A Review of Low-carbohydrate Ketogenic Diets

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In response to the emerging epidemic of obesity in the United States, a renewal of interest in alternative diets has occurred, especially in diets that limit carbohydrate intake. Recent research has demonstrated that low-carbohydrate ketogenic diets can lead to weight loss and favorable changes in serum triglycerides and high-density lipoprotein cholesterol. This review summarizes the physiology and recent clinical studies regarding this type of diet.

Introduction

Obesity has been implicated as the second leading preventable cause of death in the United States, and studies support that intentional weight loss leads to a reduction in overall mortality [1,2]. In response to the emerging epidemic of obesity, there has been a renewal of interest in alternative diets. Given the current unfavorable trends with conventional approaches, a reconsideration of previously unevaluated alternative diet therapies is not unreasonable.

Based on lay-press book sales, the most popular alternative weight-loss diet is the very low-carbohydrate diet. Diets that limit carbohydrate intake have been called "low-carbohydrate," "very-low-carbohydrate," "high-protein," "high-fat," and "ketogenic." Presently, there is no consensus on a precise quantitative definition for a low-carbohydrate diet. A low-carbohydrate diet may or may not be a "high-protein diet" depending upon the food choice and caloric intake. For the purpose of this review, we define a "low-carbohydrate ketogenic diet" (LCKD) as daily consumption of fewer than 50 g of carbohydrate, regardless of fat, protein, or caloric intake.

Low-carbohydrate Ketogenic Diet Physiology

From glucocentric to adipocentric

A typical human cell may contain nearly one billion molecules of adenosine triphosphate (ATP) in solution at any given instant. Remarkably, this amount of ATP can be utilized and resynthesized every 3 minutes [3]. Given such a great demand for ATP, the existence of complementary pathways for its synthesis is not surprising, as such pathways confer survival advantages during extreme perturbations in macronutrient consumption. Under conditions of extreme carbohydrate limitation, cellular metabolism can still be supported if essential nutrients are provided, as demonstrated by the cultural precedent of the traditional Inuit (Eskimo) people. Cells that can employ fatty acids will derive energy from fatty acids, glucose, and ketones, but will shift to preferentially use more fatty acids. Cells that cannot use fatty acids must be supported by glucose and ketones, and will shift to preferentially use more ketones (*eg*, nervous tissue). Cells with few or no mitochondria are entirely glucose dependent and must still be sustained by glucose (cells with no mitochondria include erythrocytes, cornea, lens, and retina; cells with few mitochondria include renal medulla, testis, and leukocytes). So, under conditions of extreme carbohydrate limitation, the same energy sources are used, but a greater amount of energy must be derived from fatty acids and ketones ("adipocentric") and less energy from glucose ("glucocentric") (Table 1).

Similar to prolonged fasting

Although molecular-based research directly examining an LCKD is limited, the current models of whole-body metabolism can be used as a framework for understanding LCKD physiology. The classic model of whole-body metabolism is the human starve-feed cycle, which is composed of four global nutritional states: 1) well fed, 2) early fasting, 3) prolonged fasting (or starvation), 4) early re-fed. Despite biochemical differences associated with each state, all four states are guided by two general principles. Firstly, the human body must contain adequate levels of energy to sustain obligate and facultative glucose metabolizing tissues. This is particularly important for the central nervous system (CNS) because protein-bound fatty acids are unable to cross the blood-brain barrier, and the CNS requires between 20% to 50% of resting metabolic energy [4]. Secondly, the human body must retain endogenous protein in order to sustain healthy structural and functional physiologic capacity. Of these four global nutritional states, the most relevant model for LCKD whole-body metabolism is the metabolism of prolonged fasting.

Table 1. Major fuel sources on a low-carbohydrate ketogenic diet

I. Dietary fat: triglyceride →fatty acid + glycerol
A. Fatty acids
i. Ketone bodies ("ketogenesis")
B. Glucose ("gluconeogenesis")
II. Dietary protein
A. Glucose ("gluconeogenesis")

During fasting in humans, blood glucose levels are sustained by the breakdown of glycogen in liver and muscle and de novo production of endogenous glucose ("gluconeogenesis"), primarily from muscle amino acids. [5]. Concurrent hepatic generation of ketone bodies supplements glycogenolysis and gluconeogenesis to produce energy-yielding substrates for glucose-dependent tissue. Therefore, generation of ketone bodies in fasting humans is critical to providing an alternative fuel to glucose [6,7] while also avoiding muscle breakdown [7,8].

Fatty acids and ketogenesis from fat

The main fuel produced by an LCKD would logically be fatty acids derived from exogenous dietary fat or endogenous adipose tissue. The average respiratory quotient associated with an LCKD is approximately 0.70, indicating the use of fatty acids primarily [9]. In addition, serum free fatty acids are higher on an LCKD compared with a conventional diet [10,11••].

Although most energy is derived from fatty acids, ketone bodies increase in importance as a substitute for glucose. The term ketone bodies (KB) refers to three metabolites: acetoacetate, β-hydroxybutyrate, and acetone. Whereas acetone is primarily an excretory product, the other KB are dimers of acetyl coenzyme A (CoA) and, therefore, serve as transportable forms of energy. During prolonged fasting, fatty acids are generated from the breakdown of stored triglyceride in adipocytes (lipolysis) [12]. On an LCKD, the fatty acids are derived from dietary fat, or adipose tissue if the diet does not meet the daily caloric requirement (Fig. 1). Free fatty acids are delivered to the liver for conversion to KB. KB then exit the liver to provide energy to all cells with mitochondria. Within a cell, KB are converted to acetyl CoA for generation of ATP via the tricarboxylic acid cycle and oxidative phosphorylation.

Although usually viewed as a response to fasting, the synthesis of KB can also be stimulated by a marked reduction of carbohydrate [13]. Reducing carbohydrate and protein intake leads to a reduced serum insulin level, which, in turn, increases the serum glucagon level. The insulin/glucagon (I/G) ratio is a key determinant of lipolysis, glycogenolysis, and gluconeogenesis [14,15]. A high I/G ratio induces lipid and glycogen production via insulin-mediated influx of glucose, whereas a low I/G ratio induces glucagon-mediated lipolysis.

Ketone formation and a shift to using more fatty acids during an LCKD reduce the body's overall requirement for endogenous glucose. Even during high-energy demand from submaximal exercise, an LCKD has "glucoprotective" effects [10]. In essence, ketosis arising from an LCKD is capable of accommodating a wide spectrum of metabolic demands to sustain function while sparing the use of protein from lean muscle tissue. KB also mediate glucose-sparing effects by serving as the preferred energy substrate for highly active tissues such as heart and muscle [16]. Consequently, more serum glucose is available to the brain as well as other obligate glucose-dependent tissues.

Gluconeogenesis from protein

Gluconeogenesis refers to the production of glucose from amino acids ("glucogenic amino acids"), glycerol, and lactate when glucose is in demand but dietary sources are limited [5,17]. For example, during prolonged fasting or during an LCKD there is a reduction in glucose supply, which initiates compensatory gluconeogenic mechanisms to sustain glucose-dependent tissue [18]. However, unlike prolonged fasting, during which endogenous glucogenic amino acids (muscle) are used for glucose production, the source of glucogenic amino acids on an LCKD is dietary protein (Fig. 1). As minimal protein supplementation (1 to 1.5 g of protein/kg/d) is necessary to attain nitrogen balance during prolonged fasting, protein intake at this level associated with the LCKD may sustain positive nitrogen balance and preserve muscle mass [19•]. Casein and meat protein can be converted to glucose at about 50% efficiency, so approximately 100 g of protein can produce 50 g of glucose via gluconeogenesis [20].

Another substrate for gluconeogenesis is glycerol from dietary fat (Fig. 1). During prolonged fasting, glycerol released from lipolysis of triglycerides in adipose tissue may account for nearly 20% of gluconeogenesis [21,22]. As nearly 10% of triglyceride by weight is glycerol, and two molecules of glycerol combine to form one molecule of glucose, 80 g of triglycerides may be converted into 8 g of glucose (5% efficiency). Lactate is believed to be a negligible glucosynthetic precursor [23] and likely does not play a major role in such compensatory mechanisms in prolonged fasting or LCKD, but may play a role during high-intensity exercise when lactate levels increase several-fold.

The need for gluconeogenic substrate may explain how lipolysis can continue when caloric intake exceeds caloric expenditure. If only fat is consumed, for example, 1000 g of fat per day would be needed to provide enough gluconeogenic substrate (glycerol) for conversion to 50 g of glucose—representing a caloric intake of 9000 kcal/d! (This is the estimated minimal amount of glucose needed to prevent lipolysis and ketogenesis.) One controlled study found that a eucaloric intravenous lipid infusion did not reduce ketogenesis when compared with the ketogenesis associated with starvation [13]. Under conditions when the I/G ratio is low and glucose availability from dietary carbohydrate and protein is also very low, it is theoretically possible that lipolysis might occur to supply glycerol as

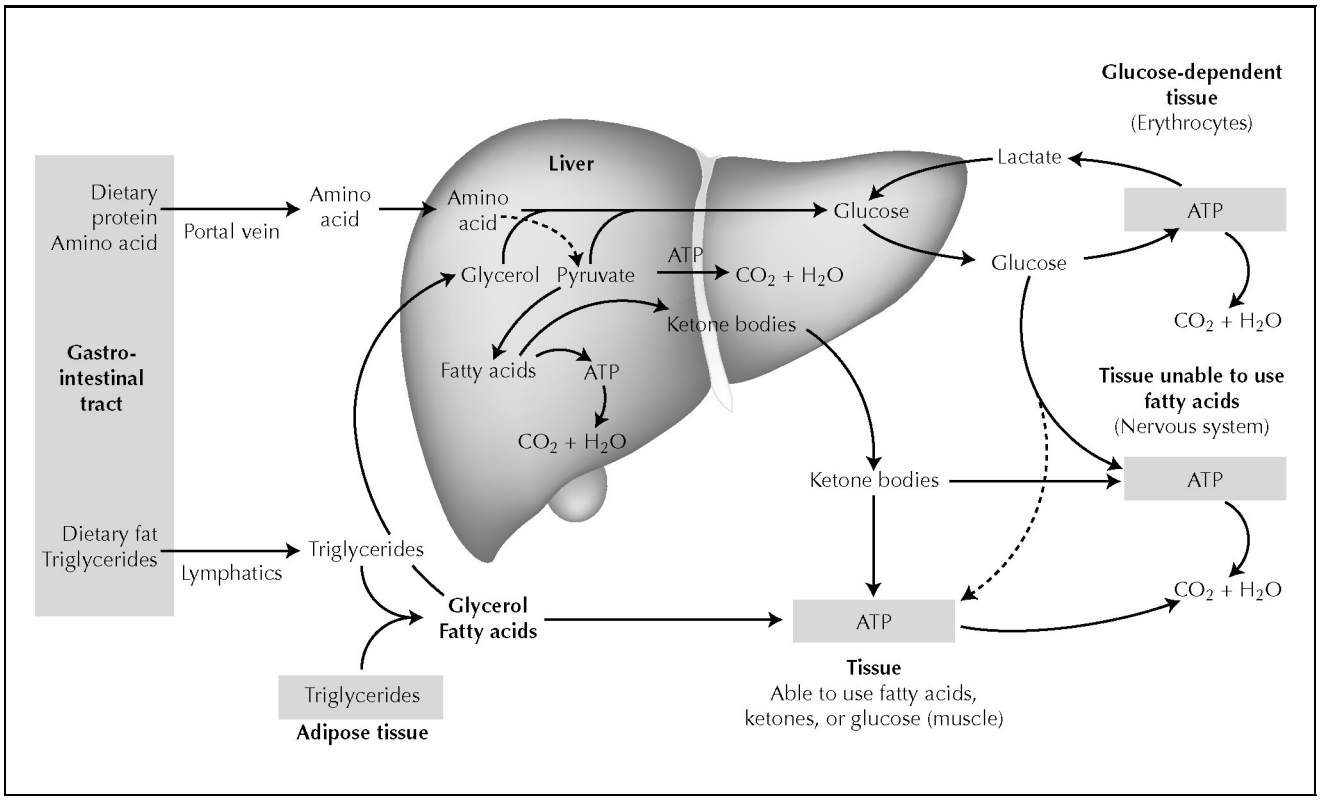

Figure 1. Projected fuel utilization for a low-carbohydrate ketogenic diet. (ATP—adenosine triphosphate.)

gluconeogenic substrate, even when caloric intake far exceeds caloric expenditure.

Low-carbohydrate Ketogenic Diet and Exercise

Many animal and human studies have consistently demonstrated that low-carbohydrate/high-fat diets consumed for more than 7 days decrease muscle glycogen content and carbohydrate oxidation, which is compensated for by markedly increased rates of fat oxidation [24–27], even in well-trained endurance athletes who already demonstrate increased fat oxidation. The source of the enhanced fat oxidation appears to be circulating fatty acids, ketones, and triglyceride-derived very low-density lipoproteins [26,28,29], the latter probably resulting from enhanced skeletal muscle lipoprotein lipase activity [30]. In the face of reduced muscle glycogen, the increase in the capacity of skeletal muscle to oxidize fat after a low-carbohydrate diet has failed to alter or enhance exercise capacity. However, if the enhanced fat utilization is combined with increased carbohydrate availability, this might provide a more consistent benefit for endurance performance, especially for ultra-endurance type activities that deplete glycogen and rely heavily on alternative lipid fuel sources. Importantly, the enhanced capacity for fat oxidation and muscle glycogen sparing after a high-fat diet persist even when carbohydrate is provided before exercise (*eg*, one study carbohydrate loaded for 7 days) or when glucose is ingested during exercise [31]. Thus, chronic low-carbohydrate/high-fat diets induce powerful metabolic adaptations to enhance fat oxidation, and when combined with short periods of carbohydrate intake, have been shown to produce superior results compared with other dietary strategies to enhance exercise performance [31–35], especially for ultra-endurance exercise [27,33]. The specific metabolic adaptations that occur on a high-fat diet are numerous, and the ones that underlie the favorable changes in exercise capacity remain unclear. High-fat diets are associated with robust metabolic and enzymatic adaptations. These enzymatic adaptations are to some extent muscle fiber-type specific and depend on the increase in dietary fat. The time course of metabolic adaptations also remains unclear, but at least several weeks are necessary to completely transition to optimal fat utilization.

Low-carbohydrate Ketogenic Diet and Obesity Studies

Several recent reviews of short-term out-patient clinical and in-patient laboratory studies concluded that there were insufficient data to dismiss or recommend the LCKD for weight loss [36–38]. Clinical experience and a few studies regarding LCKDs suggest that each person has a threshold level of dietary carbohydrate intake (from 65 to 180 g/d) where ketosis and lipolysis are initiated [13]. If a person is consuming below this threshold, then triglyceride will be broken down

Table 2. Summary of randomized, controlled trials of low-carbohydrate ketogenic diets for obesity: study design and baseline characteristics

Study	Patients, *n*	Duration, *mo*	Visits	Age, *y*	BMI	Weight, *kg*	Gender
Sondike *et al.* [45••]	30	3	Every 2 wk	15	36	96	NA
Brehm *et al.* [46••]	42	6	Every 2 wk for 6 wk, then at 6 mo	43	34	92	100% F
Samaha *et al.* [47••]	132	6	Weekly for 4 wk, then monthly	53	43	130	80% M
Foster *et al.* [48••]	63	12	Every 2 wk for 2 wk, then monthly for 4 wk, then wk 26, 34, 42, and 52	44	34	98	73% F
Yancy *et al.* [49••]	120	6	Every 2 wk for 6 wk, then monthly	46	34	96	77% F

BMI—body mass index; F—female; M—male.

from adipose tissue to generate ketones to supply the CNS. Most of the small feasibility studies showed that LCKD compliance in a clinical outpatient setting showed promise for weight loss, so more formal randomized, controlled trials (RCTs) were justified [39–44].

Since the publication of these reviews, there have been five RCTs comparing an LCKD to a low-fat reduced calorie diet (Table 2). The first RCT examined the weight loss and cardiovascular risk factor effects of an LCKD in adolescents [45••]. Thirty-nine obese (body mass index [BMI] >95th percentile for age) adolescents (mean age, 14.7 years) were randomized to either an ad libitum LCKD diet (<20 g/d of carbohydrate for 2 weeks, then <40 g/d of fat) or an ad libitum low-fat (LFD) diet (<40 g/d of fat) for 12 weeks total. The LCKD subjects lost more weight (10 kg) than the LFD subjects (4 kg; $P<0.04$ for comparison). In regard to serum lipid measurements, between-group comparisons (LCKD vs LFD) of total cholesterol and high-density lipoprotein (HDL) cholesterol were not significant, whereas comparison of triglyceride changes was of borderline significance (decrease of 48 mg/dL vs decrease of 6 mg/dL; $P=0.07$), and comparison of LDL cholesterol was significant (increase of 4% mg/dL vs decrease of 25% mg/dL; $P=0.006$). No serious adverse effects related to the intervention were reported.

In another study, 53 healthy, obese women were allocated to either an ad libitum LCKD or a calorie-restricted LFD (55% carbohydrate, 15% protein, 30% fat) [46••]. Twenty-two of 26 (85%) subjects from the LCKD and 20 of 27 (74%) subjects from the LFD completed the 6-month study, with both groups reducing their energy intake from baseline by approximately 450 kcal. LCKD subjects lost 8.5 kg over 6 months compared with 4.2 kg in the LFD group ($P<0.001$ for comparison). In both groups, 50% to 60% of the weight lost was fat mass as measured by dual X-ray absorptiometry. There were no significant differences between groups in the effects on serum lipids, glucose, insulin, and leptin except triglycerides, which decreased significantly more in the LCKD group.

Another study was performed at the Philadelphia Veterans Affairs Medical Center and randomized 132 severely obese (mean BMI, 43 kg/m^2) medical out-patients to either an ad libitum LCKD or a calorie-restricted LFD [47••]. Subjects received weekly group counseling sessions for 4 weeks, then monthly sessions, with 67% of LCKD subjects and 53% of LFD subjects completing the study. At 6 months, there was greater weight loss (5.8 kg vs 1.9 kg; $P=0.002$) and triglyceride reduction (20% vs 4%; $P=0.001$) in the LCKD group compared with the LFD group. In addition, the diabetic subjects in the LCKD group demonstrated improved serum glucose (decrease of 25 mg/dL vs a decrease of 5 mg/dL; $P=0.01$) compared with their LFD group counterparts, whereas the nondiabetic subjects in the LCKD had improved insulin sensitivity by the quantitative insulin-sensitivity check index (6% vs -3%; $P=0.01$) compared with their LFD group counterparts. Seven LCKD subjects had a reduction of diabetic medication dosage compared with only one from the LFD group.

In a three-center study, 63 obese, healthy subjects were randomized to either the ad libitum LCKD or a reduced-energy LFD to examine the effectiveness of the LCKD from a consumer's point of view [48••]. Therefore, each subject received a popular diet book pertaining to his/her assigned diet and met with a dietician at baseline and for three brief visits thereafter over the 1-year trial. Of the original 63 subjects, 37 completed the 12 months. The LCKD subjects lost more weight than the LFD subjects (7.0% reduction vs 3.2% reduction; $P=0.02$) at 6 months, but the difference between groups was no longer statistically significant (-4.4% vs. -2.5%; $P=0.26$) at 12 months. The lower weight loss compared with other studies is likely a result of the low intensity of the intervention. In regard to serum fasting lipid profiles, the LCKD group experienced greater improvements in HDL cholesterol (increase of 11.0% vs decrease of 1.6%; $P=0.04$) and triglycerides (decrease of 17.0% vs increase of 0.7%; $P=0.04$) compared with the LFD group. Serum glucose and insulin measurements were not different between groups.

In the fifth study, the ad libitum LCKD combined with nutritional supplements was compared with a low-fat, low-cholesterol, reduced-calorie diet in healthy, hyperlipidemic individuals [49••]. Eligible subjects were overweight, had total cholesterol, LDL, or triglycerides above recommended levels, and had no chronic medical conditions. LCKD participants were instructed to restrict carbohydrate intake to less than 20 g initially and methodically add carbohydrates back into their diet as goal body weight was approached. Similar to the previously reviewed studies, energy intake was not restricted in the LCKD group. A higher percentage of LCKD than reduced-calorie subjects (75% vs 53%; P=0.03) completed the study. Weight loss was greater in the LCKD subjects who completed the study compared with their LFD counterparts (14% reduction vs 9% reduction; P<0.001). In addition, the LCKD group had beneficial serum lipid effects: triglycerides decreased by 42% and HDL cholesterol increased by 13%, whereas total cholesterol and LDL cholesterol did not change significantly. The improvements in triglycerides and HDL cholesterol were significantly greater than changes that occurred in the reduced-calorie group.

An unexpected finding of the LCKD studies for obesity was the favorable effect on fasting serum lipids. The LCKD was predicted to lead to a significant increase in blood cholesterol [50]; however, there was a consistent reduction in fasting serum triglycerides and an increase in HDL cholesterol, with little change in LDL cholesterol or total cholesterol.

Other metabolic effects

As predicted by the physiologic model, there was an increase in ketones and free fatty acids on an LCKD. [10,11••]. Serum insulin and glucose levels either improved or remained the same. Insulin sensitivity was measured in two of the RCTs. One study showed improvements in insulin sensitivity on an LCKD at 3 and 6 months (5.9% and 8.7%), but the 5.4% improvement at 12 months was no longer statistically significantly different from baseline [48••]. In the other study, subjects on the LCKD had a greater increase in insulin sensitivity than those on the low-fat diet (6% vs 3%) [47••]. A possible mechanism for this improvement in insulin resistance may be that a low-carbohydrate, high-fat diet leads to a reduction in cellular glucose uptake of 50% and an enhancement of fat oxidation [9,10,51,52].

Very little information is available regarding the LCKD physiology after several months, but ketonuria decreases almost to baseline after 6 months [46••]. One of the remaining questions about the LCKD is what will happen to the serum lipids when the dieter has reached a maintenance weight? This question was partially addressed in a study of the LCKD on 12 normal-weight, normolipidemic, healthy men compared with eight men who maintained their usual diet [53]. Subjects following the LCKD experienced significant increases in mean fasting serum β-hydroxybutyrate (250%) and total cholesterol (4.7%), and decreases in triglycerides (33%), very low-density lipoprotein (29%), insulin (34%), and postprandial lipemia after a fat-rich meal (peak, 24%; area under the curve, 29%). LDL cholesterol did not change significantly at 6 weeks (increase of 4.2%), but was increased at 3 weeks, and HDL cholesterol tended to increase (12%). Weight loss was noted to be solely from fat mass (3.4 kg), whereas fat-free mass increased (1.1 kg) [19•].

In another crossover study examining the effects of an LCKD in normal-weight, normolipidemic women, subjects consumed both a low-fat and an LCKD diet for 4 weeks [55]. Compared with the low-fat diet, the LCKD resulted in significant increases in total cholesterol (16%), LDL cholesterol (15%), and HDL cholesterol (33%), and significant decreases in serum triglycerides (30%), total cholesterol to HDL ratio (13%), and the area under the 8-hour postprandial triglyceride curve (31%). There were no significant changes in LDL size or markers of inflammation (C-reactive protein, interleukin-6, tumor necrosis factor α) after the LCKD. Thus, in normal-weight, normolipidemic women, a short-term LCKD modestly increases LDL cholesterol, yet there are favorable effects on cardiovascular disease risk status by virtue of a relatively larger increase in HDL cholesterol and a decrease in fasting and postprandial triglycerides.

In the clinical trials for obesity, one death occurred in an LCKD group, but the investigators judged that it was probably not related to the diet [47••]. Minor adverse effects observed included constipation, headache, and halitosis.

Related Diets

The traditional Inuit (Eskimo) diet meets the definition of an LCKD, and is very similar in regard to percentages of macronutrient intake to the LCKD obesity studies [55]. The traditional diet was comprised of seal, whale, salmon, and a very limited amount of berries. On this diet, the average fasting lipid profiles showed high total cholesterol, low triglycerides, and very high free fatty acids [56,57]. It is interesting to note that the Inuit were of research interest to epidemiologists because of their low rates of ischemic heart disease and diabetes mellitus [58,59]. Although their good health has been attributed to the high levels of omega-3 fatty acids in their blood and diet, it is possible that a component of their good health was due to their low carbohydrate consumption.

The ketogenic diet used as a treatment for refractory pediatric epilepsy meets the definition of an LCKD, but is higher in fat content than the diet consumed in the LCKD obesity studies [60]. The ketogenic diet has been associated with adverse effects including calcium oxalate and urate kidney stones, acidosis, persistent vomiting, amenorrhea, hypercholesterolemia, and water-soluble vitamin deficiencies [61–63].

Potential Adverse Effects

Adverse effects that may occur, but have not yet been observed in monitored clinical trials, include kidney stones,

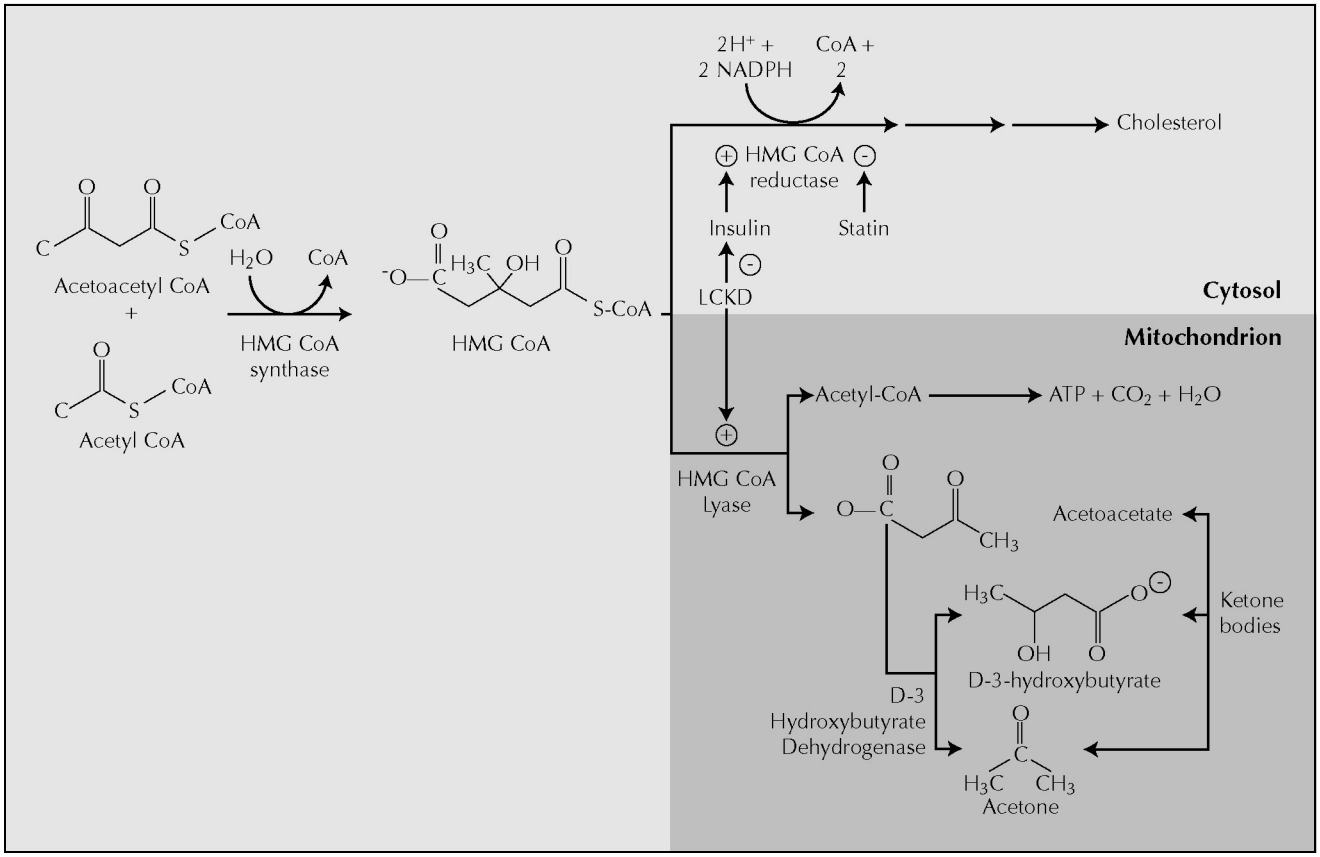

Figure 2. Potential biochemical mechanism of cholesterol reduction of a low-carbohydrate ketogenic diet (LCKD). (ATP—adenosine triphosphate; HMG CoA—3-hydroxy-3-methylglutaryl coenzyme A.)

electrolyte deficiencies (hypokalemia and hypomagnesemia) if a large water loss occurs, elevated fatty acids, and gout (if too much protein is consumed) [10,64,65]. One case report describes an individual who ate cheese, meat, and eggs (no vegetables) and then developed thiamine-deficient optic neuropathy [66]. Another dieter may have developed a relapse of acute variegate porphyria [67]. One case report described the death of an unmonitored adolescent dieter from a probable hypokalemia-associated arrhythmia [65].

The use of this diet, or any strong weight-loss diet, in patients taking medications for diabetes mellitus or hypertension should be done with caution, as the patients will probably require medication reduction to avoid hypoglycemia and hypotension. Until further research is conducted, patients with medical conditions should not use this diet without supervision by medical personnel experienced with the use of weight-loss diets.

Therapeutic Potential

Because of the importance of triglycerides and HDL cholesterol to cardiovascular disease, the LCKD should be examined further for the prevention or treatment of cardiovascular disease [68]. The reduction in triglycerides occurs before significant weight loss [40]. As insulin has been shown to be a promoter of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity, a possible mechanism for the lowering of cholesterol on an LCKD is a shunting of metabolic substrate from cholesterol synthesis to ketone synthesis because of the lower insulin levels associated with the diet (Fig. 2) [69]. Current scientific models permit the possibility that the LCKD would have an effect similar to an HMG CoA reductase inhibitor in hyperinsulinemic individuals.

Based on the metabolic changes of an LCKD, which include a reduction in insulin resistance, there is potential for therapeutic use of this diet for many conditions, including type 2 diabetes, atherosclerosis, and cancer. Anecdotal reports of the use of an LCKD involve conditions potentially improved by enhanced ketone utilization or decreased glucose utilization [8,9,70–73]. The elimination of sugar and carbohydrate on an LCKD may also ameliorate carbohydrate-related problems such as dental caries, periodontal disease, and gluten-related disorders.

Conclusions

In controlled trials, the LCKD has been demonstrated to lead to weight loss and improvements in fasting triglycerides, HDL cholesterol, and cholesterol/HDL ratio over a 6-month period. Clinical trials assessing the long-term safety and effectiveness of the LCKD are needed. The LCKD needs to be evaluated not only for obesity, but also for conditions

that have a theoretical basis for improvement by a reduction in dietary carbohydrate and a shift from a glucocentric to adipocentric metabolism.

Although the basic physiology of an LCKD resembles the state of prolonged fasting, there are key differences such that basic studies regarding LCKD physiology are urgently needed. Fundamental questions regarding fuel utilization and the regulation of gluconeogenesis and ketogenesis in the presence of protein and fat intake need to be addressed. The cultural example of the Inuit demonstrates the remarkable adaptability of the human organism to withstand extremes of macronutrient intake, necessitating the questioning of whether dietary carbohydrate is required for human function [74]. Because these findings from clinical trials have been counterintuitive, clinical research strongly suggests that studying the LCKD may lead to unexpected advances in molecular cell biology and clinical therapeutics.

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