Diabetes, Metabolic Syndrome and Obesity

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REVIEW

Effect of Ketogenic Diet on Obesity and Other Metabolic Disorders: Narrative Review

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Abstract: Obesity is defined as an abnormal or excessive accumulation of fat that increases the burden of different chronic diseases in the population. It has reached epidemic proportions and is a major risk factor for a variety of diseases, including hypertension, cardiovascular disease, type 2 diabetes, dyslipidaemia, atherosclerosis, and some malignancies. Weight gain is a result of excessive energy intake compared to energy expenditure (energy loss from metabolism and physical exercise). A ketogenic diet has a more useful effect on obesity than other diets. A ketogenic diet is a low-carbohydrate, high-fat, moderate-protein diet that induces the production of ketone bodies by mimicking the breakdown of a fasting state. The mechanism behind the ketogenic diet is still unknown, although it obviously helps people with obesity lose weight. Several pathways for the ketogenic diet effect on weight loss have been hypothesized by researchers, including reduced appetite due to effects on appetite control hormones and a possible direct appetite suppressant action of ketone bodies; reduced lipogenesis and increased lipolysis; greater metabolic efficiency; and increased metabolic costs.

Keywords: obesity, ketogenic diet, Ketone Body, metabolic disorder

Introduction

Obesity is defined as a body mass index above 30 kg/m2, which leads to negative effects on health. It is a risk factor for diabetes, cardiovascular diseases, several malignancies, and musculoskeletal disorders. A chronic energy imbalance between calories burned and calories ingested leads to obesity. Obesity is a result of several interactions between genetic, endocrine, psychological, economic, environmental, and behavioural factors.[1] More than 1.9 billion people were overweight, with 650 million of them being obese, accounting for approximately 13% of the adult population of the world. Obesity is a preventable condition through lifestyle changes involving eating habits, physical activity, and behaviour therapy.[2] Various diets have been proposed for weight loss; carbohydrate restriction has been considered the single most effective method for minimizing obesity. A ketogenic diet has a more useful effect on obesity than other diets. A ketogenic diet is a low-carbohydrate, high-fat, moderate-protein diet that induces the production of ketone bodies by mimicking the breakdown of a fasting state. Regardless, the basic principle of ketogenic diets (KDs) is that reducing carbohydrates will result in less insulin release, which will then encourage the oxidation of fatty acids without changing the amount of protein consumed.[3] With only small effects on lean body mass, fat mobilization will happen if a caloric deficit is formed, which is made possible by the anorectic effect of ketone bodies. The mechanism behind the ketogenic diet is still unknown, although it obviously helps people with obesity lose weight.[4] The aim of the current review was to describe the current evidence on the potential effect of KDs on obesity and other metabolic disorders.

Obesity

Obesity is defined as an abnormal or excessive accumulation of fat that increases the burden of different chronic diseases in the population.[5] In 2016, the WHO reported that 650 million persons worldwide were considered obese and about 2 billion adults were overweight. In Europe, it is estimated that up to half of the population might have overweight.[6]

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The Global Burden of Disease Study states that deaths connected to obesity occur more frequently than deaths due to undernutrition and starvation.[7] Obesity is a main public health concern that increases the risk of developing comorbidities such as cardiovascular disease, diabetes, cancer, and musculoskeletal disorders, as well as respiratory issues, impaired cognitive functions, CVD, and an increased risk of premature death.[8,9]

Pathophysiology of Obesity

Obesity pathophysiology is complicated by the interaction of multiple elements, including environmental, socioeconomic, genetic, and internal factors, as well as changes in central nervous system (CNS) endocrine signalling.[10] The CNS perceives information about adipose tissue, liver, stomach, muscle, and bone metabolic demands. In order to minimize food intake, hormones such as cholecystokinin, glucagon-like peptide (GLP)-1, insulin, and leptin are released in response to satiety. In response to glucose and adipose tissue mass, respectively, insulin and leptin are largely released. A powerful orexigenic called ghrelin promotes feeding (Figure 1).[11]

Leptin, ghrelin, insulin, and glucose, which are molecules that signal the availability of energy in the hypothalamus, are responsive to Agouti-Related Peptide/Neuropeptide (AGRP/NPY), Pro-opiomelanocortin/Cocaine and Amphetamine Regulated Transcript (POMC/CART). The sympathetic nervous system (SNS), on the other hand, plays a role in restoring energy balance, and obesity is a result of altered SNS activity. For instance, although meal consumption, especially an excess of carbohydrates, increases SNS activity, fasting decreases SNS activity. These changes in SNS activity are most likely mediated by leptin and insulin. As a result, there is a synergistic relationship between neurohormonal activation and obesogenic variables, resulting in even more variation in obesity-related phenotypic expression.[12]

As an environmental factor, the gut microbiome has a role in obesity. The gut microbiota ferments carbohydrates and proteins that escape digestion in the small intestine into short-chain fatty acids (SCFA), namely propionate, butyrate, and acetate, in the colon. The composition of the gut bacteria is thought to influence the quantity of energy harvested.[13] By decreasing MP-activated protein kinase (AMPK), the gut microbiota is hypothesized to limit muscle and liver fatty acid oxidation, resulting in reduced muscle and hepatic fatty acid oxidation and increased fatty acid storage in these tissues.[14] Increased fat storage occurs in the white adipose tissue as a result of the decreased expression of fasting-induced adipose factor, a circulating lipoprotein lipase inhibitor. The endocannabinoid system in the gut is activated by changes in the microbiota. This method helps to promote gut permeability, which raises plasma levels of lipopolysaccharides (LPS) and exacerbates the disintegration of the gut barrier. LPS levels and enhanced endocannabinoid tone both lead to an increase in adipogenesis.[15]

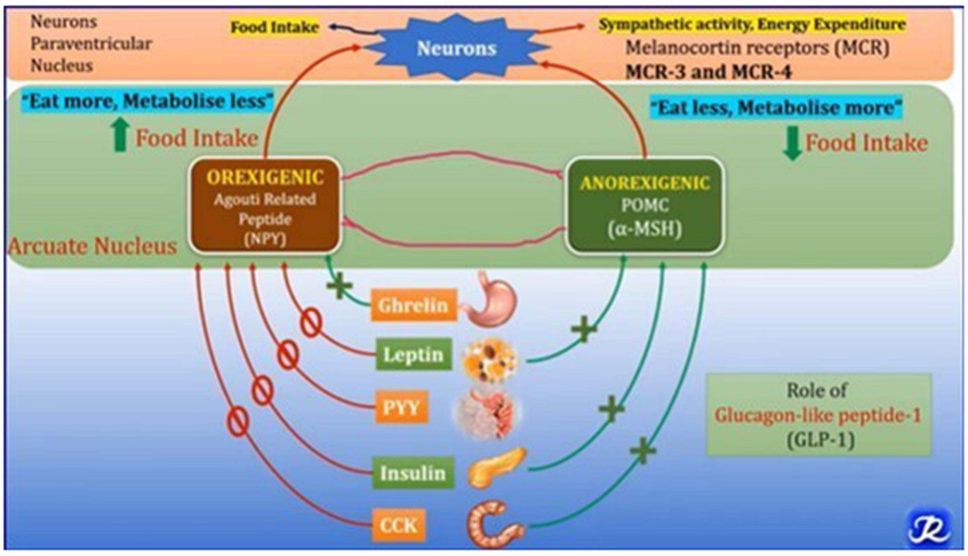

Figure 1 CNS-endocrine signalling to regulate food intake and energy expenditure.[11]

The volume of skeletal muscle, liver, and other organs and tissues of the body grows when the energy balance is positive. Compared to in individual with a normal BMI, the obese individual has more fat and typically more lean body mass. This elevation in tissue requires increase resting energy expenditure, blood pressure and cardiac output.[10]

Consequences of Obesity

Hypertension, CVD, diabetes, several kinds of cancers, non-alcoholic fatty liver disease (NAFLD), reduced pulmonary function, gallbladder disease, weight-bearing joint damage obstetric difficulties, and immunologic impairment are some of obesity-related disorders.[16]

Excessive adipokine production is a key factor in the pathophysiology of diabetes, insulin resistance, dyslipidaemia, hypertension, and atherosclerosis. Fat cell's secretion of cytokines, particularly IL-6, promotes the proinflammatory state that, is associated with obesity. Excess adiposity causes adipocyte hyperplasia in people with metabolically unhealthy obesity, which is primarily fuelled by the recruitment of adipogenic progenitors and growth factors like IGF-1, TNF alpha, Ang II, and M-CSF.[17,18]

The excessive accumulation of triacylglycerol in obesity leads to the release of excessive fatty acids from increased lipolysis, which is driven by obesity, raised sympathetic state. Lipids and their metabolites cause oxidative stress in the mitochondria, and endoplasmic reticulum, the release of excessive FFAs increases lipotoxicity. This affects both adipose and nonadipose tissue, and it is responsible for the pathophysiology of numerous organs, including the liver and pancreas, as well as the metabolic syndrome.[19]

As immune stimulators, these macrophages increase the activity of the mitogen-activated protein kinase family, which includes the C-Jun N-terminal kinase, inhibitor of NF-KB kinase b, and PI3K. This increases the transcription factor NF-KB, which then promotes the dephosphorylation of the insulin receptor substrate (IRS)-1 and −2 docking proteins. The latter prevents glucose from being transported by GLUT4 and causes insulin resistance.[20]

Obesity has been linked to cancer, including malignancies of the colon, thyroid, kidney, uterus, gallbladder, oesophagus, and breast. The fundamental processes of all cancers caused by obesity are not always obvious, but chronic inflammation is thought to play a major role. It is thought that higher oestrogen levels produced from adipose tissue in obese women cause uterine and breast malignancies.[21]

Researchers believe that a number of metabolic factors, including the inflammatory mediator C-reactive protein and the energy-regulating hormone leptin released by adipocytes, are responsible for the association between chronic pain and obesity. Obesity plays a direct role in osteoarthritis, since greater weight causes higher mechanical load on joints, making it a leading cause of impairment.[16] Figure 2 illustrates common pathways by which the metabolic and physiological effects of excessive adiposity conduct to coexisting disorders and diseases in obesity.

Ketogenic Diet

A ketogenic diet is low in carbohydrate, moderate in protein, and high in fats. It forced the body to burn fats rather than carbohydrates. KD has a high fat content (50–60%), protein (30–35%), and carbohydrate content (less than 5%).[22] KD attempts to imitate fasting without actually fasting. Ketosis is not observed with low-carbohydrate, high-protein diets. Instead of breaking down carbohydrates, the body uses lipolysis and β-oxidation of fatty acids to meet its energy needs during KD. It is possible to classify a diet as "ketogenic" if it contains dietary fat necessary for ketone production, which acts as an alternative fuel for bodily tissues.[23]

Lennox and Stanley, two neurologists, examined the effects of fasting in the treatment of refractory epilepsy in both children and adults in the 1920s, and they recognized the advantages of a KD at that time.[22] Recent studies have shown that KDs could be useful for the management of CVD, type 2 diabetes, infertility and cancer as well as the treatment of overweight and obesity.[24,25] Based on carbohydrate restrictions, there are four major types of KD: the classic (CKD), medium-chain triglyceride (MCT) KD, modified Atkins diet (MAD), and low glycaemic index treatment.[26]

The most conventional form of KD is CKD, which is often used in therapeutic settings. The ratio of fat to protein plus carbohydrate is 4:1 (in grams). Ninety percent of calories come from fat; the most popular source is LCT produced from food, which can be used in a 3:1 or lower ratio. In addition, infants respond best to low ratios for KD introduction, whereas older children may benefit more from a 4:1 ratio initiation followed by a decreased ratio. Furthermore, there is proof that calorie and

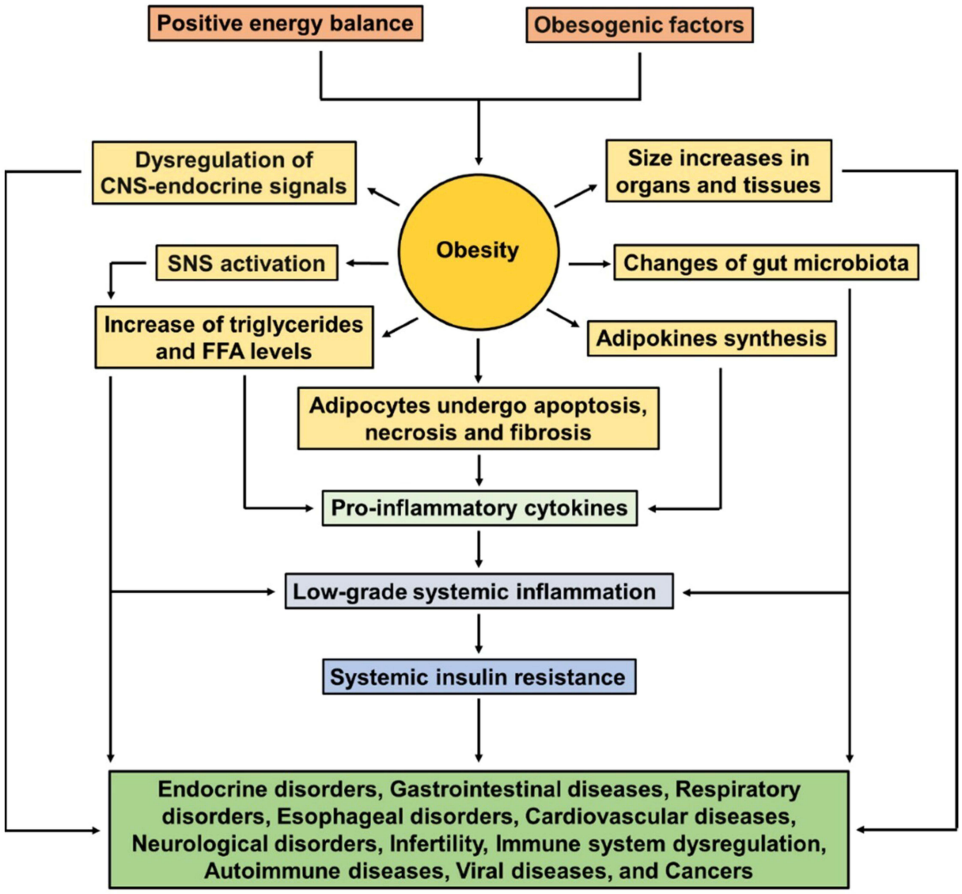

Figure 2 The Pathways of Excess Adiposity Leads to Major Risk Factors for Common Chronic Diseases.[10]

hydration restriction is unnecessary because it has been established that neither of these two factors has any positive effects. Due to the significant carbohydrate restriction, CKD is uncomfortable, difficult to prepare, and hence, difficult to maintain.[27]

The MCT KD was created in 1971. It is more ketogenic and more tolerable in the diet than CKD. Diet ratios in the MCT KD are more flexible than in the CKD, and calorie intake is determined depending on the percentage of energy produced from MCT. There is also clinical evidence that MCTs and CKDs are equally effective. MCT KD, on the other hand, is usually linked to gastrointestinal adverse effects.[28]

The conventional ketogenic ratio, which typically ranges from 1:1 to 1.5:1 and sometimes exceeds 4:1, is not followed by the MAD. It is based on the Atkins diet, a popular weight-loss plan that provides comparable food choices to the original KD without requiring precise component measuring. Additionally, there are no calorie, protein, or hydration limitations in the MAD. For the first month of the MAD, intake of carbohydrates is limited to 10–15 g/day; after that, it can be increased to 20 g/day (32).[29]

The low glycaemic index therapy, which has a more lenient regimen with low-carbohydrate composition to prevent glycaemic increases (glycaemic indices 50), is an effective antiepileptic intervention in children with intractable epilepsy because it is based on the theory that the protective effect of KD depends on stable glucose levels.[29]

When the body lacks Carbohydrates due to a lower intake of fewer than 50 g per day, insulin production is considerably reduced and the body enters a catabolic state. Diminished glycogen stores cause a variety of metabolic changes in the body. There are two metabolic processes that take place when the amount of carbohydrates in bodily tissues is low: gluconeogenesis and ketogenesis.[30]

Glucose is the body's primary fuel, particularly for the central nervous system (CNS). In fact, because free fatty acids (FFAs) cannot pass the blood–brain barrier, the CNS cannot utilize lipids as an energy source blood brain barrier (BBB).[31]

When the body's supply of dietary CHO is depleted or nonexistent, such as during KD or fasting, the CNS turns to ketone bodies for energy (KBs).[32] Ketone bodies are the outcome of a physiological state in which glucose reserves are insufficient to produce oxaloacetate for fat oxidation during the Krebs cycle. To meet the energy demands of cells, the body enters a metabolic condition known as "ketosis".[33]

The body switches to fatty-acid oxidation to produce energy; excessive acetyl-CoA production causes the hepatic mitochondrial matrix to produce acetoacetate, β -HB, and acetone at rates proportionate to total fat oxidation.[34]

As a ketogenic diet follows, ketone bodies accumulate in the body. "Nutritional ketosis" is the term for this metabolic state. As long as the body is devoid of carbohydrates, the metabolism continues in a ketotic state. Given that ketone bodies are created in small amounts and there is no change in blood pH, the nutritional ketosis state is thought to be fairly safe. On the other hand, ketone bodies occur in exceptionally high amounts during the potentially fatal sickness known as ketoacidosis, which causes the blood pH to change to an acidic state.[32]

Ketone bodies are fat-derived, water-soluble molecules that can penetrate the BBB and serve as a source of energy for the brain. The main KB produced is acetoacetate, which when produced in excess is converted to acetone and -HB, the former of which has been shown to cause ketonemia and ketonuria, and the latter of which is a nonmetabolized substance with the distinctive "fruity breath" that is used as a clinical diagnostic marker.[33]

Ketolysis is required to obtain energy from ketone substances. Through succinyl CoA: 3-oxoacid CoA transferase (SCOT) and acetyl CoA acetyltransferase (ACAT1), acetoacetate and BHB are transformed back to acetyl CoA (Figure 3). Following the TCA cycle, 22 ATP molecules are produced as acetyl CoA is further oxidized. Although the liver is the primary generator of ketones, the ability to use them is restricted by the lack of SCOT because ketolysis is mostly present in extrahepatic tissue.[35]

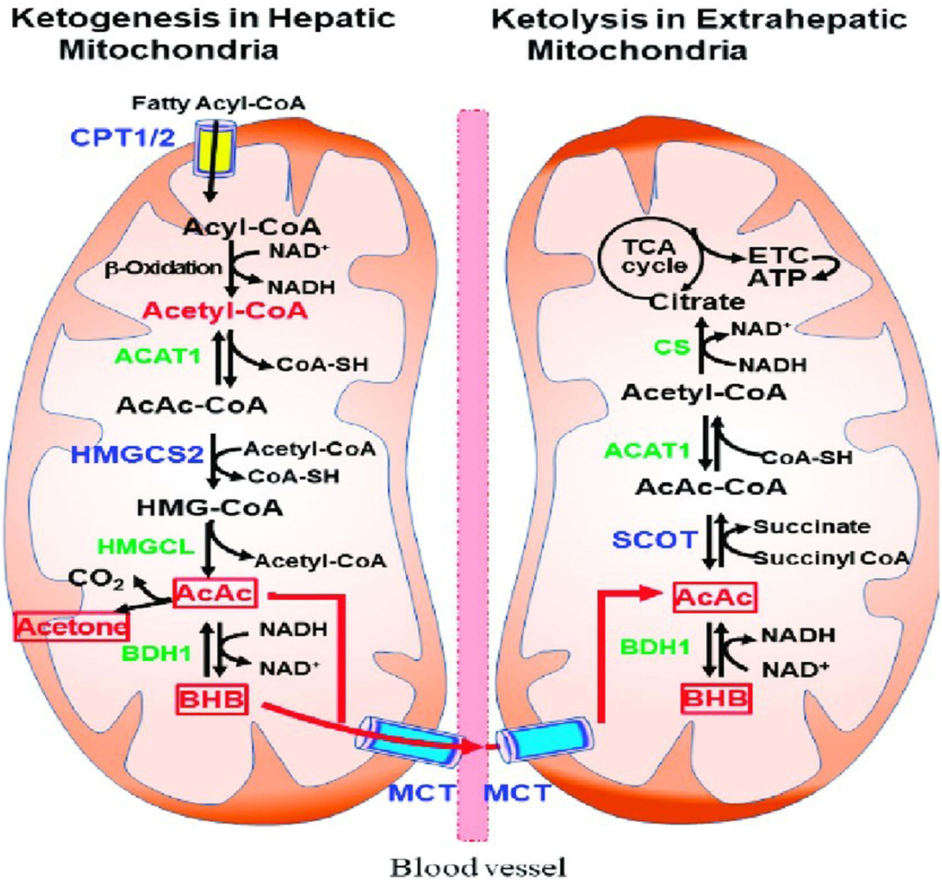

Figure 3 The Metabolic pathways involved in ketogenic diet.[36]

Ketogenic Diet and Obesity

Various diets have been proposed for weight loss; carbohydrate restriction has been considered the single most effective method for minimizing obesity.[4] Despite initial weight loss, there was no longer any weight loss after 22 weeks of following the ketogenic diet. There was an initial weight decrease in mice fed a ketogenic diet after 80 weeks, but this stopped after 18 weeks.[37] Several diets, including KD, low CHO, a nonketogenic diet and a Mediterranean diet, were used. Weight loss and decreased fat percentages were observed in the ketogenic diet when compared to the other diets.[38]

A study of 132 people with obesity with metabolic syndrome with a mean BMI of 43 kg/m2 revealed that those following a ketogenic diet lost more weight than those following other diets. This signifies that a high decrease in total calorie intake is responsible for the weight loss rather than macronutrient composition[39] Although the KD is clearly helpful in helping people with obesity lose weight, the underlying mechanism is still unknown. Researchers have suggested several mechanisms for the KD effect on weight loss, including the following:

(1) Reduced appetite due to increasing concentrations of "satiety" hormones, such as glucagon-like peptide-1, cholecystokinin, and[40] and a possible direct suppression of appetite by KBs, such as β-HB, which act both in energy/satiety signalling and in mediating the central satiety signal.[41] Ketosis has a direct or indirect effect on the secretion of appetite related hormones, as they seem to exert an action on both orexigen and anorexigen signals, mainly BHB.[42] While working in the CNS to control eating behaviour through elevated gamma-amino butyric acid (GABA) and AMP-activated protein kinase (AMPK) phosphorylation in the orexigen pathways, KD increases circulatory levels of adiponectin. An increase in circulating free fatty acids after meals is part of the anorexigenic pathway, which is followed by a decrease in NPY, a neuropeptide that controls appetite by acting on the hypothalamic arcuate nucleus (ARC). The appetite hormone ghrelin is reduced in the bloodstream by KD, but the CCK postprandial anorexigenic response is not altered. There is a general decrease in felt hunger and, as a result, a decrease in food consumption as a result of the net balance of the conflicting impulses.[34] (2) Improved insulin resistance reduces lipogenesis, while enhanced expression of lipolytic enzymes such as adipose triglyceride lipase, hormone-sensitive lipase, and lipoprotein lipase increases lipolysis. KD impacts adipose tissue and dyslipidemia by changing the subject's metabolic pathways, reducing lipogenesis and increasing lipolysis[32,43] (3). Higher metabolic efficiency in consuming fats that is indicated by the reduction in the resting respiratory quotient;[44,45] and (4) Enhanced energy consumption as a result of increased gluconeogenesis, a high-energy process that costs 400–600 Kcal/day, and the thermic action of protein, which has the greatest energy cost of the three macronutrients.[46,47]

Gut bacteria may also play a role in weight loss, as consumption of KD increase the level of bacterially derived SCFA, which are known to decrease the appetite and energy intake. of Boosting the amount of bacteria that make SCFA. SCFAs can also be produced by fermenting ingested proteins.[48] In mice and humans, a ketogenic diet reduced Bifidobacterium levels, resulting in higher BHB production and lower levels of proinflammatory Th17 cells. This is an important finding since low-grade inflammation is a hallmark of insulin resistance and obesity, and lowering Th17 cells may help reverse this process.[49]

AKetogenic diet has been linked to antioxidant benefits in animals, with decreased levels of reactive oxygen species (ROS) in mitochondria and higher glutathione (GSH) and glutathione peroxidase activity.[50] β-HB has been discovered to control inflammation via two mechanisms: activation of the Gi-protein-coupled receptor hydroxy-carboxylic acid receptor 2(HCA2), which contributes to the neuroprotective impact, and suppression of the NLRP3 inflammasome, which controls the generation of IL-1 and IL18 in human monocytes.[51,52] Ketone bodies may have epigenetic cellular effects by inhibiting histone deacetylase (HDAC) enzymes, altering transcription differently and upregulating specific genes that code for bioenergetics enzymes (Figure 4).[53,54]

In many studies, the KD has shown hopeful results in a variety of metabolic disorders such as T2DM, NAFLD, PCOS and CVD.[56] KDs have positive effects on several risk factors for cardiovascular disease. Most research indicates that reducing carbohydrate intake lowers TG and total cholesterol while increasing HDL levels. The size and volume of LDL particles are also enhanced by a KD, potentially reducing the risk of cardiovascular disease linked to smaller LDL particles' greater atherogenicity. Additionally, KD affects endogenous cholesterol production, and appropriate cholesterol intake along with reduced carbohydrate uptake prevents cholesterol biosynthesis.[57]

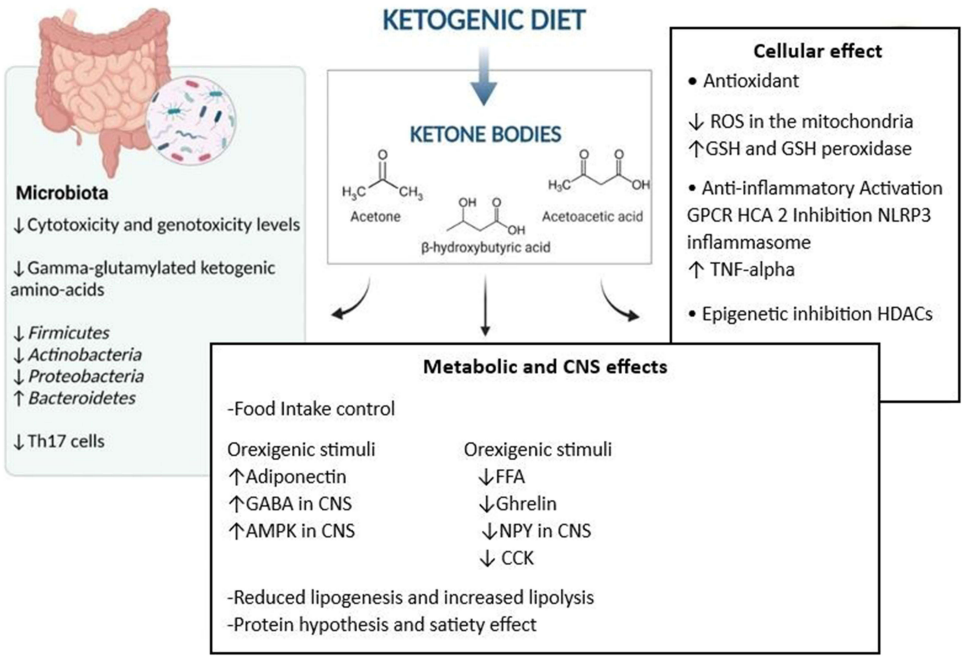

Figure 4 Mechanisms of a ketogenic diet for weight loss.[55]

The most common symptom of T2DM is hyperglycemia; however, insulin resistance and hyperinsulinemia are also involved in the pathophysiology of T2DM. In patients with T2DM, KD ingestion reduced the homeostatic model assessment of insulin resistance.[58] Proteins implicated in KD-induced pathways, such as Hydroxyacy1-CoA dehydrogenase 1 and Acyl-coenzyme an oxidase 1, are closely correlated with GLUT 4, an insulin-resistance pathway effector protein.[59]

In diabetic mice, KD treatment reduced glucose transporter type 2 mRNA expression while increasing fibroblast growth factor 21 mRNA expression. Glucose transporter type 2 is involved in glucose-induced insulin release in pancreatic cells; hence its expression is reduced. In T2DM, the expression of glucose transporter type 2 indicates a lower insulin level and reduced insulin resistance. Peroxisome proliferator-activated receptor enhances lipid catabolism and improves insulin resistance, and fibroblast growth factor 21 is a key target gene. Nuclear factor B (NF-B) signalling, an uncontrolled inflammatory mechanism linked to T2D development, could be inhibited by β-HB.[60,61]

The KD may also protect against NAFLD via a variety of mechanisms. On the one hand, the low carbohydrate content of the KD may lower insulin levels, resulting in greater fat oxidation and decreased lipogenesis, as well as a micro biome shift with higher folate production and reduced oxidative stress and inflammation. On the other hand, KD-induced KBs may result in (1) satiety, which lowers food intake and promotes weight reduction, and (2) epigenetic alterations, which are crucial in the pathogenesis of NAFLD. For instance, -HB increases the histone acetylation of genes encoding oxidative stress resistance proteins; (3) it stimulates GPR109A, a protein that is highly expressed in immune cells and has anti-inflammatory effects in a range of conditions, such as obesity, inflammatory bowel disease, and cancer; and (4) it inhibits NLRP3, a crucial inflammasome that activates proinflammatory cytokines like IL-1 and IL-18, which are closely associated with.[62–64]

The actual mechanism through which KD has a therapeutic effect in PCOS is unknown. Insulin resistance has been implicated in the etiology of PCOS in a number of studies. Insulin induces enhanced androgen synthesis in theca cells isolated from PCOS women, which is mediated by the insulin receptor. Excess insulin inhibits the production of sex hormone-binding globulin in the liver, resulting in an increase in the transport of free androgens to target tissue. AMPK, a cellular metabolism and energy balance regulator, is important in the progression of KD toward PCOS (Figure 5).[65]

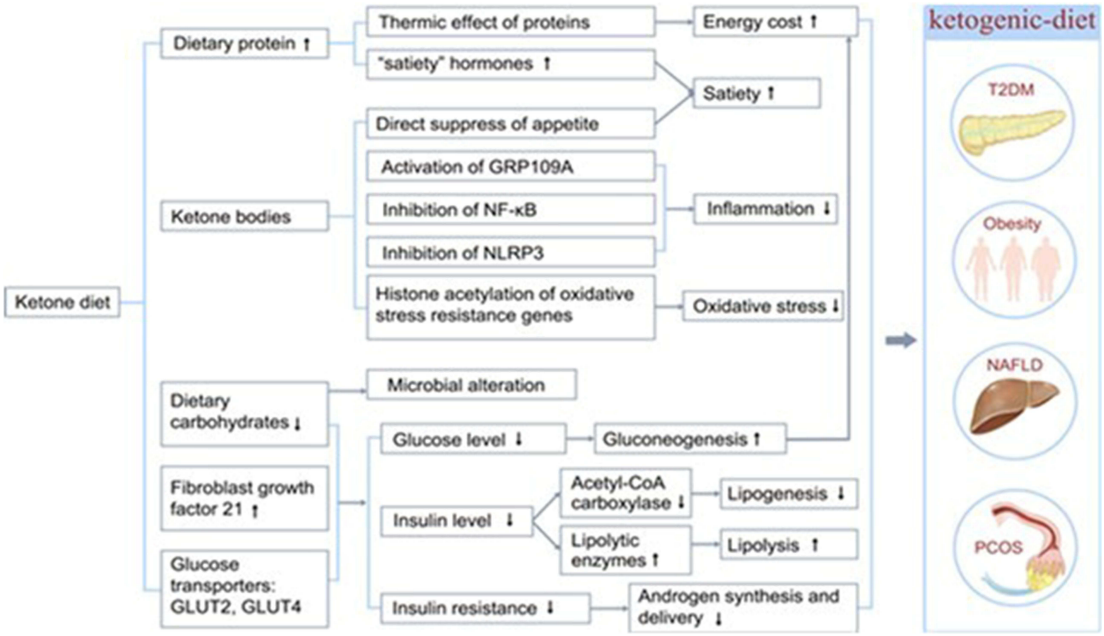

Figure 5 Effects of ketogenic diets on metabolic disorders.[57,62,66]

Conclusion and Future Directions

Obesity is described as an abnormal or excessive accumulation of fat, which leads to an increase in health problems. Obesity has been associated with an increased risk of hypertension, CVD, diabetes, numerous types of cancer, gallbladder and NAFLD. In obese patients, KD tends to be a helpful treatment approach after they have attempted unsuccessful diets to quickly drop unhealthy weight. Metabolic studies and evaluations of hormone fluctuations, among other things, are vital. Without a question, KDs have demonstrated their effectiveness as a tool against obesity, hyperlipidaemia, and some cardiovascular risk factors, at least in the short to medium term. Although many different weight-loss plans have been put forth, KD is believed to be the most successful approach to improving obesity. The mechanisms of the KD effect on obesity include decreased appetite, reduced lipogenesis, increased lipolysis, higher metabolic efficiency in consuming fats, as indicated by a reduction in the resting respiratory quotient, and increased energy consumption. The short-term effects of a ketogenic diet have been extensively documented. Due to a lack of literature, the long-term health consequences are unknown; thus, the researcher will need to conduct additional research. In obesity, the mechanisms of action of the KD remain uncertain, particularly at the cellular and molecular levels. More research on KD's intrinsic therapeutic processes is needed. Further research into the precise molecular models of a ketogenic diet's effect on obesity is needed.

Abbreviations

α MSH, melanocyte stimulating hormone; AGRP, Agouti-Related Peptide; Ang II, angiotensin II; *β*HB, *β*-hydroxybutyrate; AcAc, Acetoacetate; CCK, Cholecystokinin; CART, Cocaine and Amphetamine Regulated Transcript; FFA, Free Fatty Acid; GLP-1, Glucagon-Like Peptide-1; KLCD, ketogenic Low-Carbohydrate Diet; LCT KD, Classic Long-Chain Triglyceride; LGIT, Low Glycaemic Index Treatment; M-CSF, macrophage colony stimulating factor; MCTKD, Medium-Chain Triglyceride Ketogenic Diet; MAD, Modified Atkins Diet; NPY, Neuropeptide, SNS, sympathetic nervous system; Y; PYY, Total Peptide YY; POMC, Pro-opiomelanocortin.

Data Sharing Statement

The corresponding author can provide supporting information upon reasonable request.

Ethics Approval

Since the publication's data was taken from previously published publications and not from its own investigations, ethical approval is not necessary.

Author Contributions

All authors contributed significantly to the work that was reported, whether it is in the conception, study design, implementation, data collection, analysis, and interpretation, or in all of these areas. They also all participated in writing, revising, or critically evaluating the article, gave their final approval for the version that would be published, agreed on the journal to which the article would be submitted, and agreed to be responsible for all aspects of the work.

Disclosure

The authors report that they don't have any competing interests in this work.

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