Low-carbohydrate nutrition and metabolism[1–3]

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ABSTRACT

The persistence of an epidemic of obesity and type 2 diabetes suggests that new nutritional strategies are needed if the epidemic is to be overcome. A promising nutritional approach suggested by this thematic review is carbohydrate restriction. Recent studies show that, under conditions of carbohydrate restriction, fuel sources shift from glucose and fatty acids to fatty acids and ketones, and that ad libitum–fed carbohydrate-restricted diets lead to appetite reduction, weight loss, and improvement in surrogate markers of cardiovascular disease. *Am J Clin Nutr* 2007;86:276–84.

KEY WORDS Nutrition, metabolism, macronutrients, glucose, insulin

INTRODUCTION

The persistence of an epidemic of obesity and type 2 diabetes suggests that new nutritional strategies are needed if the epidemic is to be overcome. A historical perspective and recent research point to some form of carbohydrate restriction as a likely candidate for a new nutritional approach, and we present a thematic review regarding carbohydrate restriction.

The examination of diets before modernization can remind us of the remarkable ability of humans to adapt to their environment and can provide a context within which to view current diets. In contrast to current Western diets, the traditional diets of many preagricultural peoples were relatively low in carbohydrate (1, 2). In North America, for example, the traditional diet of many First Nations peoples of Canada before European migration comprised fish, meat, wild plants, and berries. The change in lifestyle of several North American aboriginal populations occurred as recently as the late 1800s, and the numerous ensuing health problems were extensively documented (3–5). Whereas many aspects of lifestyle were altered with modernization, these researchers suspected that the health problems came from the change in nutrition—specifically, the introduction of sugar and flour.

In a similar manner, before the discovery of insulin, the removal of high-glycemic carbohydrates such as sugar and flour from the diets of diabetics was found to be a successful method of controlling glycosuria. An analysis of the pattern of food consumption during the more recent obesity and diabetes epidemic found that the increase in calories was almost entirely due to an increase in carbohydrate (6). Given this context, it is reasonable to postulate that diets low in carbohydrate may be as healthy as, or even healthier than, the higher-carbohydrate diets introduced into modern society only recently.

This thematic review summarizes studies involving low-carbohydrate diets (LCDs) published over the 4 y since the last comprehensive reviews of the topic (7, 8). Articles were identified by us through attendance at scientific meetings, reading of publications, reference searching, manuscript reviews, and weekly Medline searches from January 2002 to December 2006 with the use of the terms "diet," "carbohydrate," and "fat."/SEC

THEMATIC REVIEW

Definition of low-carbohydrate diet

Much of the controversy in the study of LCDs stems from a lack of a clear definition. The rationale of carbohydrate restriction is that, in response to lower glucose availability, changes in insulin and glucagon concentrations will direct the body away from fat storage and toward fat oxidation. There is a suggestion of a threshold effect, which has led to the clinical recommendation of very low concentrations of carbohydrate (<20–50 g/d) in the early stages of popular diets. This typically leads to the presence of measurable ketones in the urine and has been referred to as a very-low-carbohydrate ketogenic diet (VLCKD) or a low-carbohydrate ketogenic diet (LCKD). Potent metabolic effects are seen with such diets but, beyond the threshold response, there appears to be a continuous response to carbohydrate reduction. The nutritional intake of <200 g carbohydrate/d has been called an LCD, but most experts would not consider that to provide the metabolic changes associated with an LCKD. We suggest that LCD refers to a carbohydrate intake in the range of 50–150 g/d, which is above the level of generation of urinary ketones for most people.

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TABLE 1
Fuel sources in a low-carbohydrate ketogenic diet

Fatty acids (≈70% of caloric requirements)
Dietary fat
Lipolysis
Adipose stores
Ketone bodies (≈20% of caloric requirements)
Dietary fat and protein
Lipolysis and ketogenesis
Adipose stores
Glucose (≈10% of caloric requirements)
Gluconeogenesis
Dietary protein and fat (glycerol)
Glycogenolysis

Other macronutrients

Because an instruction only to restrict carbohydrate intake could theoretically create a diet containing any level of daily energy intake from protein and fat, confusion exists among researchers and the lay public about what constitutes an LCD. As early as 1980, LaRosa found that subjects following an LCD do not necessarily replace the carbohydrate with either protein or fat, but that they, rather, reduce starch and sugar intake (9). Under such conditions, even though the absolute amounts of fat and protein do not increase, the percentage of fat and protein will increase. Recent research reviewed below has determined that the reduction in calorie intake is a result of appetite and hunger reduction. In this way, LCDs are also low-calorie diets that include an increase in the percentage of calories from fat and protein but not necessarily an increase in absolute amounts of fat and protein.

General physiologic principles in carbohydrate restriction

A review outlined the way in which a marked reduction in carbohydrate intake leads to a general change in metabolism from a "glucocentric" (glucose) to an "adipocentric" (ketone bodies, fatty acids) metabolism (8). The main fuel sources become fatty acids (from dietary fat and adipose stores) and ketones (from dietary fat, protein, and adipose stores) (**Table 1**). Glucose-dependent tissues (ie, red blood cells, retina, lens, and renal medulla) receive glucose through gluconeogenesis and glycogenolysis. (Even if no dietary carbohydrate is consumed, it is estimated that 200 g glucose/d can be manufactured by the liver and kidney from dietary protein and fat.) The metabolic state experienced by a person who is following an LCKD is often compared with the condition of starvation. The main similarities in metabolism between LCDs and starvation are that there is no (or little) intake of exogenous carbohydrate and that there is a shift from the use of glucose as fuel toward the use of fatty acids and ketones as fuel. Under conditions of starvation, endogenous sources (eg, muscle protein, glycogen, and fat stores) are used as energy supplies (10). However, under conditions of LCKD intake, exogenous sources of protein and fat provide energy, along with endogenous glycogen and fat stores if caloric expenditure exceeds caloric intake. Whereas the loss of lean body mass (LBM) is typical with weight loss, under certain circumstances when sufficient dietary protein is provided, an LCKD may preserve LBM even during hypoenergetic conditions of weight loss (11, 12). Under low-carbohydrate conditions, unlike those of starvation, glucose concentrations are sustained despite the lack of carbohydrate intake (13). The maintenance of glucose concentrations and the lack of breakdown of endogenous protein are important differences between starvation and very low carbohydrate intake.

Recent studies in healthy subjects

Only in the past several years have detailed studies regarding LCD metabolism been performed (**Table 2**). In a metabolic ward study, 8 healthy volunteers were provided a 2-d eucaloric (weight-maintaining) diet in which 60% of energy was from carbohydrate and 30% of energy was from fat; this diet was followed by a 7-d eucaloric diet in which 5% of energy was from carbohydrate and 60% of energy was from fat. Both diets were consumed while the subjects maintained their typical sedentary lifestyle (14). With the 5% carbohydrate diet, serum glucose initially declined but then returned to baseline after a few days. Whereas fasting insulin did not differ between the 2 diets, the 24-h area under the curve (AUC) for insulin was >50% lower

TABLE 2
Studies of low-carbohydrate ketogenic diet metabolism[1]

			Macronutrients									
Study	Duration	Subjects	CHO	Pro	Fat	Energy	RQ	Insulin	Glucagon	Glucose	Fatty acids	β-Hydroxybutyrate
	d	*n*	*% of daily intake*			*kcal/d*		*μU/mL*	*pg/mL*	*mmol/L*	*mmol/L*	*mmol/L*
Bisschop et al, 2000 (16)	11	6	2	15	85	—[2]	0.73	3.7	65	4.7	0.78	
	11	6	44	15	41	—	0.81	8.4	57	5.2	0.36	
	11	6	85	15	15	—	0.86	8.4	60	5.4	0.36	
Allick et al, 2004 (22)[3]	14	5	0	11	89	3500	0.73	10	79	6.8	0.79	
			89	11	0	3500	0.79	12	73	8.2	0.70	
Harber et al, 2005 (14)	7	8	5	35	60	—		7.0		5.0	0.45	0.5
	2		60	10	30	—		7.0		5.0	0.3	0.05
Boden et al, 2005 (13)[3]	7	10	4	28	68	2164		6.7	89	6.3		0.65
			39	17	44	3190		9.2	78	7.3		0.13
Noakes et al, 2006 (21)	84[4]	24	12	31	54			7.1		5.3		<0.1
		21	49	21	28			7.4		5.3		<0.1
		22	66	20	13			9.9		5.2		<0.1

[1] CHO, carbohydrate; Pro, protein; RQ, respiratory quotient. Insulin, glucagon, glucose, fatty acids, and β-hydroxybutyrate were fasting serum samples.
[2] Weight-maintaining diet; the same caloric content in each group (all such).
[3] Patients had type 2 diabetes.
[4] 8 wk of isocaloric weight loss and then 4 wk of weight maintenance.

with the 5% carbohydrate diet than with the 60% carbohydrate diet. After 1–2 d of the 5% carbohydrate diet and persisting through the 7-d period, serum β-hydroxybutyrate increased from 0.1 to 0.4 mmol/L and free fatty acids increased from 0.2 to 0.4 mmol/L. In addition, muscle glycogen (measured by muscle biopsy) was reduced by 20% after 9 d.

Glucose kinetics were assessed by stable-isotope techniques while resting metabolic rates were calculated from oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) was measured by using a metabolic cart. By day 2 of the 5% carbohydrate diet, both the glucose rate of appearance and rate of disappearance decreased by 20%, and they remained suppressed on day 7. In addition, postabsorptive carbohydrate oxidation decreased progressively over the 7-d duration, and this decline was greater than the decline in glucose uptake. This means that the rate of nonoxidative glucose disposal (ie, carbohydrate storage) increased in the postabsorptive state with the 5% carbohydrate diet. These changes suggest that there is a shift from the use of glucose to the use of ketones and free fatty acids as metabolic fuels, and that glycogen formation increases from baseline.

Another set of studies was performed to evaluate the metabolic effects of diets consisting of 0–2% carbohydrate, 11–15% protein, and 83–88% fat in healthy volunteers (15–19). (These experimental diets contained a higher percentage of fat than is typically observed in an ad libitum LCD, and thus they were more characteristic of an ancestral Inuit diet or the ketogenic diet for epilepsy.) Nonetheless, these studies elucidate many metabolic aspects of carbohydrate restriction. Serum glucose, insulin, and C-peptide concentrations with the 2% carbohydrate diet were lower than those with the 85% carbohydrate control diet. After 11 d of the 2% carbohydrate diet, gluconeogenesis was 15% higher and glycogenolysis was 55% lower than that after 11 d of the 85% carbohydrate diet (15). In a related study by the same group, weight-maintaining diets containing either 89% carbohydrate, 11% protein, and 0% fat or 0% carbohydrate, 11% protein, and 89% fat were compared over a 15-d period (18). In that study, gluconeogenic rates did not differ significantly between the diets. When a hyperinsulinemic euglycemic clamp technique (200 pmol/L) was used, insulin-mediated suppression of glucose production and stimulation of glucose disposal did not differ significantly between the diets. The investigators wrote, "After 14 d on this [0% carbohydrate, 11% protein, and 89% fat] diet, 3 h of hyperinsulinemia were not sufficient to suppress fat oxidation and increase glucose oxidation. Because fatty acid use and oxidation [are] impaired in patients with type 2 diabetes, the 14-d high-fat diet seemed to have reversed this defect by allowing adaptation of fuel selection toward fatty acids as the main energy substrates and maintaining glucose oxidation at a minimum."

Other findings support the metabolic differences between "starvation" and "carbohydrate deprivation." After 7 d of a 2% carbohydrate, 15% protein, and 83% fat weight-maintenance (33 kcal/kg) diet, 24-h nitrogen excretion was higher, without a change in postabsorptive hepatic or whole-body protein metabolism, than it was with the 2 comparison diets composed of 0% fat and 41% fat (15). A previous study found that this rise in nitrogen excretion after carbohydrate withdrawal is short-lived, however, as both nitrogen balance and LBM retention were observed after a 1–2-wk adaptation to a 0% cholesterol, 15% protein, and 85% fat diet (20).

The 2% carbohydrate, 15% protein, and 83% fat weight-maintenance diet also resulted in lower absorptive and postabsorptive plasma insulin concentrations than did the 0% fat and 41% fat diets (15). Postabsorptive rates of appearance of leucine and of leucine oxidation—measures of proteolysis—did not differ significantly among the 3 diets. In addition, dietary carbohydrate did not affect the synthesis rates of fibrinogen and albumin. However, this study was limited in that the experimental manipulation did not provide sufficient potassium or sodium intake, nor did it allow time for keto-adaptation to reflect the conditions of chronic, very low carbohydrate consumption. Both mineral nutriture and time for adaptation have been addressed in earlier eucaloric, very-low-carbohydrate feeding studies (20).

Another outpatient feeding study randomly assigned 83 subjects to 1 of 3 diets ranging in carbohydrate content from 12% to 66% for 8-wk weight-loss and 4-wk weight-maintenance periods (21). During the weight-maintenance period, the 3 diets contained an estimated 66% carbohydrate, 20% protein, and 13% fat; 49% carbohydrate, 21% protein, and 28% fat; or 12% carbohydrate, 31% protein, and 54% fat. The 12% carbohydrate diet led to the greatest reduction in fasting insulin concentrations, whereas fasting glucose concentrations did not differ significantly among the groups. That study confirmed that the postprandial rise of glucose and insulin after typical meals does not occur after a 12% carbohydrate meal when given to a person who has been adapted to a 12% carbohydrate diet.

Recent studies in diabetic subjects

Another metabolic ward study examined the effects of an ad libitum LCKD in obese persons with type 2 diabetes (13). Ten subjects were monitored while eating their usual diet for 7 d and then a VLCD for 14 d. Carbohydrate intake was reduced to ≈21 g/d, but patients could eat as much protein and fat as they wanted and as often as they wanted. The final diet consumed was weighed and estimated to contain a daily average of 21 g carbohydrate, 151 g protein, and 164 g fat, representing a spontaneous reduction in caloric intake of 947 kcal, which resulted in a mean weight loss of 2 kg over 14 d ($P = 0.042$). During the low-carbohydrate-diet period, mean fasting glucose decreased from 7.5 mmol/L (135 mg/dL) on day 8 to 6.3 mmol/L (113 mg/dL) on day 22 ($P = 0.025$), glycated hemoglobin decreased from 7.3% to 6.8% ($P = 0.006$), and 24-h glucose and insulin concentrations decreased significantly. This reduction in glucose concentrations required a decrease in diabetes medication in 5 of the 10 patients.

During the euglycemic hyperinsulinemic clamp procedure, the mean glucose infusion rate needed to maintain euglycemia increased by 30%, from 12.9 $\mu mol \cdot kg\ body\ wt^{-1} \cdot min^{-1}$ during the usual diet to 16.8 $\mu mol \cdot kg\ body\ wt^{-1} \cdot min^{-1}$ after the LCD ($P = 0.03$). After adjustment for the differences in clamp insulin concentrations on the 2 diets, glucose infusion rates increased by ≈75%. Mean insulin-stimulated rates of glucose disappearance (ie, insulin sensitivity), after adjustment, increased from 0.01 $\mu mol \cdot kg^{-1} \cdot min^{-1}/pmol \cdot L^{-1}$ to 0.03 $\mu mol \cdot kg^{-1} \cdot min^{-1}/pmol \cdot L^{-1}$. So, the increase in glucose disappearance effectively explained all of the increase in the glucose infusion rates, whereas endogenous glucose production did not change significantly. Therefore, insulin sensitivity improved largely because of an increase in peripheral glucose uptake.

In another study involving persons with type 2 diabetes, a 3500-kcal weight-maintenance diet of 89% carbohydrate, 11% protein, and 0% fat was compared with a 3500-kcal diet of 0%

carbohydrate, 11% protein, and 89% fat in 7 persons. This research group used stable-isotope and euglycemic hyperinsulinemic clamp techniques to partition glucose disposal into oxidative and nonoxidative disposal (22). In findings similar to those of Harber et al (5), oxidative glucose disposal decreased 90%, whereas nonoxidative glucose disposal increased. The main finding was that, "in subjects with mild type 2 diabetes, maximal eucaloric variation in carbohydrate to fat ratio modulates plasma glucose concentration exclusively by alterations in hepatic glucose production." Allick et al concluded that it was remarkable that, in the context of diabetes risk, 2 aspects of glucose homeostasis actually improved after consumption of the high-fat, low-carbohydrate diet: basal endogenous glucose production decreased, and insulin-stimulated nonoxidative glucose disposal increased.

The role of ketogenesis

Ketone concentrations after LCD intake have now been measured in several studies. In a study of persons with type 2 diabetes, urinary ketone body excretion increased from a mean of 0.10 mmol/d at the end of the usual diet to a peak of 2.75 mmol/d after 1 wk of the LCKD ($P < 0.001$); it then decreased gradually for a week but remained above baseline (13). The mean plasma total-body ketone concentrations were 130 μmol/L (91.5% β-hydroxybutyrate) at the end of the usual diet and increased 5-fold to 653 μmol/L (97.4% β-hydroxybutyrate) at the end of the LCKD ($P < 0.001$). Two longer-term studies, in persons without diabetes, that measured fasting blood β-hydroxybutyrate concentrations over 10 wk found that, whereas the concentrations increased over the first 2–4 wk, they then decreased and, after 10–12 wk, remained only slightly higher than those of dieters following other diets (21, 23).

Effects on appetite and satiety factors

Several studies confirm that there is a spontaneous reduction in caloric intake when carbohydrate intake only is restricted to 5–10% of caloric intake (24). In the most controlled study to date, an LCD led to hunger levels similar to those of a low-fat diet, even though the daily caloric intake with the LCD was 1000 kcal lower (13). Another study used the Eating Inventory, a validated questionnaire assessing hunger and cognitive restraint, and found that hunger was reduced by 50% when measured after 1 wk of an LCD (25). Another study examining a 20-g carbohydrate diet found that fasting serum leptin was reduced by 50% and fasting serum neuropeptide Y was reduced by 15% (26). It may also be that the mere lowering of serum insulin concentrations, as is seen with LCDs, may lead to a reduction in appetite. In support of this idea, several studies have found that insulin increases food intake, that foods with high insulin responses are less satiating, and that suppression of insulin with octreotide leads to weight loss (27–29).

In summary, new metabolic studies of very-low-carbohydrate conditions have found that serum glucose homeostasis is maintained and serum ketone concentrations are increased. Muscle glycogen is reduced but still present. With the exception of one study (20), these metabolic studies are limited by the short study duration (typically, 7–14 d), which probably does not allow sufficient time for full adaptation to low-carbohydrate conditions.

Unanswered questions on low-carbohydrate metabolism

The study of LCD metabolism has been used to illustrate metabolic pathways in medical school curricula and has also highlighted some of the gaps in our current understanding of biochemistry and metabolism (30). Whereas a spontaneous reduction in caloric intake is a major effect of LCDs, there are many reports indicating a so-called "metabolic advantage"—that is, a greater amount of weight lost per calorie consumed. This is a controversial idea, and there are perceptions that variable weight loss with isocaloric diets would somehow violate the laws of thermodynamics and that there must be some experimental error. It is widely held that only caloric intake is important (as expressed by the statement, "A calorie is a calorie."). Variable energy efficiency, however, is known in many contexts: hormonal imbalance (31, 32), studies of weight regain (33, 34), and, most strikingly, in knockout experiments in animals (35–37). The fat-specific insulin receptor knock-out mouse weighs only ≈60% as much as the wild-type mouse, even though the 2 types of mice eat the same amount of food (35). Most of the time, of course, a calorie *is* a calorie, and we do not maintain that, in carbohydrate restriction, metabolic advantage always occurs, but only *1*) that it can occur (11), *2*) that it is not excluded by a correct thermodynamic analysis, and *3*) that, because of the importance of obesity, it is sensible to try to identify the conditions under which it can occur and to maximize the effect. The thermodynamic analysis leads to the conclusion that variable efficiency is the expected outcome from physical principles, and therefore, when a calorie is a calorie, it is not explained by thermodynamics but rather by the unique characteristics of living systems. In other words, it is energy balance that needs to be explained. The mechanisms that explain metabolic advantage emphasize the inefficiencies introduced by substrate cycling and the requirements for increased gluconeogenesis (38, 39). In addition, that thermogenesis varies for different macronutrients is widely accepted, but it is somehow expected to be ignored in weight-loss experiments, even though the levels are in the range of 20% for protein compared with 5% for carbohydrate. Moreover, discussion generally centers on equilibrium thermodynamics, but living systems are maintained far from equilibrium, and nonequilibrium thermodynamics, which emphasizes kinetic fluxes as well as thermodynamic forces, is more relevant. Most simply, the argument that "a calorie is a calorie" rests on the fact that free energy and other thermodynamic variables are state variables—that is, that they are independent of mechanism or path. In fact, the change in a weight-loss experiment is extremely far from the total change embodied in free energy values, and the change that is measured (technically, the partial derivative of the energy with respect to reaction) is not path-independent and is notably influenced by the activity of enzymes (40, 41).

Studies suggested that xylulose-5-phospate (Xu-5-P) is a signal for the coordinated control of glucose metabolism and lipogenesis (42). Xu-5-P is generated from glucose metabolism in the hexose monophosphate pathway, which activates phosphofructokinase and promotes the transcription carbohydrate-responsive element–binding protein (ChREBP), thereby increasing the enzymes of lipogenesis, the hexose monophosphate shunt, and glycolysis, all of which are required for lipogenesis. The control of both glycolysis and lipogenesis by one transcription factor shows the close relation between these pathways.

TABLE 3
Randomized outpatient trials of a low-carbohydrate ketogenic diet for obesity: estimated dietary intake and effect on weight and fasting serum lipids[1]

			Low-fat diet								Low-carbohydrate diet							
			Macronutrients								Macronutrients							
Reference	Duration	Subjects	CHO	Fat	Pro	Energy	Weight	LDL	TG	HDL	CHO	Fat	Pro	Energy	Weight	LDL	TG	HDL
		n	*% of energy*			*kcal/d*	*kg*	*%*	*%*	*%*	*% of energy*			*kcal/d*	*kg*	*%*	*%*	*%*
Brehm et al, 2003 (54)	6 mo	42	53	29	18	1245	−3.9	−5	2	8	23	46	30	1302	−8.5	0	−23	13
Foster et al, 2003 (51)	6 mo	63	—[2]	—	—	—	−5.3	−3	−13	4	—	—	—	—	−9.7	4	−21	20
	12 mo						−4.5	−6	1	3					−7.3	1	−28	18
Meckling et al, 2004 (23)	10 wk	40	62	20	18	1447	−6.8	−32	−25	−15	15	56	26	1528	−7.0	0	−29	12
Samaha et al, 2003 (52)	6 mo	132	51	33	16	1576	−1.9	3	−4	−2	37	41	22	1630	−5.8	4	−20	NC
	12 mo						−3.1	−3	2	−12					−5.1	6	−29	−2
Sondike et al, 2003 (50)	3 mo	30	56	12	32	1100	−4.1	−17	−6	2	8	60	32	1830	−9.9	4	−48	4
Yancy et al, 2004 (55)	6 mo	119	51	18	31	1588	−6.5	−3	−15	−1	10	60	30	1472	−12.0	2	−42	13

[1] CHO, estimated daily carbohydrate intake; Pro, estimated daily protein intake; Energy, estimated daily calorie intake; weight, total body weight; TG, triacylglycerols; NC, no change.
[2] Not measured (all such).

It is also likely that the regulation of hepatic glucose output is substantially altered after adaptation to an LCKD (keto-adaptation). For example, one study compared a very-low-energy (624 kcal), low-carbohydrate (20% of daily energy intake) diet to a baseline isoenergetic (30 kcal/kg), high-carbohydrate (55%) diet in obese subjects with type 2 diabetes (43). After 3 wk of adaptation, the very-low-energy, LCD diet resulted in significantly less hepatic glucose output, and, across all subjects and diets, basal hepatic glucose output was negatively correlated with plasma ketones ($r = -0.71$, $P < 0.05$).

Insulin resistance is reduced with an LCKD, possibly by a reduction in the availability of dietary glucose, which causes hyperinsulinemia (44, 45). A consideration of the physiology of very-low-carbohydrate dieting leads to a different perspective on insulin resistance. That is, rather than treating insulin resistance by increasing glucose disposal through an increase in nonstorage cellular influx (eg, by increasing either the insulin dose or its effect), it could be treated by reducing glucose availability to insulin-resistant tissue (eg, by reducing carbohydrate intake or absorption and basal hepatic glucose output), which would reduce the nonstorage cellular influx. Reductions in dietary carbohydrate should be used as a strategy to treat insulin resistance.

Low-carbohydrate diets and exercise

Over the past several years, 2 reviews focused on LCKD and exercise have been published. One of these reviews concluded that submaximal endurance performance can be sustained despite the virtual exclusion of carbohydrate from the human diet (46). The other review addressed the intramuscular enzyme adaptation that occurs with these diets (47).

Several important issues arise in the consideration of LCKD studies in general and of exercise studies in particular: *1*) the time allowed for keto-adaptation, *2*) the use of electrolyte supplementation, and *3*) the amount of protein intake. To try to examine the first issue, we can consider the multiple studies comparing low-carbohydrate with high-carbohydrate diets to test the hypothesis that "carbohydrate loading" can enhance physical performance. None of the studies that support this hypothesis maintained the LCD for >2 wk (48), and most maintained the LCDs for ≤7 d (49). No studies have carefully examined the process or duration of keto-adaptation, but clinical observation suggests that it probably takes from 2 to 4 wk for keto-adaptation to occur.

The second issue has to do with the maintenance of adequate mineral supplementation as long as the ketogenic state is maintained. One group of investigators provided supplements containing 3–5 g sodium/d and 2–3 g potassium/d and found that circulatory competence during submaximal exercise was sustained. These supplements also allowed the subjects to achieve nitrogen balance, which had not been achieved in studies that did not use supplements (20).

The third issue affecting physical performance is adequate protein intake. It is generally accepted that the preservation of LBM and of physical performance during any degree of energy restriction occurs when protein is in the range of 1.2 to 1.7 $g \cdot kg$ reference body $wt^{-1} \cdot d^{-1}$. The use of the mid-range value of 1.5 $g \cdot kg^{-1} \cdot d^{-1}$ for adults with reference weights ranging from 60 to 80 kg, this translates into total daily protein intakes of 90 to 120 g/d. When adequate protein intake is expressed in the context of total daily energy expenditures of 2000 to 3000 kcal/d, ≈15% of daily energy expenditure should be provided as protein.

Further research on exercising under conditions of LCDs is needed. These studies may be optimized by careful attention to the time needed for keto-adaptation, to mineral supplementation, and to the daily protein dose. Therapeutic use of ketogenic diets should not limit most forms of physical activity, with the caveat that anaerobic performance (ie, weight lifting or sprinting) may be limited by lower-muscle glycogen concentrations.

Outpatient clinical trials for obesity

The efficacy of an LCKD for weight loss has now been established in 6 outpatient randomized controlled trials (23, 50–55). All of these trials used the most widely recommended diet at that time, a 30%-fat, reduced-calorie diet, as the comparison diet (**Table 3**). There were differences in the intensity of the interventions in these outpatient studies. For example, the amount of behavioral support ranged from simply providing a popular diet book along with minimal education to providing biweekly group sessions with extensive handouts and close monitoring (51, 55). Across these studies, there appeared to be better adherence and greater weight loss as the intensity of the intervention increased.

One study (23) used a tapering of carbohydrate, whereas all other studies used a sudden reduction in carbohydrate.

Several of these studies collected detailed outpatient nutritional intake information (23, 54). Whereas instruction in an LCD does not mention calories, the restriction of dietary carbohydrate leads to a reduction in caloric intake from baseline. The ad libitum intake can vary from person to person, but, in many cases, the protein and fat intakes, in absolute terms, are not much higher than those of a typical American diet, because the total caloric intake is lower. As such, the LCD is not necessarily a high-protein diet or a high-fat diet. In addition, whereas the diet typically contains high amounts of saturated fat, it also contains high amounts of monounsaturated and polyunsaturated fats.

Cardiovascular disease risk factors

As shown in Table 3, the outpatient obesity studies found a consistent reduction in fasting serum triacylglycerols and a fairly consistent increase in HDL cholesterol, but little change in total or LDL cholesterol, in the LCD groups. Two of these studies published examinations of the fasting serum lipid concentrations by using a lipid subfraction technique, and both found an average change in LDL-cholesterol type from small LDL to large LDL cholesterol, which corresponded with a decrease in LDL particle concentration for subjects following the LCKD for 6 mo (56, 57).

Two studies assessed the effectiveness and adherence rates of several popular diet plans with minimal behavioral counseling (58, 59). Several outpatient diet studies have shown reductions in CVD risk factors after an 8–12-wk LCKD, during weight loss, and during weight maintenance (21, 60–62).

Clinical practice summaries

Several retrospective and prospective clinical series on the potential effectiveness of an LCD in the clinical setting have been published. A group in Kuwait published 2 case series involving 185 patients following a diet with 20–40 g carbohydrate/d; those investigators found reductions in weight, cholesterol, and LDL cholesterol and an increase in HDL cholesterol (63, 64). A group in Bahrain conducted a pilot study of 13 obese patients and found positive effects (65). Two clinical studies from the United States used LCDs in conjunction with statin therapy (66, 67). Five other clinical series involving 229 patients suggested that the LCD has a potent effect on obesity and type 2 diabetes (68–74). Another clinical series involved 37 adolescents who were instructed to follow either an LCD (<30 g/d; $n = 27$) or a low-calorie diet ($n = 10$) for 2 mo. Compliance and weight loss were better in the LCD group (75).

Whereas these studies are limited because of their clinical measures and possible selection bias, they show that many clinicians already find that it is feasible to implement the LCD in clinical practice. All of the case series studies showed improvements in clinical measures, which indicates that these outcomes can be obtained in the outpatient practice setting in at least a subset of adherent patients.

Ancestral nutrition

Whereas some traditional diets may have had lower carbohydrate content than current diets, only a few studies have directly addressed the question of whether a return to the traditional lifestyle may help contemporary aboriginal peoples (76). In one study, 10 city-dwelling Australian aboriginal men with type 2 diabetes lived for 7 wk as hunter-gatherers. At the end of the study period, there were significant improvements in weight and fasting serum glucose, insulin, and triacylglycerol concentrations (77). When the study subjects returned to their previous urban lifestyle, the weight and diabetes returned. In another study, 25 Canadian Cree subjects who lived a traditional lifestyle for 3 mo in the bush were compared with 26 control subjects who stayed in the community. However, the subjects who lived in the bush were able to obtain store-bought food, and thus the effects on diabetes indexes were limited (78). If the traditional nutritional intake is healthier, as these studies suggest, then further research could be directed toward developing sustainable modern lifestyles that use these principles.

Therapeutic potential

In addition to its usefulness in the treatment of obesity, hypertension, and hyperlipidemia, the LCD may be useful for other medical conditions. Whereas no prospective, randomized trials have specifically examined an LCKD as a treatment of the metabolic syndrome, that would be a logical next step because of an LCKD's ability to improve glucose, serum triacylglycerol, HDL cholesterol, abdominal circumference, and blood pressure—the elements of the metabolic syndrome (79). Preliminary studies have suggested that an LCD may be useful in the treatment of both epilepsy and narcolepsy (80, 81). Persons following an LCD also have noted a reduction in heartburn (82, 83). Because an LCD typically excludes gluten-containing foods, a case of improvement in dermatitis herpetiformis, a condition resulting from gluten sensitivity, has been reported (84). Because of the improvement in insulin resistance, LCDs could, in theory, be useful for any condition related to insulin resistance, and thus any such condition should be a topic of future research.

An LCD combined with weight loss also may be useful in treating inflammation. A substudy from one of the outpatient obesity trials found that both the low-carbohydrate and low-fat diets led to reductions in C-reactive protein and plasma serum amyloid A (85). The effects of the reduction in inflammatory markers were proportional to the weight loss: ie, the LCD group had greater reductions in the inflammatory markers and a greater weight loss over a 3-mo period than did the low-fat diet group. Another study found a reduction in the inflammatory biomarkers human soluble tumor necrosis factor-α, interleukin-6, C-reactive protein, and soluble intercellular adhesion molecule-1 (61).

The elimination or reduction of dietary carbohydrate removes many processed foods from the diet. In this way, an LCD may reduce exposure to allergens or disease-provoking substances such as gluten (which can trigger celiac disease or nontropical sprue), food additives, and artificial coloring (86). A carbohydrate-elimination test could determine whether one of the carbohydrate-related factors is contributing to a disease process.

In an article reviewing the therapeutic potential of ketogenic diets, it was hypothesized that the metabolism of ketones and fatty acids changes the intracellular milieu to decrease the formation of reactive oxygen species (ROS) (87). This suggests that disease processes related to ROS generation may be ameliorated by an LCD that is associated with an increase in ketones. Another report proposed a theoretical basis for why a ketogenic diet might be useful for the treatment of neoplasia (88).

Potential adverse effects

As with any large change in nutrient intake, the change to an LCD in patients taking medications for diabetes or hypertension should be made under supervision by clinicians familiar with the effects of the diet. Frequently, a reduction in medication will be required to avoid hypoglycemia and hypotension due to overmedication. In addition, most clinical studies to date have included a daily multivitamin and mineral supplement along with the diet. As mentioned previously, sodium and potassium supplements have also been used.

Only one of the clinical trials has assessed symptomatic side effects of an LCKD (55). In that study, subjects following an LCKD were more likely to experience constipation, headache, muscle cramps, diarrhea, weakness, and skin rash than were those following a low-fat diet. Serious adverse events, such as hospitalization, procedure utilization, or death, were not reported in any of the evaluated studies with enough frequency to allow an assessment of whether the diet may have contributed to those events.

A recent controlled study evaluated a 20-g carbohydrate/d diet for its effects on bone turnover over a 3-mo period (89). In that study, bone turnover markers in subjects who followed the diet did not increase compared with controls at any time. One case report suggested that an LCD contributed to an episode of hypertriglyceridemia-related pancreatitis (90). Another case report raised the possibility that the diet contributed to an episode of mania, perhaps by altering the metabolism of valproic acid (91). Because a large change in dietary intake may alter the availability of vitamins such as vitamin K, the monitoring of patients receiving anticoagulation therapy is important (92, 93). All of these case reports are limited by the difficulty of determining a causal relation.

Official recommendations

The growing number of studies examining the effects of carbohydrate restriction should provide data for organizations that advocate for patients with CVD and diabetes as they update recommendations for optimal diets. Until research has solved the problem of perfectly matching an individual to a diet, flexibility in choosing among many diets with measurement of intended outcomes in individual patients should be recommended.

SUMMARY

Recent studies have outlined LCD metabolism and shown that LCDs improve glycemic control and insulin resistance in healthy persons and in persons with type 2 diabetes. The instruction to limit carbohydrate intake, without specific reference to calorie intake, leads to a spontaneous reduction in calorie intake. In controlled trials for weight loss, the LCD leads to weight loss and improvements in fasting triacylglycerols, HDL cholesterol, and the ratio of total to HDL cholesterol over a 6–12-mo period. Clinical trials assessing the long-term safety and effectiveness of LCDs are needed. In the interim, the use of the LCD with careful monitoring of CVD risk factors and other variables associated with health appears reasonable.

The clinical use of and clinical research on LCDs have raised fundamental questions about insulin resistance and the regulation of cellular fuel utilization, as well as questions about whether dietary carbohydrate is an essential nutrient, and whether dietary fat causes heart disease. Because of their glucose- and insulin-lowering effects, LCDs should be evaluated as possible treatments for conditions related to hyperglycemia, hyperinsulinemia, and insulin resistance.

We emphasize that strategies based on carbohydrate restriction have continued to fulfill their promise in relation to weight loss and that, contrary to early concerns, they have a generally beneficial effect on most markers of CVD, even in the absence of weight loss. In combination with the intuitive and established efficacy in relation to glycemic control in diabetics, some form of LCD may be the preferred choice for weight reduction as well as for general health.

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