Abstract
Carbohydrate-restricted ketogenic diets (KD) were introduced in the mid-19th century as a weight loss method with a resurgence of its use in epilepsy treatment in the 1920’s. Research conducted over the last several years provides evidence that KD’s can confer beneficial effects for several chronic metabolic diseases, including obesity, type-2 diabetes, and polycystic ovary syndrome. In recent years, emerging evidence suggests KD’s may also have therapeutic benefits for some cancers and for neurological conditions such as Alzheimer’s disease, Parkinson's' disease, multiple sclerosis, traumatic brain injury, and spinal cord injury. Finally, as the physiological mechanisms by which a KD operates become increasingly understood, we speculate that several other health conditions (e.g., autism, cystic fibrosis, COVID-19) that may improve from consuming a KD. The potential to reduce or eliminate long-term pharmaceutical treatments and their potential adverse effects by modifying diet patterns justifies additional research, particularly rigorously conducted clinical trials with long-term follow-up. This brief review describes a selection of the recent studies of KD as applied to chronic metabolic diseases, and provides an estimate of the quality of the evidence for KD’s effects. We also describe and appraise some of the risks and misconceptions attributed to KD which may limit the widespread use of KD’s among physicians and healthcare providers.
Keywords
Carbohydrate-restriction; ketogenic diet; insulin resistance; metabolic disease

1. Introduction

The ketogenic diet (KD: a high fat, very-low carbohydrate, moderate protein diet) has become an increasingly popular dietary pattern [1, 2]. Emerging evidence suggests that it may have a therapeutic value for treating, and possibly preventing, a range of chronic diseases thought to be metabolic in origin. While the KD and its variants, defined by the proportion of “permissible carbohydrates” in the diet (see Table 1), has been practiced for most of human history, largely as a function of the sparsity of carbohydrate-containing foods prior to the onset of agriculture, it came into ascendency with the publication of Letter on Corpulence in the 1860s. Letter by obese British undertaker William Banting documented his dramatic weight loss from avoiding “bread, and everything else made of flour, cereal and milk puddings, potatoes and white root vegetables and all sweets.” The so-called “Banting Manifesto” remains influential and provided the impetus for contemporary low-carbohydrate variants as a treatment for obesity such as the Atkins Diet®, the Modified Atkins® Diet, the South Beach Diet®, the Zone Diet®, as well as ketosis-inducing medically-supervised programs such as Optifast® and Medifast®, the new keto options available from commercial weight loss programs (e.g., Nutrisystem®, Weight Watchers®) and the recent preponderance of so-called “keto-friendly” food items.

Table 1 Spectrum of Low Carbohydrate Diets (after Feinman et al., 2015) [3].

| Diet                       | Carbohydrate grams/day |
|----------------------------|------------------------|
| Ketogenic Diet             | ≤20                    |
| Very Low-Carbohydrate Diet | 20-50                  |
| Low-Carbohydrate Diet      | <130                   |

Apart from its increasing popularity as a dietary pattern to treat obesity, KD’s have been used, since the 1920s, to treat children and adults with medication-resistant epilepsy [4]. Research over the last several years appears to have established that KD’s confer beneficial effects for several chronic diseases, including obesity, type-2 diabetes, and polycystic ovary syndrome. Moreover, emerging evidence suggests that KD’s may have therapeutic benefits for some cancers, as well as for neurological conditions such as Alzheimer's disease, Parkinson's disease, traumatic brain injury and spinal cord injury. As the mechanisms by which KD’s operate are progressively articulated, we speculate that other conditions might improve (e.g., Amyotrophic lateral sclerosis, Autism spectrum disorder, Cystic fibrosis, Heart failure, COVID-19) in response to a KD. This short narrative review describes some of the evidence of the effects of KD on these conditions, as well as the risks and misconceptions attributed to KD.
2. Ketosis: What It Is and How It Works

It is beyond the scope of this brief review to describe the process of ketogenesis (there are many fine expositions already published e.g., [5-8]). In brief, ketosis is the metabolic state in which the body switches from using glucose as its primary energy source to using ketones as an alternative source of fuel. This metabolic state, as noted above, is achieved when one consumes a low-carbohydrate, moderate protein, high-fat diet or when one fasts for a few days or experiences starvation. Because of the need to maintain stable glucose levels, even in the context of little or no consumption of carbohydrates, glucose is supplied by gluconeogenesis (GNG). Since protein is the major substrate for GNG, it can be depleted quickly, representing the primary threat from starvation or prolonged fasting. The reduction in the hormone insulin, driven by the depletion of glucose, promotes lipolysis providing fatty acids as a major energy source. To reduce the potentially dangerous depletion of lean body protein, fatty acids provide ketone bodies which become a secondary fuel source that partially replaces the brain and CNS’s demand for glucose.

Within the context of the typical, generally recommended high-carbohydrate, low-fat diet, our bodies burn carbohydrates (i.e., glucose) for fuel. Because such a diet promotes excessive levels of glucose in the bloodstream, the body efficiently, primarily via insulin, takes up the excess glucose into lean tissue and organs to be used as fuel. Simultaneously, the burning of dietary fat is inhibited and the fat moves back into the circulation when it can then be stored in fat cells. Apart from its role in moving excess glucose out of the bloodstream, insulin also causes fat tissue to hold onto fat, not allowing it to be accessed as fuel (this helps to explain why carbohydrate-rich diets are obesogenic).

Along with conditions such as type 1 diabetes, alcoholism, fasting and starvation, and the chronic consumption of a high-carbohydrate diet prompts the development of insulin resistance (IR), in which cells become increasingly sluggish and, eventually, stop responding to insulin, effectively producing both chronic fat storage and the inability to access stored body fat for fuel. IR is becoming increasingly established as the mechanism underlying what might be thought of as “energy toxicity”, culminating in the development of a number of health conditions that constitute the so-called metabolic syndrome (e.g., hypertension, high triglycerides, high fasting glucose, central obesity), as well as a range of chronic diseases thought to be metabolic in origin (e.g., type 2 diabetes, Alzheimer’s Disease, Non-alcoholic fatty liver disease and certain cancers).

Apart from fasting, KD is the most carbohydrate-restricted eating pattern. Therefore, KD keeps circulating insulin levels low which, in turn, gives access to fat stores to be burned as fuel. This explains why diets lower in carbohydrates tend to promote the greatest magnitude of selective depletion of body fat in the treatment of obesity [9, 10].

3. Established Clinical Applications of KD

3.1 Obesity

The obesity epidemic continues to sweep across the United States, as 42.4% of adults are considered obese, and nearly 75% of adults being either overweight or obese as of 2018 [11]. It is well-established that a KD confers beneficial effects with respect to weight loss and weight control. Recent meta-analyses of the effects of KD on weight have shown a significant reduction in weight compared to low-fat diets [12-14]. A recent systematic review and meta-analysis of studies
evaluating the safety and efficacy of KD in overweight or obese participants found diets which included a ketogenic phase of at least 4 weeks, promoted an average weight loss of 10-15.6 kg, with the majority of the weight loss being the depletion of fat mass [15]. Similarly, in a representative trial in the literature, a randomized control trial consisting of 34 men and women aged 60-75, who consumed a ketogenic diet lost 9.7% of their initial body fat compared to an only 2.1% loss of initial body fat for those following a low-fat diet. Additionally, those ketogenic dieters lost three times more visceral adipose tissue than the low-fat dieters [1].

Overall, the vast majority of dietary weight loss trials indicate that KD promotes significantly greater weight loss compared to the traditional low-fat diet (see Figure 1). In addition, some studies demonstrate KD promotes the selective depletion of body fat as opposed to muscle, organ tissue and bone density loss.

![Figure 1](image_url) **Figure 1** Comparison of KD and low-carbohydrate diets and low-fat diets in randomized trials ([5] reprinted with permission of the author).

### 3.2 Type 2 Diabetes

Type 2 diabetes (T2D) has long been considered an incurable metabolic disease. In 2017, about 425 million people had a diagnosis of T2D worldwide, and it is projected to markedly increase in the coming years [16, 17]. Moreover, depending on how it is defined, the global prevalence rate of pre-diabetes (an intermediate state of hyperglycemia with glucose levels above the normal state but below the diagnostic levels of diabetes) ranges from about 3% in South-East Asia to 15% in North America and the Caribbean [18]. Pre-diabetes and T2D are, therefore, major and escalating public health epidemics which impose significant health, quality of life and economic burdens [19].

Even with recent pharmaceutical advances, about 50% of persons with diabetes go on to require insulin therapy within a decade of their diagnosis [20]. Although the remission rate for T2D has long been thought to be less than 1%, there has been a shift in the perspective in that it is now seen as potentially reversible [21]. Given that the salient feature of T2D is hyperglycemia, reducing
the consumption of carbohydrates and sugary food was, for many, years the preferred therapeutic intervention [22, 23]. However, with the discovery of the hormone insulin in 1921 coupled with the ascendancy of the low-fat diet, in response to fears about the role of dietary fat in the development of heart disease, lower carbohydrate diets gradually diminished as a treatment for T2D. Moreover, because T2D is so strongly linked to obesity, it was thought that simply reducing energy intake to promote weight loss would improve T2D without having to reduce carbohydrates (this view has been refuted by studies showing reducing carbohydrates improves metabolic syndrome, including markers of T2D, independent of weight loss; e.g., see: [3, 24]. This point needs to be underscoring because one of the most persistent barriers to the acceptance of KD is the insistence on the need for weight loss, despite data indicating that: (1) significant improvements in glycemic control in persons with T2D on a KD under conditions of weight maintenance, and (2) even when weight is lost, it does not correlate with improvements in T2D [25]. This is particularly important because it is estimated that 10 to 20% of persons with T2D are not obese [26].

To date, there are over 30 studies, of varying methodological quality, evaluating the effects of reducing dietary carbohydrates to treat T2D [27]. Generally speaking, these studies find significant short-term between-groups differences, favoring lower carbohydrate diets. However, with few exceptions [28], in longer-term follow-up studies, the benefits conferred with lower carbohydrate diets, including KD’s, tend to be reduced over time. This is primarily driven by fluctuations in participant adherence. While greater attention and support from study personnel may attenuate the drop in adherence, ultimately, the benefits of the KD are dependent upon following the eating pattern as closely as possible for the rest of their lives. In perhaps the largest, long-term study on the effects of consuming a low carbohydrate, 262 adults with T2D enrolled in a continuous care intervention (CCI) that included a eucaloric diet, designed to induce nutritional ketosis, were compared to 98 adults with T2D in usual care [29]. At one-year, the CCI group decreased their hemoglobin A1c (HbA1c) by 1.3%, with 60% of those who remained in the trial achieving a HbA1c below 6.5% (the diabetes threshold) without hypoglycemic medication, other than metformin. Moreover, other medications were significantly reduced, including the elimination of sulfonylureas and reducing or eliminating insulin therapy in 94% of the patients [29]. No significant improvements were observed in the usual care group. Subsequent analyses indicated that most cardiovascular risk factors were also significantly improved [30]. The two-year results showed sustained improvements, with 54% of completers maintaining HbA1c below 6.5% without medication, other than metformin. The retention rate was 74% and weight loss averaged 10% despite being prescribed an eucaloric KD. It should be noted that study participants, on average, had T2D for about 8.5 years prior to trial enrollment, further underscoring the significance of the results. Overall, this long-term trial suggests that KD, delivered in a continuous care model that includes biomarker tracking (ketones) and ongoing support confers significant benefits and is capable of reversing T2D in many patients.

To summarize, there is overwhelming and irrefutable evidence that adherence to a KD promotes significant improvements in multiple markers of T2D and, in some cases, may reverse the disease. Although, the American Diabetes Association and the European Association for the Study of Diabetes now recommend both low-carbohydrate and low-calorie eating patterns for weight loss, they stop short of advocating a low-carbohydrate or KD as a possible means of managing or reversing T2D, independent of weight loss [21].
3.3 Epilepsy

Nearly 100 years ago, Dr. Russell Wilder published the first study successfully applying KD to pediatric epilepsy. Until the rise of pharmaceutical anti-seizure drugs in the 1940’s, KD was a dominant form of treatment for epilepsy in both children and adults with about half of patients reporting at least a 50% decrease in seizures. Modern pharmaceuticals consigned the use of KD as an alternative or adjunctive therapy for seizures [4]. However, largely on the basis of the 1994 film Do No Harm, which portrayed the experience of a 2-year-old child, the son of movie producer Jim Abrahams, whose seizures ceased within days of starting a KD, the value of this eating plan to mitigate epilepsy experienced a resurgence of interest. The KD is currently used and studied with regard to several forms of epilepsy (e.g., refractory non-surgical, infant spasms and Dravet Syndrome) reviewed briefly below.

Refractory nonsurgical epilepsy is defined as unsuitable for a potentially curative surgery and includes lesional and non-lesional, focal, multifocal, and secondary generalized epilepsies. For patients who are ineligible for surgery, alternative therapies or diet manipulation are considered. In a multicenter prospective study, nearly half of the children diagnosed with refractory epilepsy and following a KD, reported more than a 50% reduction in seizure frequency after 6 months. Freeman and colleagues [31] conducted the first blinded trial in 2009 randomizing patients to KD plus a daily supplement of saccharin (treatment) or glucose (control) or no change in standard of care groups. The study indicated a non-significant trend towards decreased seizure frequency in the treatment group compared to controls. In another trial, Neal et al. [32] randomized children with refractory epilepsy into a KD treatment group or standard of care control group and found that the KD patients had decreased their seizure frequency by 50% compared to controls. Patients diagnosed with nonsurgical epilepsy, showing no improvements in drug therapy should be considered for ketogenic dietary therapy, as findings suggest a better chance of efficacy than with other methods. There is also evidence showing that KD confers benefits in drug-resistant, refractory nonsurgical epileptic patients and other epileptic syndromes with refractory generalized seizures [4].

Infantile spasms occur in children between 6 and 18 months of age and are characterized by clusters of severe body jerks. KD could be considered as an alternative treatment for infantile spasms if the first-line treatment (pharmacological) options are ineffective. In a retrospective review [33] of the use of a KD for infantile spasms conducted by Nordli, 17 of 32 infants had both infantile spasms and refractory epilepsy. The KD eliminated the seizures of 6 infants, while another 6 achieved “worthwhile improvements” in seizure frequency. The majority of the infants (18/23) remained on the KD at 6 months, with 13 experiencing a > 50% reduction at both 6 and 12 months with 3 others being seizure-free at both time periods. In a prospective case study of 20 patients with infantile spasms, 70% experienced over a 50% decrease in seizures at 3 months and 72% in 6 months on KD. “In summary, studies of modest quality indicate that KD is a moderately effective therapy for refractory IS, and is generally safe and tolerable in this young population [4] (p.44)”.

Dravet Syndrome is a rare pharmaco-resistant clinical syndrome characterized by initial febrile seizures during the first year of life. Caraballo reported success in a clinical study evaluating the efficacy of KD therapy on quality of life, explicitly seizure reduction, in children with Dravet Syndrome. Of the 59 patients sampled, from 1990-2007, 24 were treated with a 4:1 (fat: protein + carbohydrate) KD and studied for 2 years. Sixteen participants remained on the diet for 2 years,
with 2 remaining seizure free. Ten others had a 75%-99% reduction in seizure frequency, and 4 had a 50%-74% reduction in seizure frequency [34]. Additionally, a greater than 75% reduction in seizures was achieved by 10 of the 15 patients followed by Nabbout et al. [35].

Overall, the use of a KD in those with various forms of epilepsy appears to confer considerable benefits, particularly with respect to reducing seizure frequency.

3.4 Polycystic Ovary Syndrome (PCOS)

PCOS is the most common endocrine disorder and a primary cause of infertility in the U.S., affecting 6% to 12% of childbearing-aged women [36]. It is characterized by infertility, irregular or absent menses, loss of hair, acne, and excess hair growth on the face and body due to higher levels of androgens (male hormones) which can stop ovulation and cause other side effects [36]. PCOS’s association with other metabolic and endocrinological issues such as IR, hyperandrogenism, and T2D suggests a common metabolic pathway [37].

Obese or overweight women with PCOS are at greater risk of experiencing a range of symptoms (most notably infertility) heart attack, stroke, and heart disease. Moreover, at least 50% of overweight and obese women with PCOS develop T2D by the age of 40 [36]. Current treatments for PCOS involve weight loss interventions, hormone therapy, and improving IR (e.g., use of metformin) [37]. In a crossover diet-intervention, Goss et al. [38] examined the results of a reduced carbohydrate diet in 30 women diagnosed with PCOS. They consumed a low carbohydrate diet ratio of 41:19:40% (CHO: protein: fat) for 8 weeks followed by a standard diet ratio (55:18:27) for 8 weeks. When consuming the low carbohydrate diet, the women achieved a 3.7% total fat reduction as compared to the 2.2% loss found in the standard diet results. Interestingly the low carbohydrate diet promoted a reduction in subcutaneous-abdominal, intra-abdominal, and thigh intermuscular adipose tissue of -7.1%, -4.6%, and -11.5, respectively. In contrast, the standard diet promoted a decrease in total lean mass as opposed to body fat loss. Furthermore, circulating insulin decreased when the women consumed the low carbohydrate diet.

In a 12-week study, overweight women with PCOS consumed a 1700 kcal ketogenic/Mediterranean diet with no restrictions on vegetables, 120g of protein, and 3.5g of carbs per portion. The diet produced a 9.3 kg reduction in body weight (the vast majority of which was fat mass), a 3.4-point reduction in body mass index, as well as decreases in glucose, insulin, cholesterol, and hormone levels [39-41].

Overall, the research suggests that KD could be an effective alternative treatment to PCOS. However, because the studies were generally short term with small sample sizes, larger, more rigorous or robust studies determining longer-term studies are needed to determine the efficacy of KD and PCOS.

4. Emerging Therapeutic Applications

4.1 Cancer

Despite continued advances in screening, early diagnosis and treatment, cancer remains a major worldwide public health problem. In the United States, it is the second leading cause of death, with 1,806,590 new cases and 606,520 deaths projected to occur in 2020 [42]. The most common cancer sites are lung, colorectal, breast and prostate.
Even in the presence of oxygen, most cancer cells derive their energy from glucose. This shift from oxidative phosphorylation to glycolysis is called the Warburg effect [43] and is observed very early in tumorigenesis and is considered a hallmark of the disease [44]. Although an oversimplification, KD can be thought of as a way to “starve” cancer cells by depriving them of glucose (their primary energy source), thereby serving as an adjuvant cancer therapy [45-48]. It has been demonstrated in a growing number of studies that KD has potentially beneficial effects related to retarding the growth of tumors, protecting healthy cells from the damage imposed by chemotherapy or radiation treatment, accelerating the effects of chemotherapy on cancer cells and reducing inflammation [49-51]. Other potential mechanistic pathways by which the KD may confer benefits includes altering: mitochondrial function, the amino acid metabolism of cancer cells, signaling molecules, angiogenesis and the vascularization of tumor environment, regulation of gene expression and reducing the production of reactive oxygen species [8, 52].

There have been many mechanistic articulations and case reports [53], most notably among patients with aggressive brain cancer (glioblastoma)[46, 54-62], suggesting that the KD may have beneficial effects, as an adjunct therapy alone, or in combination with hyperbaric oxygen and oxaloacetate in promoting progression-free survival, while also reducing inflammation and edema. A recent comprehensive review [63] of preclinical (N = 57) and clinical studies (N = 30) evaluating the effects of KD on cancer on a range of outcomes, including tumor size and weight, survival, tumor glucose-uptake, metabolic parameters, body composition, tumor vascularization and tolerance and side effects related to the KD has been published. The clinical studies involved an array of cancer sites (e.g., breast, prostate, lung, pancreatic, head and neck, and brain). As the authors conclude, “The KD seems to create an unfavorable metabolic environment for cancer cell proliferation and, thus, represents a promising adjuvant for a multifactorial patient-specific therapeutic regime. One clear benefit of the KD is its potential to increase the response to therapeutic drugs, which has been widely demonstrated in vitro and in vivo. Thus, combining the KD with standard therapy or even novel treatment approaches to enhance the therapeutic response in humans should be a research focus in this field (p. 115).”

Although many of the clinical studies generally lack methodological rigor, the findings suggest that a strict KD may confer significant benefits across a range of cancers. Fortunately, as the number of clinical trials designed to elucidate the effects of KD on cancer increases, along with their methodological quality, we should be in a better position to assess the value of KD on the burden of cancer.

4.2 Nonalcoholic Fatty Liver Disease (NAFLD)

NAFLD is a spectrum of liver diseases, ranging from simple fatty liver to severe fibrosis and inflammation that is not associated with significant alcohol intake or other known causes of hepatic fat accumulation. NAFLD is the second cause of liver transplant in the United States [64]. Given NAFLD’s dramatic increase in prevalence, studies are beginning to evaluate whether nutritional ketosis might mitigate this condition. A recent review of 21 dietary studies to treat NAFLD (4 of which were KD) found significant improvement in body weight, aminotransferase level and decreased hepatic lobe volume. Given this, the authors concluded, “This finding suggests that ketosis might exert beneficial effects independent of dietary composition and therefore
warrants studies aiming at identifying the specific role played by ketone bodies in NAFLD pathophysiology, possibly paving the way for new therapeutic targets and strategies [65] (p. 9).”

In a recent pilot trial, 32 children and adolescents with NAFLD, aged 9 to 17 years, were randomized to either a eucaloric carbohydrate- (< 25% energy) or fat-restricted (20% energy) diet for 8-weeks [66]. Primary outcomes were hepatic lipid content (measured via magnetic resonance imaging), body composition and insulin resistance via a fasting blood sample. Although the change in hepatic lipid did not differ as a function of diet, it did decline significantly (mean of 6%, p <.001) in the carbohydrate-restricted group compared to baseline. There were also significantly greater decreases in insulin resistance (p <.01) and body fat mass (p <.01) in the carbohydrate-restricted group. While, strictly speaking, the level of carbohydrate restriction was not that of a KD, the results suggest that even a moderate restriction in carbohydrates, over a relatively short time period, may confer significant benefits on markers of NAFLD, even in the absence of caloric restriction and significant weight loss.

Overall, the preponderance of evidence suggests that KD is likely a viable treatment to deplete liver fat which may be critical for reducing the risk of disease progression in persons with NAFLD.

4.3 Parkinson’s Disease

Parkinson’s disease (PD) is a progressive neurodegenerative disorder characterized by selective loss of dopaminergic neurons in the substantia nigra (SN) and their striatal projections fibers. PD’s primary symptoms include resting tremor, rigidity, bradykinesia and slowness of movement. Although the pathological mechanisms are not entirely clear, neuroinflammation and activated microglia appear to play a major role in both its pathology and progression [67-69]. IR has been shown to prevalent in PD and may associate with the development and acceleration of the progression of motor and non-motor PD symptoms [70].

Both animal and in-vitro studies show a beneficial effect of ketone bodies on the course of PD [see 73]. With regard to humans, Van Itallie et al. observed [72] 5 PD patients for 28 days who followed a KD (2% carbohydrates, 8% protein and 90% fat) and observed an, on average, 43% improvement in the Movement Disorders Society-Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) scores. In a recent 8-week, pilot randomized-controlled trial, Phillips et al. [73] 47 PD patients were randomized to either a 1750 kcal low-fat (56% carbohydrates) or KD (5% carbohydrates). Both diet groups showed significantly improved motor and non-motor symptoms; however, the KD group showed greater improvements in non-motor symptoms, as assessed by the MDS-UPDRS, than did the low-fat diet (41% vs. 11%, P <.001). Finally [74], a recent randomized trial investigated the 12-week effects of KD versus a regular diet (RD) on voice quality, using the Voice Handicap Index (VHI), among 74 PD patients (68 of whom completed the trial). At baseline, both groups were comparable (KD: 21.2 ± 4.9 vs. RD: 22.2 ±5.1). However, at 12-weeks, compared to RD, the KD group experienced a significant improvement in both the VHI total score (20.9 ± 4.8 vs. 5.3 ± 1.2, respectively) and the 10 parameter sub-scale scores (all p <.01). Although the data on the effects of KD on selected symptoms in PD patients is sparse, preliminary studies, such as those reported above, suggest that it merits further investigation.
4.4 Alzheimer's Disease (AD)

AD is a chronic neurodegenerative disorder that affects about 50 million people worldwide, interfering with memory, thinking, and behavior [75]. Because of the increasing evidence, in both animals and humans, that neurons in the brain become IR and that this appears to play an important role in the cognitive decline, AD is now sometimes referred to as type 3 diabetes [76-80] (i.e., diabetes of the brain). Although AD's underlying pathology is not fully understood, it has been demonstrated that abnormal glucose metabolism uptake, reduced mitochondrial-associated brain energy metabolism, changes in the release of neurotransmitters, and increased neuroinflammation are hallmarks of this disease [81]. Because the brain imposes tremendous energy demands and patients with AD typically present with mitochondrial dysfunction and metabolic changes (i.e., impaired glucose utilization in the brain) indicative of a “starving” brain [82]. It is hypothesized that increasing ketones, via fasting, KD and/or exogenous ketones, may influence metabolic and signaling changes that underlie the pathophysiology of AD and, potentially, other neurodegenerative disorders [81, 83-85].

Animal studies consistently show that feeding rats a high-sugar diet impairs brain function [86]. Moreover, it has been shown that elderly humans with Alzheimer’s who consume high-carbohydrate diets tend to manifest the worst neurological symptoms and cognitive and memory impairments [87]. Because there are few approved drugs to treat AD, as well as no effective therapies to either prevent AD’s development or progression [89, 90], various dietary patterns (e.g., caloric restriction, Mediterranean diet, and KD) and lifestyle modifications (e.g., exercise) have been proposed as possible treatment approaches for AD [85, 91, 92].

Nutritional ketosis, whether through KD and/or increased consumption of dietary medium-chain triglycerides (i.e., MCT oil, which rapidly metabolizes into ketones) has been shown to produce beneficial effects in those with Alzheimer’s who suffer from mild cognitive impairment [93-97]. To date, very few clinical investigations have been conducted to evaluate the effects of KD, or less restrictive low-carbohydrate diets, on AD. A recent comprehensive review of the effects of KD for AD concluded, “Based on the limited animal studies and clinical trials, KD has beneficial effects for enhancing mitochondrial function and cellular metabolism. It is associated with improved cognitive performance in elderly adults with AD. The improvement of the cognitive outcomes depends on the level and duration of ketosis. Also, further studies are necessary for the long-term effects of KD on nutritional status, general well-being, and the progress of AD in patients. However, this novel metabolic treatment seems to be intriguing and deserves further clinical investigations in the progress of AD [98] (p. 12).”

4.5 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory central nervous system disease characterized by recurrent and progressive demyelination (i.e., damage to the myelin sheath around nerves) and remyelination cycles [99]. MS damages white and gray matter, promotes axonal destruction and neuro-inflammation which leads to disability and, eventually, the loss of neuronal functionality [100, 101]. It is estimated that over 2 million people worldwide suffer from MS and it is one of the major causes of disability and early retirement in young adults [102]. There is no cure for MS but several immunomodulatory drugs are available which attempt to slow disease progression, but
they often produce major and deleterious side effects [103]. Because insulin resistance (IR) appears to be more common in adults with MS and associates with higher disability scores, the western diet (i.e., high energy, high fat, high sugar) has been proposed as a possible contributor to MS [104]. That is, the cerebral glucose hypometabolism that occurs with MS might reflect mitochondrial dysfunction in nerve cells [105, 106]. Given this, it has been proposed that severe caloric or carbohydrate restriction (i.e., KD), to decrease both glucose and insulin and promote ketone bodies derived from fat, might provide an alternative energy source for the brain and stimulate mitochondrial biogenesis [107].

To date, support the potential efficacy of KD has been derived from animal models showing that it may slow disease progression, improve motor disability, reverse lesions and suppress inflammation [108]. In human studies, the feasibility and safety of KD (and fasting) has been demonstrated, as well as beneficial effects on health-related quality of life [109]. However, a recent 12-week small pilot study among 15 individuals with MS, randomized to either a modified Paleolithic diet, a medium-chain triglyceride (MCT)-based KD or usual diet found that, although the KD achieved ketosis none of the changes in outcomes (i.e., quality of life, cognitive function, fatigue and physical function) were significant [110]. Given the physiological rationale for the potential value of KD and fasting for MS larger trials are needed to provide a rigorous evaluation their effects.

### 4.6 Spinal Cord Injury (SCI) and Traumatic Brain (TB)

Emerging research suggests the neuroprotective effects of a KD in neurological function [111-115]. To better understand these potential neuroprotective effects, a rodent spinal cord injury model was used to test whether KD could promote neuroprotection and recovery. Rodents were fed with either a standard diet or a KD (i.e., fat: protein + carbohydrate ratio of 3:1) for 12 weeks. The KD rodents used limbs on the injured side more frequently than their standard diet counterparts and continued to show improvements in movement beyond 12 weeks. The KD rodents also improved their ability to reach and grasp for food pellets, as well as to maintain the supination movement that then directs the pellet towards the mouth. Histological analysis revealed smaller grey matter damage and protection of neuronal survival in the area of the lesion of the KD rodents [116].

Given the successes of KD found in animal models, Demirel [117] conducted a randomized, parallel-controlled study of patients with acute SCI. Participants were randomized to a ketogenic diet (3:1 ratio fat + carb: protein) or a standard diet (45-50% carb energy, 30% fat energy, 20% protein energy) for 5 weeks. Those consuming the KD had significantly improved upper extremity motor function and lower levels of neuroinflammatory blood proteins, suggesting that KD may induce anti-inflammatory effects promoting motor function [117]. While further studies are needed to confirm these initial findings, the results point to promising neuroprotection and recovery with the use of KD [116].

With regard to TBI, KD’s have also been shown to improve some functional outcomes in adolescent rats following TBI. Adolescent rats (35 days old) fed a KD with a fat: protein + carbohydrate ratio of 7:1 produced significant improvements in time to traverse a beam, a measure of fine motor coordination and balance, and reduced foot slips. However, these results were not applicable to the adult rats (75 days old) possibly due to increased hyperactivity noted in other KD
studies involving adult rats [116]. At this writing, only two studies are known to extend into human trials, examining the short-term effects of KD in a hospital setting. In one study, 20 patients were randomized to a control or a carbohydrate-free, moderately high fat diet. Those randomized to the carbohydrate free diet experienced lower blood lactate concentration, higher ketone bodies and better urinary nitrogen balance, however, long term follow up was not reported [117, 118]. A scoping review of KD in regard to TBI concluded KD is a safe and effective treatment in rats and holds promise to treatment in humans. After reviewing the literature, the authors came to the following conclusions, “KD is an effective therapy to enhance cognitive and pathological outcomes after TBI in rats. The KD has shown to be safe and well tolerated in humans [119, 120]. There is currently no evidence to indicate that a standard diet would provide a benefit in TBIs compared to the KD in rats. The KD is a potential treatment for TBI in humans and may be differentially more effective in pediatric populations based on animal models. The mechanisms of action of the KD for TBI treatment are beginning to be understood in animal models; however, more research is needed to elucidate these mechanisms, especially in humans [119] (p. 421).”

5. Speculative Applications

5.1 Autism Spectrum Disorder (ASD)

ASD is a developmental spectrum disorder that can cause varying behavioral, social, and communication challenges [121]. The causes of ASD are unknown, however, there are many reported likely causes of ASD including biologic and genetic risk factors. The Childhood Autism Rating Scale (CARS) is widely used as a diagnosis tool and consists of 14 domains assessing behaviors associated with ASD. Each domain is measured on a scale of 1 through 4, with higher scores associated with a higher level of impact [122]. Current treatment for ASD focuses on early intervention behavioral therapy in children with specialized treatment for symptoms (speech or occupational therapy). The unknown etiology of ASD and therapy limited to symptom management provides a strong rationale for alternative therapy.

While there are limited studies of KD as an ASD treatment, some case studies have shown positive results. In one pilot study of 18 patients aged 4-10 years old, two patients manifested significant improvements in their CARS scores, while eight patients showed average or minor improvements [123]. Herbert and Buckley [124, 125] conducted a case study in which a KD was implemented at age 12 and lasted at for least 14 months. The child was both autistic and epileptic and saw significant improvements in both areas. Over the course of several years, the child’s CARS scores decreased from 49 to 17, constituting a change from severe autistic scores to those of a non-autistic state. Moreover, after 14 months the child was essentially seizure free. Similarly, KD was the highest rated treatment for epilepsy seizure control for ASD in a parent survey. Parents also reported positive effects on core and ASD symptoms when compared to antiepileptic drugs, which previously showed negative effects of core and ASD symptoms [125]. Although larger scale clinical studies are needed to further explore the therapeutic use of KD and ASD, the preliminary studies are promising [126-129].
5.2 Amyotrophic Lateral Sclerosis (ALS)

ALS is an incurable neurodegenerative disease in which alteration of the mitochondria of motor neurons causes progressive neuron death. Animal models of ALS suggest that ketones may be neuroprotective by improving energy balance, thereby increasing motor neuron survival. For example, in one study [130, 131], mice fed a KD manifested significantly better motor control and enhanced survival compared to controls, suggesting that targeting energy metabolism may provide a possible means of prolonging survival in humans with ALS. While it is premature to definitively claim that KD would produce significant benefits in ALS patients, a recent comprehensive review of the potential neuroprotective effects of eating patterns that produce ketosis, concluded that, “In short, KDs could be considered as a promising option to treat ALS, representing an alternative source to glucose in motor neurons by providing neuroprotection” and “Consequently, taking into account the mitochondrial dysfunction in these patients and the main cause of motor neuron degeneration, it seems that a ketogenic alternative is promising since it interferes with the main pathogenic mechanisms of the disease [132] (p. 30).”

5.3 Cystic Fibrosis (CF)

CF is a progressive, genetic disease that causes persistent lung infections and limits the ability to breathe over time. Infection and inflammation play seminal roles in exacerbating respiratory dysfunction in CF, with the secretion of pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-8 and IL-17 [133, 134]. Although neutrophils are the predominant cells in CF airways and provide the first defense against bacterial and fungal pathogens, their repeated activation causes tissue remodeling and irreversible structural damage. IL-8 is considered the most important cytokine driving the influx and decreased clearance of neutrophils in CF [135]. Given this, identifying pharmacological and/or nutritional strategies that reduce systemic inflammatory responses would be expected to dramatically improve respiratory function in CF.

A pre-clinical study of exogenous D-β HB, but not acetoacetate, decreased activation of the nucleotide - binding domain, leucine - rich repeat, pyrin domain containing 3 (NLRP3) and reduced production of the inflammatory cytokines IL-1β, IL-8 and IL-18 [136]. Thus, one could hypothesize that through a mechanism that involves inhibition of NLRP3 inflammasome, administration of exogenous D-βHB (or adopting the KD eating pattern) might be a well-tolerated, safe, and effective strategy to improve respiratory function and quality of life in CF.

5.4 Heart Failure (HF)

Heart failure (HF) affects millions of people worldwide, imposing substantial morbidity and mortality [137]. Traditionally, pharmacological interventions target neurohormonal axes and hemodynamic disturbances. However, emerging evidence suggests the possibility that ketone metabolic modulation might become a viable treatment paradigm for HF [137, 139]. Recent studies indicate that enhanced myocardial ketone use is adaptive in HF, and limited data demonstrate beneficial effects of exogenous ketone therapy in studies of animal models [140] and humans with HF [138, 140-146]. As noted in a recent review from Selvaraj and colleagues, “Although a number of important questions remain regarding the use of therapeutic ketosis and
mechanism of action in HF, current evidence suggests potential benefit, in particular, in HF with reduced ejection fraction, with theoretical rationale for its use in HF with preserved ejection fraction. Although it is early in its study and development, therapeutic ketosis across the spectrum of HF holds significant promise [147] (p. 1800).”

5.5 Human SARS-CoV-2 Infection (COVID-19)

The relatively high mortality rate in those infected by COVID-19 is due primarily to the development of a large innate immune response (i.e., a cytokine storm culminating in an acute respiratory distress syndrome [ARDS]). ARDS is characterized by decreased energy metabolism, altered redox state, oxidative damage, and, eventually, cell death [148, 149]. As such, treatments such as KD or exogenous ketones that significantly raise levels of beta-hydroxybutyrate might be capable of restoring energy metabolism, thereby blunting the cytokine storm and inhibiting the acute inflammatory response to the infection [150-153]. As Bradshaw and colleagues note, given the compelling mechanistic rationale, “A clinical study is warranted where COVID-19 patients consume a permissive diet combined with ketone ester to raise blood ketone levels to 1 to 2mM with measured outcomes of symptom severity, length of infection, and case fatality rate [148] (p.1).” As of this writing, at least two clinical trials have been initiated to examine the effects of KD, or the use of exogenous ketones, to remediate the cytokine storm in COVID-19 [154, 155].

6. Risks and Common Misconceptions

6.1 Ketosis vs. Ketoacidosis

Perhaps the most common misconception is the inability to make the distinction between ketosis and ketoacidosis. Many people, healthcare professionals included, are unfamiliar with the differentiation, often citing ketoacidosis as a risk of KD’s. [156, 157]. To emphasize the distinction between ketosis and ketoacidosis, Volek and Phinney noted, “Nutritional ketosis is by definition a benign metabolic state that gives human metabolism the flexibility to deal with famine or major shifts in available dietary fuels. By contrast, ‘diabetic ketoacidosis’ is an unstable and dangerous condition that occurs when there is inadequate pancreatic insulin response to regulate B-OHB. This occurs only in type-1 diabetes or in late stage type-2 diabetes with advanced pancreatic burnout. In this setting of deficient insulin, when exogenous insulin is withheld, serum B-OHB levels reach the 15-20 nM range – 5-to-10-fold higher than the levels characteristic of nutritional ketosis [158] (p. 5).” Essentially, the lack of insulin does not allow feedback control on lipolysis to function, so ketones become dangerously elevated.

6.2 Renal Damage

Some argue that KD’s, due to high protein content, might promote high levels of nitrogen excretion that could cause hyperfiltration and renal damage. This is based on the common misconception that, since KD’s are very low in carbohydrates, the diet must be high in protein. However, in KDs protein intake is moderated in proportion to fat intake (i.e., typically > 70% fat). That is, the central macronutrient in a KD is fat, with moderate amounts of protein and very low amounts of carbohydrate.
Studies comparing various weight loss diets, even those with longer duration, e.g., [159, 160] find no association with markers of renal dysfunction. A recent prospective-observational prospective study [161] among 92 patients who followed a very-low calorie KD for 3 months to promote weight loss, found no deleterious changes in renal function, even among the 38 patients with mild kidney failure. Indeed, nearly 28% of those patients experienced normalization of glomerular filtrate, indicative of improved function.

Overall, the data suggests that, in the absence of major kidney disease, the KD does not compromise renal function.

6.3 Dyslipidemia

Dyslipidemia is a risk factor for cardiovascular disease (CVD). Although higher levels of lipids, particularly low-density lipoprotein cholesterol (LDL-C), have been reported in some KD trials, systematic reviews and meta-analyses of KD and very low calorie KD trials [162] found favorable changes (reductions) in total cholesterol, triglycerides, with no significant changes in LDL or high-density lipoprotein cholesterol (HDL-C) [163]. Other studies report increases HDL-C and a decrease of triglycerides as a favorable lipid profile, despite some rise in LDL-C [7]. A recent study of the effects of 2-years on KD on CVD risk factors among 194 patients with T2D found a 23% decrease in small particles (those linked to CVD) and a 29% increase in larger LDL particles (thought to be innocuous)[164]. They also found no progression in carotid-artery intima-medial thickness, a strong marker of CVD risk. Overall, the preponderance of data suggests that the KD generally improves lipid profile, likely reducing CVD risk. Nevertheless, more long-term studies are needed to definitively establish whether, indeed, a KD promotes a beneficial lipid profile and reduces CVD risk.

6.4 Carbohydrates are not an Essential Macronutrient in a Healthy Diet

Of the three macronutrients, only proteins and fats, contain essential components that cannot be derived without being present [165] in the diet. On the other hand, carbohydrates are not an essential macronutrient in that glucose can be “manufactured” from protein (gluconeogenesis), primarily in the liver, to provide the energy requirements of the brain, heart and muscles. It is well-established that during starvation an adequate amount of substrate for energy needs is provided through gluconeogenesis and ketogenesis [166-168]. Although non-essential to sustain energy needs, some carbohydrate containing foods, most notably those containing fiber, may be beneficial to health.

6.5 We don’t Know the Long-Term Effects of KD

While it is certainly the case that clinical trials evaluating the long-term (i.e., several year) effects of KD are yet to be conducted, the long-term effects of the current dietary recommendations appear to be clear. In the United States, for nearly 40 years, the Dietary Guidelines for Americans (high-carbohydrate [45-65% of daily calories], moderate-protein, low-fat eating) which strong evidence suggests people have been adhering to, [169] has likely contributed to the doubling the obesity rate, with nearly 75% of adults either overweight or obese [170, 171]. In addition, this eating pattern associates strongly with the development of the spectrum of...
chronic metabolic diseases that continue to increase in prevalence (e.g., T2D, cardiovascular disease, cancer) [172].

7. Conclusions

Although traditionally, KD was used primarily as a treatment for reducing the frequency of epileptic seizures, it has become a popular eating pattern, largely because of its value for weight control and the management of T2D. Because it is becoming increasingly clear that IR plays an essential role in the development of the spectrum of chronic metabolic diseases, there is great interest in implementing and testing the effects of KD’s on a variety of conditions, including cancer, Alzheimer’s disease and traumatic brain injury. As shown in Table 2, we conclude that the strength of the evidence of KD’s effects for most conditions remains weak-to-moderate. Moreover, the evidence pertaining to conditions where there is a reasonable physiological/biochemical rationale for the beneficial effects of ketosis [92, 173] is either unknown or, at best, preliminary. While there continue to be questions about the long-term effects and safety of KD’s [174], the preponderance of data [175], from short- and intermediate-term trials indicates that a KD improves most health parameters, particularly markers of metabolic syndrome and CVD. Although a great deal of excitement has been generated by the potential of KD to provide [176] beneficial effects for an array of chronic metabolic diseases, without additional, rigorously conducted randomized, controlled clinical trials, particularly with longer-term follow-up, it is premature to conclude that KD is efficacious for the range of metabolic illnesses [177] that plague much of the developed world. Ultimately, of course, sustaining the beneficial effects of KD over the long-term requires consistent adherence, which is elusive for many. Because the word “diet” implies time-limited deprivation, it might be better to refer to the KD as the ketogenic eating pattern (KEP). Despite the challenging issue of adherence, the prospect of using a KD as a potential first-line of treatment for these diseases is intriguing, though it awaits further elaboration and confirmation, including efforts toward evaluating genetic variants in response to KD’s [178].

Table 2 Strength of Evidence Pertaining to the Ketogenic Diet for Selected Health Conditions.

| Condition                              | Strength of Evidence |
|----------------------------------------|----------------------|
| **Established Applications of KD**     |                      |
| Obesity                                | X                    |
| Type 2 Diabetes                        | X                    |
| Epilepsy                               | X                    |
| Polycystic Ovarian Syndrome            | X                    |
| **Emerging Applications of KD**        |                      |
| Cancer                                 | X                    |
| Non-Alcoholic Fatty Liver Disease      | X                    |
| Alzheimer’s Disease                    | X                    |
| Parkinson’s Disease                    | X                    |
| Multiple Sclerosis                     | X                    |
| TBI & Spinal Cord Injury               | X                    |
Speculative Applications of KD

Autism Spectrum Disorder  X
Amyotrophic Lateral Sclerosis  X
Cystic Fibrosis  X
Heart Failure  X
COVID-19  X

Author Contributions

JL and KRF co-wrote this article.

Competing Interests

Dr. Fontaine serves of the scientific advisory board to Simply Good Foods USA, Inc.

References

1. Abbasi J. Interest in the ketogenic diet grows for weight loss and type 2 diabetes. JAMA. 2018; 319: 215.
2. Malik VS, Hu FB. Popular weight-loss diets: From evidence to practice. Nat Clin Pract Cardiovasc Med. 2007; 4: 34-41.
3. Feinman RD, Pogozelski WK, Astrup A, Bernstein RK, Fine EJ, Westman EC, et al. Dietary carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base. Nutrition. 2015; 31: 1-13.
4. Masino S, Bergin AN. Ketogenic diet in established epilepsy indications in ketogenic diet and metabolic therapies: Expanded roles in health and disease. Oxford: Oxford University Press; 2017.
5. Feinman RD. The biochemistry of low-carbohydrate and ketogenic diets. Curr Opin Endocrinol Diabetes Obes. 2020; 27: 261.
6. Fine EJ, Feinman RD. Insulin, carbohydrate restriction, metabolic syndrome and cancer. Expert Rev Endocrinol Metab. 2014; 10: 15-24.
7. Volek JS, Phinney SD, Forsythe CE, Quann EE, Wood RJ, Puglisi MJ, et al. Carbohydrate restriction has a more favorable impact on the metabolic syndrome than a low fat diet. Lipids. 2008; 44: 297-309.
8. Vidali S, Aminzadeh S, Lambert B, Rutherford T, Sperl W, Kofler B, et al. Mitochondria: The ketogenic diet—A metabolism-based therapy. Int J Biochem Cell Biol. 2015; 63: 55.
9. Goss AM, Gower B, Soleymani T, Stewart M, Pendergrass M, Lockhart M, 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. 2020; 17: 64.
10. Lafountain RA, Miller VJ, Barnhart EC, Hyde PN, Crabtree CD, Mcswiney FT, et al. Extended ketogenic diet and physical training intervention in military personnel. Mil Med. 2019; 184: 538-547.
11. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017–2018 [Internet]. Hyattsville: National Center for Health Statistics; 2020 [cited date 2020 December 21]. Available from: https://www.cdc.gov/nchs/products/databriefs/db360.htm.
12. Masino S, Westman EC, Maguire E, Yancy WS. Ketogenic diet and metabolic therapies: Expanded roles in health and disease. Oxford, NY: Oxford University Press; 2017.
13. Johnston BC, Kanters S, Bandayrel K, Wu P, Naji F, Siemieniuk RA, et al. Comparison of weight loss among named diet programs in overweight and obese adults. JAMA. 2014; 312: 923-933.
14. Bueno NB, Melo IS, Oliveira SL, Ataide TD. 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.
15. Castellana M, Conte E, Cignarelli A, Perrini S, Giustina A, Giovanella L, et al. 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. 2019; 21: 5-16.
16. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. Available from: https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf.
17. International Diabetes Federation. In: IDF Diabetes Atlas, 8th ed.; International Diabetes Federation: Brussels, Belgium, 2017.
18. Hostalek U. Global epidemiology of prediabetes - present and future perspectives. Clin Diabetes Endocrinol. 2019; 5: 5.
19. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. 9th ed. Diabetes Res Clin Pract. 2019; 157: 107843.
20. Home P, Riddle M, Cefalu WT, Bailey CJ, Bretzel RG, Prato SD, et al. Insulin therapy in people with type 2 diabetes: Opportunities and challenges? Diabetes Care. 2014; 37: 1499-1508.
21. Davies MJ, D’Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018; 41: 2669-2701.
22. Osler W. The principles and practice of medicine. NY, USA: D. Appleton and Company; 1912.
23. Westman EC, Yancy WS, Humphreys M. Dietary treatment of diabetes mellitus in the pre-Insulin era (1914-1922). Perspect Biol Med. 2006; 49: 77-83.
24. Hyde PN, Sapper TN, Crabtree CD, Lafountain RA, Bowling ML, Buga A, et al. Dietary carbohydrate restriction improves metabolic syndrome independent of weight loss. JCI Insight. 2019; 4: 128308.
25. Westman EC, Yancy WS, Mavropoulos JC, Marquart M, McDuffie JR. 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.
26. Olaogun I, Farag M, Hamid P. The pathophysiology of type 2 diabetes mellitus in non-obese individuals: An overview of the current understanding. Cureus. 2020; 12: 7614.
27. Hallberg SJ, Gershuni VM, Hazbun TL, Athinarayanan SJ. Reversing type 2 diabetes: A narrative review of the evidence. Nutrients. 2019; 11: 766.
28. Stern L, Iqbal N, Seshadri P, Chicano KL, Daily DA, Megrory J, et al. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: One-year follow-up of a randomized trial. Ann Intern Med. 2004; 140: 778.
29. Hallberg SJ, Mckenzie AL, Williams PT, Bhanpuri NH, Peters AL, Campbell WW, 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.

30. Bhanpuri NH, Hallberg SJ, Williams PT, Mckenzie AL, Ballard KD, Campbell WW, et al. Cardiovascular disease risk factor responses to a type 2 diabetes care model including nutritional ketosis induced by sustained carbohydrate restriction at 1 year: An open label, non-randomized, controlled study. Cardiovasc Diabetol. 2018; 17: 56.

31. Freeman JM, Vining EP, Kossoff EH, Pyzik PL, Ye X, Goodman SN. A blinded, crossover study of the efficacy of the ketogenic diet. Epilepsia. 2009; 50: 322-325.

32. Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. The ketogenic diet for the treatment of childhood epilepsy: A randomized controlled trial. Lancet Neurol. 2008; 7: 500-506.

33. Nordli DR, Kuroda MM, Carroll J, Koenigsberger DY, Hirsch LJ, Bruner HJ, et al. Experience with the ketogenic diet in infants. Pediatrics. 2001; 108: 129-133.

34. Caraballo RH. Nonpharmacologic treatments of Dravet syndrome: Focus on the ketogenic diet. Epilepsia. 2011; 52: 79-82.

35. Nabbout R, Copioli C, Chipaux M, Chemaly N, Desguerre I, Dulac O, et al. Ketogenic diet also benefits Dravet syndrome patients receiving stiripentol: A prospective pilot study. Epilepsia. 2011; 52: 54-57.

36. PCOS (Polycystic Ovary Syndrome) and diabetes [Internet]. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention; 2020 [cited date 2020 December 21]. Available from: https://www.cdc.gov/diabetes/basics/pcos.html.

37. Batch JT, Lamsal SP, Adkins M, Sultan S, Ramirez MN. Advantages and disadvantages of the ketogenic diet: A review article. Cureus. 2020; 12: 9639.

38. Goss AM, Chandler-Laney PC, Ovalle F, Goree LL, Azziz R, Desmond RA, et al. Effects of a eucaloric reduced-carbohydrate diet on body composition and fat distribution in women with PCOS. Metab Clin Exp. 2014; 63: 1257-1264.

39. Muscogiuri G, Palomba S, Laganà A, Orio F. Current insights into inositol isoforms, Mediterranean and ketogenic diets for polycystic ovary syndrome: From bench to bedside. Curr Pharma Des. 2016; 22: 5554-5557.

40. Stocker RK, Aubry ER, Bally L, Nuoffer J-M, Stanga Z. Ketogene diät: Evidenzbasierte therapeutische anwendung bei endokrinologischen erkrankungen. Praxis. 2019; 108: 541-553.

41. Paoli A, Mancin L, Giacona MC, Bianco A, Caprio M. Effects of a ketogenic diet in overweight women with polycystic ovary syndrome. J Transl Med. 2020; 18: 104.

42. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020; 70: 7-30.

43. Warburg O. On the origin of cancer cells. Science. 1956; 123: 309-314.

44. Hanahan D. Weinberg RA. Hallmarks of cancer: The next generation. Cell. 2011; 144: 646-674.

45. Seyfried TN, Shelton LM. Cancer as a metabolic disease. Nut Metab. 2010; 7: 7.

46. Seyfried TN, Kiebish MA, Marsh J, Shelton LM, Huysentruyt LC, Mukherjee P. Metabolic management of brain cancer. Biochim Biophys Acta. 2011; 1807: 577-594.

47. Prince A, Zhang Y, Croniger C, Puchowicz M. Oxidative metabolism: Glucose versus ketones. Adv Exp Med Biol. 2013; 789: 323-328.
48. Vergati M, Krasniqi E, Monte GD, Riondino S, Vallone D, Guadagni F, et al. Ketogenic diet and other dietary intervention strategies in the treatment of cancer. Curr Med Chem. 2017; 24: 1170-1185.

49. Klement RJ. Fasting, fats, and physics: Combining ketogenic and radiation against cancer. Complement Med Res. 2018; 25: 102-113.

50. Klement RJ. The influence of ketogenic therapy on the SR’s of radiobiology. Int J Radiat Biol. 2019; 95: 394-407.

51. Youm YH, Nguyen KY, Grant RW, Goldberg EL, Bodogai M, Dongin K, et al. The ketone metabolite beta-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. Nat Med. 2015; 21: 263-269.

52. Branco AF, Ferreira A, Simões RF, Magalhães-Novais S, Zehowski C, Cope E, et al. Ketogenic diets: from cancer to mitochondrial diseases and beyond. Eur J Clin Invest. 2016; 46: 285-298.

53. Fine EJ, Segal-Iaacson C, Feinman RD, Herszkopf S, Romano MC, Tomuta N, et al. Targeting insulin inhibition as a metabolic therapy in advanced cancer: A pilot safety and feasibility dietary trial in 10 patients. Nutrition. 2012; 28: 1028-1035.

54. Polivka JP, Holubec L, Kubikova T, Priban V, Hes O, et al. Advances in experimental targeted therapy and immunotherapy for patients with glioblastoma multiforme. Anticancer Res. 2017; 37: 21-33.

55. Chinopoulos C, Seyfried TN. Mitochondrial substrate-level phosphorylation as energy source for glioblastoma: Review and hypothesis. ASN Neuro. 2018; 10: 1-27.

56. Zhou W, Mukherjee P, Kiebish MA, Markis WT, Mantis JG, Seyfried TN. The calorically restricted ketogenic diet, an effective alternative therapy for malignant brain cancer. Nutr Metab. 2017; 4: 5.

57. Mukherjee P, Augur ZM, Li M, Hill C, Greenwood B, Domin MA, et al. Therapeutic benefit of combining calorie-restricted ketogenic diet and glutamine targeting in late-stage experimental glioblastoma. Commun Biol. 2019; 2: 200.

58. Seyfried TN, Shelton L, Arismendi-Morillo G, Kalamian M, Elsakka A, Maroon J, et al. Provocative question: Should ketogenic metabolic therapy become the standard of care for glioblastoma? Neurochem Res. 2019; 44: 2392-2404.

59. Elsakka AMA, Bary MA, Abdelzaher E, Elnaqgar M, Kalamian M, Mukherjee P, et al. Management of glioblastoma multiforme in a patient treated with ketogenic metabolic therapy and modified standard of care: A 24-month follow-up. Front Nutr. 2018; 5: 20.

60. Bost J, Maroon J, Seyfried T, Donohue J. The role of metabolic therapy in treating glioblastoma multiforme. Surg Neurol Int. 2015; 6: 61.

61. Seyfried TN, Flores R, Poff AM, D’Agostino DP, Mukherjee P. Metabolic therapy: A new paradigm for managing malignant brain cancer. Cancer Lett. 2015; 356: 289-300.

62. Zuconi G, Marcello N, Pisanello A, Servadei F, Vaccaro S, Mukherjee P, et al. Metabolic management of glioblastoma multiforme using standard therapy together with a restricted ketogenic diet: Case report. Nutr Metab. 2010; 7: 33.

63. Weber DD, Aminzadeh-Gohari S, Tulipan J, Catalano L, Feichtinger RG, Kofler B. Ketogenic diet in the treatment of cancer - Where do we stand? Mol Metab. 2020; 33: 102-121.

64. Noureddin M, Vipani A, Bresee C, Todo T, Kim IK, Alkhouri N, et al. NASH leading cause of liver transplant in women: Updated analysis of indications for liver transplant and ethnic and gender variances. Am J Gastroenterol. 2018; 113: 1649-1659.
65. Watanabe M, Tozzi R, Risi R, Tuccinardi D, Mariani S, Basciani S, et al. Beneficial effects of the ketogenic diet on nonalcoholic fatty liver disease: A comprehensive review of the literature. Obes Rev. 2020; 21: 13024.

66. Goss AM, Dowla S, Pendergrass M, Ashraf A, Bolding M, Morrison S, et al. Effects of a carbohydrate-restricted diet on hepatic lipid content in adolescents with non-alcoholic fatty liver disease: A pilot, randomized trial. Pediatric Obes. 2020; 15: 12630.

67. Burguillos MA, Deierborg T, Kavanagh E, Persson A, Hajji N, Garcia-Quintanilla A, et al. Caspase signalling controls microglia activation and neurotoxicity. Nature. 2011; 472: 319-324.

68. Phani S, Loike JD, Przedborski S. Neurodegeneration and Inflammation in Parkinson's disease. Parkinsonism Relat Disord. 2012; 18: 207-209.

69. Hirsch EC, Hunot S. Neuroinflammation in Parkinson’s disease: A target for neuroprotection? Lancet Neurol. 2009; 8: 382-397.

70. Hogg E, Athreya K, Basile C, Tan EE, Kaminski J, Tagliati M. High prevalence of undiagnosed insulin resistance in non-diabetic subjects with Parkinson’s disease. J Parkinsons Dis. 2018; 8: 259-265.

71. Włodarek D. Role of ketogenic diets in neurodegenerative diseases (Alzheimer’s disease and Parkinson’s disease). Nutrients. 2019; 11: 169.

72. Vanitallie TB, Nonas C, Rocco AD, Boyar K, Hyams K, Heymsfield SB. Treatment of parkinson disease with diet-induced hyperketonemia: A feasibility study. Neurology. 2005; 64: 728-730.

73. Phillips MC, Murtagh DK, Gilbertson LJ, Asztely FJ, Lynch CD. Low-fat versus ketogenic diet in Parkinson’s disease: A pilot randomized controlled trial. Mov Disord. 2018; 33: 1306-1314.

74. Koyuncu H, Fidan V, Toktas H, Binay O, Celik H. Effect of ketogenic diet versus regular diet on voice quality of patients with Parkinson's disease. Acta Neurol Belg. 2020: 3. DOI: 10.1007/s13760-020-01486-0

75. Querfurth HW, LaFeria FM. Mechanisms of disease: Alzheimer’s disease. N Engl J Med. 2010; 362: 329-344.

76. Pawlosky RJ, Kemper MF, Kashiwaya Y, King MT, Mattson MP, Veech RL. Effects of a dietary ketone ester on hippocampal glycolytic and tricarboxylic acid cycle intermediates and amino acids in a 3xTgAD mouse model of Alzheimer’s disease. J Neurochem. 2017; 141: 195-207.

77. Shaughness M, Acs D, Brabazon F, Hockenbury N, Byrnes KR. Role of insulin in neurotrauma and neurodegeneration: A review. Front Neurosci. 2020; 14: 547175.

78. Taylor MK, Sullivan DK, Swerdlow RH, Vidoni ED, Morris JK, Mahnken JD, et al. A high-glycemic diet is associated with cerebral amyloid burden in cognitively normal older adults. Am J Clin Nutr. 2017; 106: 1463-1470.

79. de la Monte SM. Insulin resistance and neurodegeneration: Progress towards the development of new therapeutics for Alzheimer’s disease. Drugs. 2017; 77: 47-65.

80. Berger A. Insulin resistance and reduced brain glucose metabolism in the aetiology of Alzheimer’s disease. J Insulin Resist. 2016. 1: 1.

81. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med. 2011; 1: 006189.

82. Swerdlow RH. Brain aging, Alzheimer’s disease, and mitochondria. Biochim Biophys Acta. 2011; 1812; 1630-1639.

83. Owen OE, Morgan AP, Kemp HG, Sullivan JM, Herrera MG, Cahill Jr GF. Brain metabolism during fasting. J Clin Invest. 1967; 46: 1589-1595.
84. McDonald TJW, Cervenka MC. The expanding role of ketogenic diets in adult neurological disorders. Brain Sci. 2018; 8: 148.
85. Shippy DC, Wilhelm C, Viharkumar PA, Raife TJ, Ulland TK. β-Hydroxybutyrate inhibits inflammasome activation to attenuate Alzheimer’s disease pathology. J Neuroinflammation. 2020; 17: 280.
86. Molteni R, Barnard R, Ying Z, Roberts C, Gómez-Pinilla F. A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. Neuroscience. 2002; 112: 803-814.
87. Young KW, Greenwood CE, Van Reekum R, Binns MA. A randomized, crossover trial of high-carbohydrate foods in nursing home residents with Alzheimer’s disease: associations among intervention response, body mass index, and behavioral and cognitive function. J Gerontol A Biol Sci Med Sci. 2005; 60: 1039-1045.
88. Raina P, Santaguida P, Ismaila A, Patterson C, Cowan D, Levine, M, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: Evidence review for a clinical practice guideline. Ann Intern Med. 2008; 148: 379-397.
89. Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S, et al. Alzheimer’s disease. Lancet. 2016; 388: 505-517.
90. Barnard ND, Bush AI, Ceccarelli A, Cooper J, de Jager CA, Erickson KL, et al. Dietary and lifestyle guidelines for the prevention of Alzheimer’s disease. Neurobiol Aging. 2014; 35: 74-78.
91. Uddin MS, Kabir MT, Tewari D, Mamun AA, Barreto GE, Bungau SG, et al. Emerging therapeutic promise of ketogenic diet to attenuate neuropathological alterations in Alzheimer’s disease. Mol Neurobiol. 2020; 57: 4961-4977.
92. Christensen MG, Damsgaard J, Fink-Jensen A. Use of ketogenic diets in the treatment of central nervous system diseases: A systematic review. Nord J Psychiatry. 2020; 75: 1-8.
93. Krikorian R, Shidler MD, Dangelo K, Couch SC, Benoit SC, Clegg DJ. Dietary ketosis enhances memory in mild cognitive impairment. Neurobiol Aging. 2012; 33: 19-27.
94. Cunnane SC, Courchesne-Loyer A, Vandenbergh C, St-Pierre V, Fortier M, Hennebelle M, et al. Can ketones help rescue brain fuel supply in later life? Implications for cognitive health during aging and the treatment of Alzheimer’s disease. Front Mol Neurosci. 2016; 9: 53.
95. Rebello CJ, Keller JN, Liu AG, Johnson WD, Greenway FL. Pilot feasibility and safety study examining the effect of medium chain triglyceride supplementation in subjects with mild cognitive impairment: A randomized controlled trial. Biochim Biophys Acta Clin. 2015; 3: 123-125.
96. Reger MA, Henderson ST, Hale C, Cholerton B, Baker LD, Watson GS, et al. Effects of beta-hydroxybutyrate on cognition in memory-impaired adults. Neurobiol. Aging. 2004; 25: 311-314.
97. Augustin K, Khabbush A, Williams S, Eaton S, Orford M, Cross JH, et al. Mechanisms of action for the medium-chain triglyceride ketogenic diet in neurological and metabolic disorders. Lancet Neurol. 2018; 17: 84-93.
98. Rusek M, Pluta R, Ułamek-Kozioł M, Czuczwar SJ, Czuczwar SJ. Ketogenic diet in Alzheimer's disease. Int J Mol Sci. 2019; 20: 3892.
99. Lucchinetti C, Brück W, Noseworthy J. Multiple sclerosis: Recent developments in neuropathology, pathogenesis, magnetic resonance imaging studies and treatment. Curr Opin Neurol. 2001; 14: 259-269.
100. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med. 2000; 343: 938-952.

101. Barnett MH, Prineas JW. Relapsing and remitting multiple sclerosis: Pathology of the newly forming lesion. Ann Neurol. 2004; 55: 458-468.

102. Pfleger CCH, Flachs EM, Koch-Henriksen N. Social consequences of multiple sclerosis. Part 2. Divorce and separation: A historical prospective cohort study. Mult Scler J. 2010; 16: 878-882.

103. Dörr J, Paul F. The transition from first-line to second-line therapy in multiple sclerosis. Curr Treat Options Neurol. 2015; 17: 25.

104. Ghanim H, Abuaysheh S, Sia CL, Korzeniewski K, Chaudhuri A, Fernandez-Real JM, et al. Increase in plasma endotoxin concentrations and the expression of toll-like receptors and suppressor of cytokine signaling-3 in mononuclear cells after a high-fat, high-carbohydrate meal: Implications for insulin resistance. Diabetes Care. 2009; 32: 2281-2287.

105. Blinkenberg M, Rune K, Jensen CV, Ravnborg M, Kyllingsbak S, Holm S, et al. Cortical cerebral metabolism correlates with MRI lesion load and cognitive dysfunction in MS. Neurology. 2000; 54: 558.

106. Tenney JR, Rozhkov L, Horn P, Miles L, Miles MV. Cerebral glucose hypometabolism is associated with mitochondrial dysfunction in patients with intractable epilepsy and cortical dysplasia. Epilepsia. 2014; 55: 1415-1422.

107. Gasior M, Rogawski MA, Hartman AL. Neuroprotective and disease-modifying effects of the ketogenic diet. Behav Pharmacol. 2006; 17: 431-439.

108. Kim DY, Hao J, Liu R, Turner G, Shi FD, Rho JM. Inflammation-mediated memory dysfunction and effects of a ketogenic diet in a murine model of multiple sclerosis. PLOS ONE. 2012; 7: 35476.

109. Choi IY, Piccio L, Childress P, Bollman B, Ghosh A, Brandhorst S, et al. A diet mimicking fasting promotes regeneration and reduces autoimmunity and multiple sclerosis symptoms. Cell Rep. 2016; 15: 2136-2146.

110. Lee JE, Titcomb TJ, Bisht B, Rubenstein LM, Louison R, Wahls TL. A modified MCT-based ketogenic diet increases plasma β-hydroxybutyrate but has less effect on fatigue and quality of life in people with multiple sclerosis compared to a modified paleolithic diet: A waitlist-controlled, randomized pilot study. J Am Coll Nutr. 2020; 40: 13-25.

111. Lin J, Huang Z, Liu J, Huang Z, Liu Y, Liu Q, et al. Neuroprotective effect of ketone metabolism on inhibiting inflammatory response by regulating macrophage polarization after acute cervical spinal cord injury in rats. Front Neurosci. 2020; 14: 583611.

112. Mayr KA, Kwok CH, Eaton SE, Baker GB, Whelan PJ. The effects of a ketogenic diet on sensorimotor function in a thoracolumbar mouse spinal cord injury model. Eneuro. 2020; 7: 178-120.

113. Tan B-T, Jiang H, Moulson A, Wu X-L, Wang W-C, Liu J, et al. Neuroprotective effects of a ketogenic diet in combination with exogenous ketone salts following acute spinal cord injury. Neural Regen Res. 2020; 15: 1912-1919.

114. Yarar-Fisher C, Kulkarni A, Li J, Farley P, Renfro C, Aslam H, et al. Evaluation of a ketogenic diet for improvement of neurological recovery in individuals with acute spinal cord injury: A pilot, randomized safety and feasibility trial. Spinal Cord Ser Cases. 2018; 4: 88.

115. Guo C, Zhou J, Wu X, Jiang H, Lu K, Chen J, et al. A clinical trial of ketogenic diet in patients with acute spinal cord injury: Safety and feasibility. JSMU. 2014; 34: 571-575.
116. Masino S, Streijger F, Plunet WT, Tetzlaff W. Ketogenic diet and ketones for the treatment of traumatic brain injury and spinal cord injury. In: Ketogenic diet and metabolic therapies: Expanded roles in health and disease. Oxford, NY: Oxford University Press; 2017.

117. Demirel A, Li J, Morrow C, Barnes S, Jansen J, Gower B, et al. Evaluation of a ketogenic diet for improvement of neurological recovery in individuals with acute spinal cord injury: Study protocol for a randomized controlled trial. Trials. 2020; 21: 372.

118. Prins ML, Matsumoto JH. The collective therapeutic potential of cerebral ketone metabolism in traumatic brain injury. J Lipid Res. 2014; 55: 2450-2457.

119. Mc Dougall A, Bayley M, Munce SE. The ketogenic diet as a treatment for traumatic brain injury: A scoping review. Brain Inj. 2018; 32: 416-422.

120. Arora N, Mehta TR. Role of the ketogenic diet in acute neurological diseases. Clin Neurol Neurosurg. 2020; 192: 105727.

121. What is Autism Spectrum Disorder? [Internet]. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention; 2020 [cited date 2020 December 21]. Available from: https://www.cdc.gov/ncbddd/autism/facts.html.

122. Chlebowski C, Green JA, Barton ML, Fein D. Using the childhood autism rating scale to diagnose autism spectrum disorders. J Autism Dev Disord. 2010; 40: 787-799.

123. Masino S, Cheng N, Masino S, Rho J. Metabolic therapy for autism spectrum disorder and comorbidities. In: Ketogenic diet and metabolic therapies: Expanded roles in health and disease. Oxford, NY: Oxford University Press; 2017.

124. Herbert MR, Buckley JA. Autism and dietary therapy: Case report and review of the literature. J Child Neurol. 2013; 28: 975-982.

125. Frye RE. Mitochondrial dysfunction in autism spectrum disorder: Unique abnormalities and targeted treatments. Semin Pediatr Neurol. 2020; 35: 100829.

126. Hartman RE, Patel D. Dietary approaches to the management of autism spectrum disorders. Adv Neurobiol. 2020; 24: 547-571.

127. Karhu E, Zukerman R, Eshraghi RS, Mittal J, Deth RC, Castejon AM, et al. Nutritional interventions for autism spectrum disorder. Nutr Rev. 2019; 78: 515-531.

128. Mu C, Corley MJ, Lee RW Wong M, Pang A, Arakaki G, et al. Metabolic framework for the improvement of autism spectrum disorders by a modified ketogenic diet: A pilot study. J Proteome Res. 2019; 19: 382-390.

129. Mierau SB, Neumeyer AM. Metabolic interventions in autism spectrum disorder. Neurobiol Dis. 2019; 132: 104544.

130. Zhao Z, Lange DJ, Voustianiovou A, MacGrogan D, Ho L, Suh J, et al. A ketogenic diet as a potential novel therapeutic intervention in amyotrophic lateral sclerosis. BMC Neurosci. 2006; 7: 29.

131. Ari C, Poff AM, Held HE, Landon CS, Goldhagen CR, Mavromates N, et al. Metabolic therapy with deanna protocol supplementation delays disease progression and extends survival in Amyotrophic Lateral Sclerosis (ALS) mouse model. PLOS ONE. 2014; 9: 103526.

132. Caplliure-Llopis J, Peralta-Chamba T, Carrera-Julía S, Cuerda-Ballester M, Drehmer-Rieger E, López-Rodriguez MM, et al. Therapeutic alternative of the ketogenic mediterranean diet to improve mitochondrial activity in Amyotrophic Lateral Sclerosis (ALS): A comprehensive review. Food Sci Nutr. 2019; 8: 23-35.
133. Nichols DP, Chmiel JF. Inflammation and its genesis in cystic fibrosis. Pediatr Pulmonol. 2015; 50: 39-56.
134. Roesch EA, Nichols DP, Chmiel JF. Inflammation in cystic fibrosis: An update. Pediatr Pulmonol. 2018; 53: S30-S50.
135. Cockx M, Gouwy M, Van Damme J, Struyf S. Chemoattractants and cytokines in primary ciliary dyskinesia and cystic fibrosis: Key players in chronic respiratory diseases. Cell Mol Immunol. 2018; 15: 312-323.
136. Neudorf H, Durrer C, Myette-Cote E, Makins C, O'malley T, Little JP. Oral ketone supplementation acutely increases markers of NLRP3 inflammasome activation in human monocytes. Mol Nutr Food Res. 2019; 63: 1801171.
137. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, et al; Heart disease and stroke statistics-2019 update: A report from the American Heart Association. Circulation. 2019; 139: 56-528.
138. Sharma N, Okere I, Duda M, Chess D, Oshea K, Stanley W. Potential impact of carbohydrate and fat intake on pathological left ventricular hypertrophy. Cardiovasc Res. 2007; 73: 257-268.
139. Greenwell AA, Gopal K, Ussher JR. Myocardial energy metabolism in non-ischemic cardiomyopathy. Front Physiol. 2020; 11: 570421.
140. Nakamura M, Odanovic N, Nakada Y, Dohi S, Zhai P, Ivessa A, et al. Dietary carbohydrates restriction inhibits the development of cardiac hypertrophy and heart failure. Cardiovasc Res. 2020; cvaa298. DOI: 10.1093/cvr/cvaa298.
141. Bedi KC Jr, Snyder NW, Brandimarto J, Aziz M, Mesaros C, Worth AJ, et al. Evidence for intramyocardial disruption of lipid metabolism and increased myocardial ketone utilization in advanced human heart failure. Circulation. 2016; 133: 706-716.
142. Aubert G, Martin OJ, Horton JL, Lai L, Vega RB, Leone TC, et al. The failing heart relies on ketone bodies as a fuel. Circulation. 2016; 133: 698-705.
143. Nielsen R, Møller N, Gormsen LC, Tolbod LP, Hansson NH, Sorensen J, et al. Cardiovascular effects of treatment with the ketone body 3-hydroxybutyrate in chronic heart failure patients. Circulation. 2019; 139: 2129-2141.
144. Horton JL, Davidson MT, Kurishima C, Vega RB, Powers JC, Matsuura TR, et al. The failing heart utilizes 3-hydroxybutyrate as a metabolic stress defense. JCI Insight. 2019; 4: 124079.
145. Mccommis KS, Kovacs A, Weinheimer CJ, Shew TM, Koves TR, Ilkayeva OR, et al. Nutritional modulation of heart failure in mitochondrial pyruvate carrier-Deficient mice. Nat Metab. 2020; 2: 1232-1247.
146. Selvaraj S, Margulies KB. Exogenous ketones in the healthy heart: The plot thickens. Cardiovasc Res. 2020; 117: 995-996.
147. Selvaraj S, Kelly DP, Margulies KB. Implications of altered ketone metabolism and therapeutic ketosis in heart failure. Circulation. 2020; 141: 1800-1812.
148. Bradshaw PC, Seeds WA, Miller AC, Mahajan VR, Curtis WM. COVID-19: Proposing a ketone-based metabolic therapy as a treatment to blunt the cytokine storm. Oxid Med Cell Longev. 2020; 2020: 1-34.
149. Soliman S, Faris ME, Ratemi Z, Halwani R. Switching host metabolism as an approach to dampen SARS-CoV-2 infection. Ann Nutr Metab. 2020; 76: 297-303.
150. Kamepalli R. How immune T-cell augmentation can help prevent COVID-19: A possible nutritional solution using ketogenic lifestyle. J Respir Infect 2020; 4: 7.
151. Stubbs BJ, Koutnik AP, Goldberg EL, Upadhyay V, Turnbaugh PJ, Verdin E, et al. Investigating ketone bodies as immunometabolic countermeasures against respiratory viral infections. Med. 2020; 1: 43-65.

152. Sukkar SG, Bassetti M. Induction of ketosis as a potential therapeutic option to limit hyperglycemia and prevent cytokine storm in COVID-19. Nutrition. 2020; 79-80: 110967.

153. Paoli A, Gorini S, Caprio M. The dark side of the spoon-glucose, ketones and COVID-19: A possible role for ketogenic diet? J Transl Med. 2020; 18: 441.

154. Samir S. Eucaloric ketogenic diet in COVID-19 cytokine storm syndrome [Internet]. U.S.: NIH ClinicalTrials.gov; 2020 [cited date 2020 December 21]. Available from: https://clinicaltrials.gov/ct2/show/NCT04492228.

155. Keto-diet for intubated critical care COVID-19 [Internet]. U.S.: NIH ClinicalTrials.gov; 2020 [cited date 2020 December 21]. Available from: https://clinicaltrials.gov/ct2/show/NCT04358835.

156. Paoli A, Rubini A, Volek JS, Grimaldi KA. Beyond weight loss: A review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. Eur J Clin Nutr. 2013; 67: 789-796.

157. Misra S, Oliver NS. Diabetic ketoacidosis in adults. BMJ. 2015; 351: h5660.

158. Volek JS, Phinney SD. The art and science of low carbohydrate living: An expert guide to making the life-saving benefits of carbohydrate restriction sustainable and enjoyable. 1st ed. Florida: Beyond Obesity LLC; 2011.

159. Friedman AN, Ogden LG, Foster GD, Klein S, Miller B, et al. Comparative effects of low-carbohydrate high-protein versus low-fat diets on the kidney. Clin J Am Soc Nephrol. 2012; 7: 1103-1111.

160. Goday A, Bellido D, Sajoux I, Crujeiras AB, Burguera B, García-Luna PP, et al. Short-term safety, tolerability and efficacy of a very low-calorie-ketogenic diet interventional weight loss program versus hypocaloric diet in patients with type 2 diabetes mellitus. Nutr Diabetes. 2016; 6: 230.

161. Bruci A, Tuccinardi D, Tozzi R, Balena A, Santucci S, Frontani R, 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.

162. Di-Rosa C, Lattanzi G, Taylor SF, Manfrini S, Khazraei YM. Very low calorie ketogenic diets in overweight and obesity treatment: Effects on anthropometric parameters, body composition, satiety, lipid profile and microbiota. Obes Res Clin Pract. 2020; 14: 491-503.

163. Castellana M, Biacchi E, Procino F, Casanueva FF, Trimboli P. Very-low-calorie ketogenic diet for the management of obesity, overweight and related disorders. Minerva Endocrinol. 2020. DOI: 10.23736/S0391-1977.20.03356-8.

164. Athinarayanan SJ, Hallberg SJ, Mckenzie AL, Lechner K, King S, Mccarter JP, et al. Impact of a 2-year trial of nutritional ketosis on indices of cardiovascular disease risk in patients with type 2 diabetes. Cardiovasc Diabetol. 2020; 19: 208.

165. Westman EC. Is dietary carbohydrate essential for human nutrition? Am J Clin Nutr. 2002; 75: 951-953.

166. Cahill Jr GF. Starvation in Man. N Engl J Med. 1970; 282: 668-675.

167. Cahill Jr GF. Fuel metabolism in starvation. Annu Rev Nutr. 2006; 26: 1-22.

168. Cahill Jr GF. The future of carbohydrates in human nutrition. Nutr Rev. 2009; 44: 40-43.
169. Bentley J. U.S. trends in food availability and a dietary assessment of loss adjusted food availability, 1970-2014. USDA, Economic Research Service, EIB-166; 2017. DOI: 10.22004/ag.econ.253947.

170. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017-2018. NCHS Data Brief. 2020. Available from: https://www.researchgate.net/publication/341911217_Prevvalence_of_Obesity_and_Severe_Obesity_Among_Adults_United_States_2017-2018.

171. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007-2008 to 2015-2016. JAMA. 2018; 319: 1723-1725.

172. Buttorff C, Ruder T, Bauman M. Multiple chronic conditions in the United States. Santa Monica, CA: Rand Corporation; 2017.

173. O’Neill BJ. Effect of low-carbohydrate diets on cardiometabolic risk, insulin resistance, and metabolic syndrome. Curr Opin Endocrinol Diabetes Obes. 2020; 27: 301-307.

174. Joshi S, Ostfeld RJ, McMacken M. The ketogenic diet for obesity and diabetes-enthusiasm outpaces evidence. JAMA Intern Med. 2019; 179: 1163-1164.

175. Diamond DM, O’Neill BJ, Volek JS. Low carbohydrate diet: Are concerns with saturated fat, lipids, and cardiovascular disease risk justified? Curr Opin Endocrinol Diabetes Obes. 2020; 27: 291-300.

176. Ludwig DS. The ketogenic diet: Evidence for optimism but high-quality research needed. J Nutr. 2019; 150: 1354-1359.

177. García-García FJ, Monistrol-Mula A, Cardellach F, Garrabou G. Nutrition, bioenergetics, and metabolic syndrome. Nutrients. 2020; 12: 2785.

178. Aronica L, Volek J, Poff A, D’agostino DP. Genetic variants for personalised management of very low carbohydrate ketogenic diets. BMJ Nutr Prev Health. 2020; 3: 363-373.