015, 10, e0128517.

45. Shimazu, T.; Hirschey, M.D.; Newman, J.; He, W.; Shirakawa, K.; Le Moan, N.; Grueter, C.A.; Lim, H.; Saunders, L.R.; Stevens, R.D.; et al. Suppression of Oxidative Stress by -Hydroxybutyrate, an Endogenous Histone Deacetylase Inhibitor. Science 2013, 339, 211–214.

46. Moreno, C.L.; Mobbs, C.V. Epigenetic mechanisms underlying lifespan and age-related effects of dietary restriction and the ketogenic diet. Mol. Cell. Endocrinol. 2017, 455, 33–40.

47. Xie, Z.; Zhang, D.; Chung, D.; Tang, Z.; Huang, H.; Dai, L.; Qi, S.; Li, J.; Colak, G.; Chen, Y.; et al. Metabolic Regulation of Gene Expression by Histone Lysine β-Hydroxybutyrylation. Mol. Cell 2016, 62, 194–206.

48. Dąbek, A.; Wojtala, M.; Pirola, L.; Balcerczyk, A. Modulation of Cellular Biochemistry, Epigenetics and Metabolomics by Ketone Bodies. Implications of the Ketogenic Diet in the Physiology of the Organism and Pathological States. Nutrients 2020, 12, 788.

49. Newman, J.C.; Verdin, E. β-Hydroxybutyrate: A Signaling Metabolite. Annu. Rev. Nutr. 2017, 37, 51–76.

50. Kashiwaya, Y.; Bergman, C.; Lee, J.-H.; Wan, R.; King, M.T.; Mughal, M.R.; Okun, E.; Clarke, K.; Mattson, M.P.; Veech, R.L. A ketone ester diet exhibits anxiolytic and cognition-sparing properties, and lessens amyloid and tau pathologies in a mouse model of Alzheimer's disease. Neurobiol. Aging 2013, 34, 1530–1539.

51. Newport, M.T.; VanItallie, T.B.; Kashiwaya, Y.; King, M.T.; Veech, R.L. A new way to produce hyperketonemia: Use of ketone ester in a case of Alzheimer's disease. Alzheimer Dement. 2015, 11, 99–103.

52. Kashiwaya, Y.; Takeshima, T.; Mori, N.; Nakashima, K.; Clarke, K.; Veech, R.L. D-beta-hydroxybutyrate protects neurons in models of Alzheimer's and Parkinson's disease. Proc. Natl. Acad. Sci. USA 2000, 97, 5440–5444.

53. Chakraborty, S.; Galla, S.; Cheng, X.; Yeo, J.-Y.; Mell, B.; Singh, V.; Yeoh, B.; Saha, P.; Mathew, A.V.; Vijay-Kumar, M.; et al. Salt-Responsive Metabolite, β-Hydroxybutyrate, Attenuates Hypertension. Cell Rep. 2018, 25, 677–689.

54. Huang, Z.; Wang, W.; Huang, L.; Guo, L.; Chen, C. Suppression of Insulin Secretion in the Treatment of Obesity: A Systematic Review and Meta-Analysis. Obesity 2020, 28, 2098–2106.

55. Ahmed, S.R.; Bellamkonda, S.; Zilbermint, M.; Wang, J.; Kalyani, R.R. Effects of the low carbohydrate, high fat diet on glycemic control and body weight in patients with type 2 diabetes: Experience from a community-based cohort. BMJ Open Diabetes Res. Care 2020, 8, e000980.

56. Michalczyk, M.M.; Klonek, G.; Maszczyk, A.; Zajac, A. The Effects of a Low Calorie Ketogenic Diet on Glycaemic Control Variables in Hyperinsulinemic Overweight/Obese Females. Nutrients 2020, 12, 1854.

57. Mohorko, N.; Černelič-Bizjak, M.; Poklar-Vatovec, T.; Grom, G.; Kenig, S.; Petelin, A.; Jenko-Pražnikar, Z. Weight loss, improved physical performance, cognitive function, eating behavior, and metabolic profile in a 12-week ketogenic diet in obese adults. Nutr. Res. 2019, 62, 64–77.

58. Fumagalli, M.; Camus, S.M.; Diekmann, Y.; Burke, A.; Camus, M.D.; Norman, P.J.; Joseph, A.; Abi-Rached, L.; Benazzo, A.; Rasteiro, R.; et al. Genetic diversity of CHC22 clathrin impacts its function in glucose metabolism. eLife 2019, 8, e41517.

59. Shai, I.; Schwarzfuchs, D.; Henkin, Y.; Shahar, D.R.; Witkow, S.; Greenberg, I.; Golan, R.; Fraser, D.; Bolotin, A.; Vardi, H.; et al. Weight Loss with a Low-Carbohydrate, Mediterranean, or Low-Fat Diet. N. Engl. J. Med. 2008, 359, 229–241, Erratum in: N. Engl. J. Med. 2009, 361, 2681.

60. Dashti, H.M.; Mathew, T.C.; Khadada, M.; Al-Mousawi, M.; Talib, H.; Asfar, S.K.; Behbahani, A.I.; Al-Zaid, N.S. Beneficial effects of ketogenic diet in obese diabetic subjects. Mol. Cell. Biochem. 2007, 302, 249–256.

61. Samaha, F.F.; Iqbal, N.; Seshadri, P.; Chicano, K.L.; Daily, D.A.; McGrory, J.; Williams, T.; Williams, M.; Gracely, E.J.; Stern, L. A Low-Carbohydrate as Compared with a Low-Fat Diet in Severe Obesity. N. Engl. J. Med. 2003, 348, 2074–2081.

62. Kong, Z.; Sun, S.; Shi, Q.; Zhang, H.; Tong, T.K.; Nie, J. Short-Term Ketogenic Diet Improves Abdominal Obesity in Overweight/Obese Chinese Young Females. Front. Physiol. 2020, 11, 856.

63. Monda, V.; Polito, R.; Lovino, A.; Finaldi, A.; Valenzano, A.; Nigro, E.; Corso, G.; Sessa, F.; Asmundo, A.; Di Nunno, N.; et al. Short-Term Physiological Effects of a Very Low-Calorie Ketogenic Diet: Effects on Adiponectin Levels and Inflammatory States. Int. J. Mol. Sci. 2020, 21, 3228.

64. Walton, C.M.; Perry, K.; Hart, R.H.; Berry, S.L.; Bikman, B.T. Improvement in Glycemic and Lipid Profiles in Type 2 Diabetics with a 90-Day Ketogenic Diet. J. Diabetes Res. 2019, 2019, 8681959.

65. Castellana, M.; Conte, E.; Cignarelli, A.; Perrini, S.; Giustina, A.; Giovanella, L.; Giorgino, F.; Trimboli, P. Efficacy and safety of very low calorie ketogenic diet (VLCKD) in patients with overweight and obesity: A systematic review and meta-analysis. Rev. Endocr. Metab. Disord. 2020, 21, 5–16.

66. Goss, A.M.; Gower, B.; Soleymani, T.; Stewart, M.; Pendergrass, M.; Lockhart, M.; Krantz, O.; Dowla, S.; Bush, N.; Barry, V.G.; et al. Effects of weight loss during a very low carbohydrate diet on specific adipose tissue depots and insulin sensitivity in older adults with obesity: A randomized clinical trial. Nutr. Metab. (Lond.) 2020, 17, 1–12.

67. Moreno, B.; Crujeiras, A.B.; Bellido, D.; Sajoux, I.; Casanueva, F.F. Obesity treatment by very low-calorie-ketogenic diet at two years: Reduction in visceral fat and on the burden of disease. Endocrine 2016, 54, 681–690.

68. Bueno, N.B.; De Melo, I.S.V.; De Oliveira, S.L.; da Rocha Ataide, T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: A meta-analysis of randomised controlled trials. Br. J. Nutr. 2013, 110, 1178–1187.

69. Gibas, M.K.; Gibas, K.J. Induced and controlled dietary ketosis as a regulator of obesity and metabolic syndrome pathologies. Diabetes Metab. Syndr. Clin. Res. Rev. 2017, 11 (Suppl. S1), S385–S390.

70. Castro, A.I.; Gomez-Arbelaez, D.; Crujeiras, A.B.; Granero, R.; Aguera, Z.; Jimenez-Murcia, S.; Sajoux, I.; Lopez-Jaramillo, P.; Fernandez-Aranda, F.; Casanueva, F.F. Effect of A Very Low-Calorie Ketogenic Diet on Food and Alcohol Cravings, Physical and Sexual Activity, Sleep Disturbances, and Quality of Life in Obese Patients. Nutrients 2018, 10, 1348.

71. McClernon, F.J.; Yancy, W.S.; Eberstein, J.A.; Atkins, R.C.; Westman, E.C. The Effects of a Low-Carbohydrate Ketogenic Diet and a Low-Fat Diet on Mood, Hunger, and Other Self-Reported Symptoms. Obesity 2007, 15, 182.

72. Martin, C.K.; Rosenbaum, D.; Han, H.; Geiselman, P.J.; Wyatt, H.R.; Hill, J.O.; Brill, C.; Bailer, B.; Miller-Iii, B.V.; Stein, R.; et al. Change in Food Cravings, Food Preferences, and Appetite During a Low-Carbohydrate and Low-Fat Diet. Obesity 2011, 19, 1963–1970.

73. Choi, H.-R.; Kim, J.; Lim, H.; Park, Y.K. Two-Week Exclusive Supplementation of Modified Ketogenic Nutrition Drink Reserves Lean Body Mass and Improves Blood Lipid Profile in Obese Adults: A Randomized Clinical Trial. Nutrients 2018, 10, 1895.

74. Wyatt, P.; Berry, S.E.; Finlayson, G.; O'Driscoll, R.; Hadjigeorgiou, G.; Drew, D.A.; Al Khatib, H.; Nguyen, L.H.; Linenberg, I.; Chan, A.T.; et al. Postprandial glycaemic dips predict appetite and energy intake in healthy individuals. Nat. Metab. 2021, 3, 523–529.

75. Holsen, L.M.; Hoge, W.S.; Lennerz, B.S.; Cerit, H.; Hye, T.; Moondra, P.; Goldstein, J.M.; Ebbeling, C.B.; Ludwig, D.S. Diets Varying in Carbohydrate Content Differentially Alter Brain Activity in Homeostatic and Reward Regions in Adults. J. Nutr. 2021.

76. Gomez-Arbelaez, D.; Crujeiras, A.B.; Castro, A.I.; Martinez-Olmos, M.A.; Canton, A.; Ordoñez-Mayan, L.; Sajoux, I.; Galban, C.; Bellido, D.; Casanueva, F.F. Resting metabolic rate of obese patients under very low calorie ketogenic diet. Nutr. Metab. 2018, 15, 18.

77. Hall, K.D.; Chen, K.Y.; Guo, J.; Lam, Y.Y.; Leibel, R.L.; Mayer, L.E.; Reitman, M.L.; Rosenbaum, M.; Smith, S.R.; Walsh, B.T.; et al. Energy expenditure and body composition changes after an isocaloric ketogenic diet in overweight and obese men. Am. J. Clin. Nutr. 2016, 104, 324–333.

78. Ebbeling, C.B.; A Feldman, H.; Klein, G.L.; Wong, J.M.W.; Bielak, L.; Steltz, S.K.; Luoto, P.K.; Wolfe, R.R.; Wong, W.W.; Ludwig, D.S. Effects of a low carbohydrate diet on energy expenditure during weight loss maintenance: Randomized trial. BMJ 2018, 363, k4583, Erratum in: BMJ 2020, 371, m4264.

79. Mobbs, C.V.; Mastaitis, J.; Yen, K.; Schwartz, J.; Mohan, V.; Poplawski, M.; Isoda, F. Low-carbohydrate diets cause obesity, low-carbohydrate diets reverse obesity: A metabolic mechanism resolving the paradox. Appetite 2007, 48,

135–138.

80. Carmen, M.; Safer, D.L.; Saslow, L.R.; Kalayjian, T.; Mason, A.E.; Westman, E.C.; Dalai, S.S. Treating binge eating and food addiction symptoms with low-carbohydrate Ketogenic diets: A case series. J. Eat. Disord. 2020, 8, 1–7.
81. D’Abbondanza, M.; Ministrini, S.; Pucci, G.; Migliola, E.N.; Martorelli, E.-E.; Gandolfo, V.; Siepi, D.; Lupattelli, G.; Vaudo, G. Very Low-Carbohydrate Ketogenic Diet for the Treatment of Severe Obesity and Associated Non-Alcoholic Fatty Liver Disease: The Role of Sex Differences. Nutrients 2020, 12, 2748.
82. Bruci, A.; Tuccinardi, D.; Tozzi, R.; Balena, A.; Santucci, S.; Frontani, R.; Mariani, S.; Basciani, S.; Spera, G.; Gnessi, L.; et al. Very Low-Calorie Ketogenic Diet: A Safe and Effective Tool for Weight Loss in Patients with Obesity and Mild Kidney Failure. Nutrients 2020, 12, 333.
