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Review

Ketogenic Diet and Health

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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.

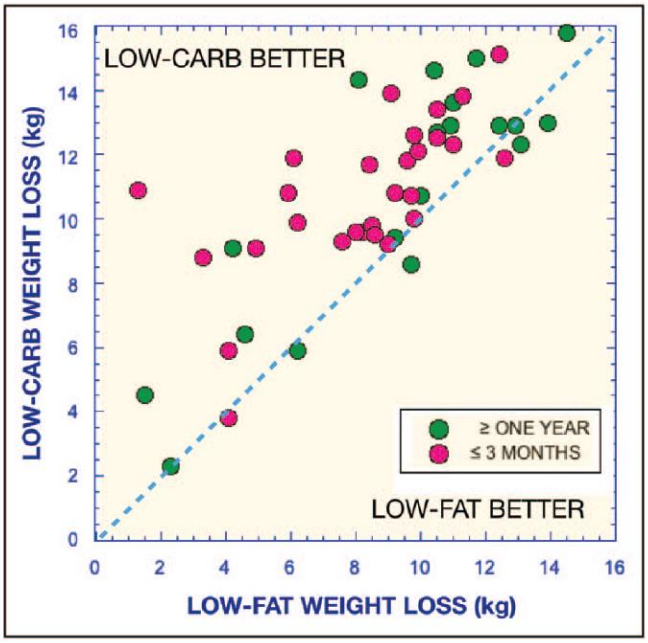

Figure 1 Comparison of KD and low-carbohydrate diets and low-fat diets in randomized trials ([5] reprinted with permission of the author).

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 underscored 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 ore 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 a as 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 + carbo 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**			
	Strong	**Moderate**	**Weak**	**Unknown**
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.

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