The Journal of Nutrition
Issues and Opinions

The Ketogenic Diet: Evidence for Optimism but High-Quality Research Needed

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ABSTRACT

For >50 y, dietary guidelines in the United States have focused on reducing intakes of saturated and total fat. However, rates of obesity and diabetes rose markedly throughout this period, with potentially catastrophic implications for public health and the economy. Recently, ketogenic diets have received substantial attention from the general public and nutrition research community. These very-low-carbohydrate diets, with fat comprising >70% of calories, have been dismissed as fads. However, they have a long history in clinical medicine and human evolution. Ketogenic diets appear to be more effective than low-fat diets for treatment of obesity and diabetes. In addition to the reductions in blood glucose and insulin achievable through carbohydrate restriction, chronic ketosis might confer unique metabolic benefits of relevance to cancer, neurodegenerative conditions, and other diseases associated with insulin resistance. Based on available evidence, a well-formulated ketogenic diet does not appear to have major safety concerns for the general public and can be considered a first-line approach for obesity and diabetes. High-quality clinical trials of ketogenic diets will be needed to assess important questions about their long-term effects and full potential in clinical medicine. *J Nutr* 2019;00:1–6.

Keywords: ketogenic diet, low-carbohydrate diet, low-fat diet, vegan diet, ketones, obesity, diabetes, cardiovascular disease, cancer, Alzheimer disease

A century ago, the ketogenic diet was a standard of care in diabetes, used to prolong the life of children with type 1 diabetes and to control the symptoms of type 2 diabetes in adults (1). Because all forms of diabetes share a basic pathophysiological problem, carbohydrate intolerance, restriction of carbohydrate on a ketogenic diet (typically ≤50 g/d with >70% fat) often produced rapid and remarkable clinical improvement. Discovery of insulin in the 1920s enabled people with diabetes to control hyperglycemia on high-carbohydrate diets. However, the human toll and economic burden from diabetes complications continue to mount, despite increasingly sophisticated insulin analogs and drugs for associated conditions such as dyslipidemia, hypertension, and coagulopathy. Contrary to expectation, adoption of a higher-carbohydrate (lower-fat) diet by the US public in the second half of the 20th century could have contributed to the increasing prevalence of obesity (2), a major risk factor for type 2 diabetes. Despite commonly voiced concerns about the safety of, and lack of supporting evidence for, this putative fad (3), the ketogenic diet has a long track record—not only in clinical medicine but also through human evolution—providing evidence for optimism in the search for more effective dietary prevention and treatment of chronic diseases.

Carbohydrate Restriction Is More Effective than Fat Restriction for Obesity Treatment

For decades, dietary fat was considered uniquely fattening due to its high energy density and palatability, leading to "passive overconsumption" relative to all carbohydrates (4). However, recent research underscores a biological basis for body weight control, by which the metabolic effects of food, more so than calorie content of specific foods or nutrients, determine body weight over the long term. According to the carbohydrate-insulin model of obesity (5, 6) the processed carbohydrates (e.g., most breads, rice, potato products, and added sugar) that replaced dietary fats during the low-fat diet era promote fat storage, increase hunger, and lower energy expenditure, predisposing to obesity and diabetes in susceptible individuals.

Most clinical trials comparing macronutrient-varying diets have employed low-intensity interventions, insufficient to produce significant long-term dietary change. Therefore, it is

The author reported no funding received for this study.
Author disclosures: DSL, has received royalties for books on obesity and nutrition that recommend a carbohydrate-modified, but not ketogenic, diet, and grants from the NIH and philanthropic organizations unaffiliated with the food industry for obesity-related research.
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Manuscript received September 23, 2019. Initial review completed October 23, 2019. Revision accepted November 22, 2019.
First published online 0, 2019; doi: https://doi.org/10.1093/jn/nxz308.

not surprising that meta-analyses of these trials would show little long-term weight loss, and little difference between diet groups. Even so, meta-analyses have found that conventional low-fat diets are inferior to all higher-fat comparisons including ketogenic diets (7–10).

Anecdotal reports for many years have suggested that low-carbohydrate diets suppress hunger to a greater degree than conventional approaches, taking rate of weight loss into account. For example, in a small clinical trial from the 1950s, female college students with high body weight were given calorie-restricted diets varying in carbohydrate-to-fat ratio. Students on the low-fat diet reported a "lack of 'pep' throughout most of the study… [and feeling] discouraged because they were always conscious of being hungry." In contrast, those on the very-low-carbohydrate diet reported "satisfaction" and that "[h]unger between meals was not a problem," even though they had lost more weight (11). In a more recent crossover study, 17 men with obesity consumed ad libitum for 4 wk very-low-carbohydrate (4%) or moderate-carbohydrate (35%) diets controlled for protein. The participants consumed less dietary energy, lost more weight, and reported less hunger on the very-low-carbohydrate diet (12). This effect could relate to the improved circulating metabolic fuel concentration observed in the late postprandial period on a low-glycemic-load diet, and also to advantageous changes in metabolic hormones (e.g., lower ghrelin) (13, 14).

Carbohydrate restriction can also increase energy expenditure, a major goal of obesity research conventionally sought with drugs and exercise (15). In a 20-wk weight-loss-maintenance feeding study with 164 participants, those assigned to a low- (20%) compared with a high- (60%) carbohydrate diet had higher energy expenditure (~200–250 kcal/d), with evidence of effect modification by insulin secretion as predicted by the carbohydrate-insulin model (13, 16). Although a meta-analysis (17) suggested no benefit of low-carbohydrate compared with low-fat diets for energy expenditure, most of the included studies were too short (median duration <1 wk) to exclude well-described transient metabolic adaptations (5, 18). Behavioral trials with more powerful interventions lasting ≥1–2 y, and feeding studies of ≥4 wk, will be needed to test the true efficacy of carbohydrate restriction and clarify mechanisms.

Low-Carbohydrate Diets Show Promise for Diabetes Treatment

The US NIH sponsored several large multicentered studies of low-fat diets, such as the Women's Health Initiative dietary modification trial (prevention of diabetes as a secondary outcome) (19) and Look Ahead [prevention of cardiovascular disease (CVD) in people with diabetes as the primary outcome] (20). In both cases, the low-fat diet showed no benefit, even though the comparison groups were given lower-intensity interventions. The Diabetes Prevention Program intensive lifestyle intervention reduced incidence of type 2 diabetes among high-risk participants (21), but the multicomponent nature of the intervention (including calorie restriction, fat restriction, exercise, and behavior modification) makes attribution of effects to the low-fat diet problematic. Unfortunately, no comparable studies of very-low-carbohydrate diets have been conducted, but smaller trials and observational studies suggest promise.

A 2019 Consensus Report from the American Diabetes Association concluded that low-carbohydrate diets (including those that aim for nutritional ketosis) "are among the most studied eating patterns for type 2 diabetes" and that these "eating patterns, especially very-low-carbohydrate … have been shown to reduce [Hb]A1C [glycated hemoglobin] and the need for antihyperglycemic medications" (22). In a pragmatic trial including 262 adults with type 2 diabetes assigned to a very-low-carbohydrate diet, mean weight loss was 11.9 kg and HbA1c decreased by 1.0%, even with substantial reductions in the use of hypoglycemic medications other than metformin (23). Few clinical trials have examined carbohydrate restriction in type 1 diabetes, possibly due in part to concerns about hypoglycemia and ketoacidosis. In a survey of 316 children and adults following a very-low-carbohydrate diet for type 1 diabetes, exceptional glycemic control (mean HbA1c = 5.7%), low rates of hypoglycemia and ketoacidosis, an overall healthful CVD risk profile, and high satisfaction with diabetes management were documented (24).

Low-Carbohydrate Diets Might Lower CVD Risk despite High Saturated Fat Content

Although LDL cholesterol—an established CVD risk factor—can increase on low-carbohydrate diets (25), in part due to high saturated fat content, lipoprotein size distribution can indicate a relatively lower risk, characterized by larger, more buoyant particles (26). Consistent with this possibility, individuals with isolated elevated LDL cholesterol, compared with those who also have high triglycerides and low HDL cholesterol, were at lower risk for coronary events and benefited less from statins in the Scandinavian Simvastatin Survival Study (27). Indeed, there is precedent for reduced cardiovascular risk in the context of higher LDL cholesterol: treatment with sodium-glucose cotransporter 2 inhibitors (28). The mechanisms elicited by this drug class share similarity on the physiological, if not molecular, level with a ketogenic diet. Both shift substrate utilization from carbohydrates to lipids, cause ketosis, reduce glycemic excursions, lower insulin concentrations, produce weight loss, promote natriuresis, and lower blood pressure—actions that can counterbalance or attenuate any adverse cardiovascular effects of elevated LDL cholesterol.

Carbohydrate restriction benefits multiple components of the metabolic syndrome, a major CVD risk factor. A low-carbohydrate diet improves hyperglycemia, triglycerides, HDL cholesterol, small dense LDL subclass phenotype, oxidized plasma lipids, and hepatic steatosis, whereas a low-fat diet can adversely affect some of these components (26, 29–34).

The relation between dietary fat and mortality in observational research is controversial due to methodological challenges involving confounding, reverse causality, and effect modification (e.g., overall diet quality, physical activity level). In a high-quality, 2-cohort study, high intake of fat as a proportion of total energy was associated with reduced risk of premature death, although the type of dietary fat importantly modified risk: decreased with unsaturated fat and increased with saturated fat (35). However, the relation between saturated fat and mortality observed in a general population might not apply to those consuming a ketogenic diet due to exceptionally high rates of saturated fat oxidation and low rates of de novo lipogenesis (36). Demonstrating this point, serum saturated fat

TABLE 1 Conditions under study with a ketogenic or low-carbohydrate diet[1]

Condition	Proposed mechanisms[2]
Cancer (ancillary treatment)	Warburg effect; reduced concentration of insulin and other growth-stimulating hormones and factors; immune modulation; reduced side effects of chemotherapy, radiation
Brain	
Breast	
Colon	
Endometrial	
Lymphoma	
Pancreaticobiliary	
Prostate	
Cardiovascular	Weight loss; reduced postprandial glycemia, insulinemia; anti-inflammatory effects of ketones
Chronic inflammation	
Dyslipidemia	
Endothelial dysfunction	
Insulin resistance	
Endocrine	
Diabetes, type 1	Reduced postprandial glycemic excursions, lower insulin requirement
Diabetes, type 2	As above; weight loss
Obesity	Reduced anabolic stimulation of adipose; partitioning of metabolic fuels
Gastrointestinal	
Fatty liver, nonalcoholic	Reduced postprandial glycemia, insulinemia; enhanced fat oxidation
Irritable bowel syndrome	Microbiome; carbohydrate fermentation
Neurological	Neuroprotective effects of ketones through reduced inflammation, edema oxidative damage, apoptosis, amyloid deposition; neural energy metabolism; epigenetic effects; microbiome
Alzheimer disease	
Epilepsy	
Mild cognitive impairment	
Multiple sclerosis	
Oxygen toxicity (underwater diving)	
Traumatic brain injury	
Spinal cord injury	
Psychological/psychiatric	Reduced withdrawal symptoms; reduced craving and reward, mediated by nucleus accumbens; reduced neuroinflammation; neuronal metabolism; microbiome
Alcoholism	
Autism spectrum disorder	
Bipolar disorder	
Mood disorders	
Schizophrenia	
Well-being/quality of life	
Miscellaneous	
Exercise tolerance, physical performance	Improved access to metabolic fuels
Gangliosidoses	Increased efficacy, reduced side effects of primary treatment
Infectious endocarditis, diagnosis	Enhanced signal-to-noise ratio with ^{18}F-FDG PET scan
Lymphedema	Endothelial cell function; lymphatic transport
Obstructive sleep apnea	Weight loss; decreased visceral fat

[1] Listed on clinicaltrials.gov as "Not yet recruiting," "Recruiting," or "Active, not recruiting" as of July 31, 2019. ^{18}F-FDG PET, [^{18}F]fluoro-2-deoxyglucose positron emission tomography.
[2] List not exhaustive.

did not increase through a wide range of saturated fat intakes for 3-wk intervals in a study of 16 adults with metabolic syndrome (37).

Chronic Ketosis Might Provide Unique Metabolic Benefits

Ketosis, an evolutionarily ancient metabolic pathway, might confer additional benefits, beyond those of prevailing high-fat diets, through modulation of the inflammasome, oxidative damage, histone acetylation, mitophagy, cellular redox state, and other mechanisms (38, 39). Ketones have been termed a "superfuel" for the brain (39), upon which infants can be especially dependent (40). Based on these pleiotropic actions, a ketogenic diet has been considered for a wide range of health conditions. The website clinicaltrials.com currently lists 85 planned or active trials of a ketogenic or low-carbohydrate diet for diseases of numerous organ systems, including cardiovascular, endocrine, gastrointestinal, neurological, and psychiatric (see **Table 1**). Additional trials have been completed but not yet published.

The metabolic effects of a ketogenic diet can have special relevance to oncology. Many cancers contain mitochondrial defects, making them reliant on glycolytic fermentation, an inefficient energy generation pathway compared with oxidative phosphorylation (41, 42). A ketogenic diet targeting this Warburg effect might starve cancer cells without toxicity to normal cells, by decreasing fasting and postprandial blood

glucose concentrations. Other mechanisms recruited by this diet include reduced secretion of insulin, a hormonal driver of some tumors, and ketones themselves, through metabolic and signaling actions. Because blood glucose concentrations remain in the low-normal range, and other fermentable fuels are available (e.g., glutamine), a ketogenic diet would not be expected to cure cancer as a stand-alone treatment. However, this diet might act synergistically with other treatments, such as phosphoinositide 3-kinase inhibitors (43), and aid prevention, possibilities that warrant investigation.

In view of the potent effects of ketones in the brain, a ketogenic diet has also generated considerable interest for neurodegenerative and neuropsychiatric disorders. Preliminary reports suggest that patients with Alzheimer disease, characterized by central insulin resistance, show clinical improvement with a ketogenic formula or exogenous ketones (44, 45). After a brief transitional period (46), a ketogenic diet can also improve general mood, although findings vary among studies (47).

Ketogenic Diets Have a Long Track Record of Safety

Concern has been expressed about the safety of ketogenic diets (3) based on case reports of children with epilepsy describing gastrointestinal problems, nephrolithiasis, cardiac abnormalities, and poor growth, but these reports need to be interpreted cautiously for several reasons. First, the ketogenic diet used in this clinical context is typically more extreme (with ≥85% energy as fat) than would be recommended for virtually any other purpose. Second, patients with epilepsy can have other health problems or medication use predisposing to complications, for which the general public would not be at risk. Third, case reports inevitably involve major selection bias; the absence of widespread adverse events in public health surveillance, despite the popularity of the ketogenic diet today (e.g., 5 of the top 10 best-selling diet books on Amazon.com), provides considerable reassurance.

Furthermore, without adequate attention to food quality, any macronutrient-focused eating pattern can have adverse effects. A low-fat diet containing high amounts of sugar and other processed carbohydrates raises risk of fatty liver and metabolic syndrome; a vegan diet without adequate attention to key micronutrients can cause growth retardation in children. Public health guidelines do not discourage low-fat and plant-based diets, but instead focus on measures to encourage healthful versions of these eating patterns to minimize risk and maximize benefits. With the substantial evidence of benefit as described above, diets that restrict carbohydrate warrant the same consideration.

There Is No Human Requirement for Dietary Fiber or Carbohydrate

Some have argued that the greatest risk "of the ketogenic diet may be the one most overlooked: the opportunity cost of not eating high-fiber, unrefined carbohydrates" (3), pointing to a meta-analysis of observational studies finding protective associations of whole-grain intake with CVD, cancer, and total mortality (48). However, such studies can only address the *relative* healthfulness of a specific food compared with foods that would have otherwise been consumed. Although strong evidence indicates benefits of consuming whole grains instead of refined grains (the typical trade-off in populations with grain-based diets), a more relevant question to this debate is how whole grains compare with low-carbohydrate foods allowed on a ketogenic diet. Bearing on this issue, a recent meta-analysis of clinical trials found that diets high in whole grains, compared with control diets, had no overall effect on measures of body fatness; among the trials with "unhealthy individuals" (having diabetes, metabolic syndrome, or overweight/obesity), whole-grain consumption increased BMI (49).

Admittedly, high-carbohydrate diets have been consumed by some populations with low rates of obesity-related chronic disease (e.g., "blue zones" in Asia), although these have typically had high levels of occupational physical activity (e.g., subsistence farming) and limited total calorie availability. However, the health benefits of grain consumption among populations with highly prevalent obesity and insulin resistance have not been established. In fact, diets with virtually no carbohydrate (and therefore, no fiber) throughout most of the year have been consumed by humans—for example, Native Americans of the Great Plains, Laplanders, the Inuit, and other traditional hunter-gatherer societies in temperate and arctic climates—much longer than a low-fat, high-carbohydrate diet as adopted by grain-based agrarian societies.

Conclusions

Both low-fat and low-carbohydrate diets can produce adverse effects in susceptible individuals (the former especially so among those with insulin resistance, comprising the majority in the United States). However, beyond fatigue and other transitional symptoms upon initial adoption, a well-formulated ketogenic diet does not appear to have major safety concerns for the general population. Based on available evidence, a ketogenic diet can be considered a first-line approach for the treatment of obesity and type 2 diabetes. A ketogenic diet also holds promise for a range of other chronic, sometimes intractable, conditions associated with metabolic dysfunction, such as type 1 diabetes, steatohepatitis, neurodegenerative disease, and cancer.

However, the lack of high-quality clinical trials hinders scientific understanding and public health translation. Key unresolved questions warranting research priority include: How does LDL cholesterol elevation with carbohydrate restriction affect cardiovascular risk versus triglyceride elevation with fat restriction? Does the reduction of HbA1c in diabetes on a ketogenic diet translate into reductions in micro- and macrovascular disease? Are there uniquely susceptible populations (e.g., LDL cholesterol "hyperresponders") or conditions (liver or kidney disease, pregnancy) for which a ketogenic diet would be relatively contraindicated? What is the efficacy of a ketogenic diet for weight loss compared with other approaches in trials incorporating powerful methods to facilitate long-term behavior change? Does chronic ketosis provide unique metabolic benefits, beyond those that can be obtained with less restrictive regimens, such as a low-glycemic index, moderate-carbohydrate diet?

Finally, it is worth noting that the ketogenic diet has elicited controversy, in part because conventional nutritional teaching has for years emphasized the harms of high total and saturated fat intakes. Polarization might have also arisen from the misconception that ketogenic diets require high intakes of animal products—engendering concern among those who advocate plant-based diets for health, ethical, or environmental reasons.

In fact, a ketogenic diet can be vegetarian (containing eggs and dairy products) or vegan, with plant-based fats (e.g., avocado, nuts, seeds, coconut, flax, olive oil), proteins (e.g., tofu, tempeh, seitan, lupini beans, pea protein), nonstarchy vegetables, and limited amounts of low-sugar fruits, as exemplified by the Eco-Atkins diet (50). This flexibility allows individualization of dietary choice on a ketogenic diet for obesity and diabetes.

Acknowledgments

The sole author was responsible for all aspects of this manuscript.

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