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REVIEW

Ketogenic diets for weight loss: A review of their principles, safety and efficacy

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Summary Low-carbohydrate ''ketogenic'' diets have increased in popularity over recent years as a means of weight loss. Published studies of these diets have been highly heterogeneous, and it remains unclear to what degree dietary carbohydrate intake must be restricted in order to induce ketosis. Despite concern that they are often relatively high in fat, ketogenic low-carbohydrate diets have been generally shown to compare favourably with low-fat diets in terms of weight loss and improvements in triglyceride and high-density lipoprotein levels. This review includes a brief overview of ketone body metabolism, and summarises the literature regarding the safety and efficacy of ketogenic diets for weight loss.

Contents

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Introduction

The increasing prevalence of overweight and obesity has been widely reported. In recent years, low-carbohydrate ''ketogenic'' diets have received much attention as a means of rapid weight loss. However, there is no clear consensus in the literature as to what carbohydrate intake constitutes a low-carbohydrate diet, or to what degree carbohydrates must be restricted in order to cause ketosis. Furthermore, since ketogenic low-carbohydrate diets are often high in fat, there have been concerns about their potential adverse effects on cardiovascular risk.

The use of ketogenic diets in refractory paediatric epilepsy has been extensively reviewed elsewhere [1]. These diets have a different composition and aim to generate higher ketone levels than the ketogenic diets used for weight loss. This article will briefly overview ketone body metabolism and review the available evidence relating to the efficacy and safety of ketogenic low-carbohydrate diets for weight loss.

Ketone body metabolism

The term ''ketone bodies'' refers to three compounds: acetoacetate (AcAc), 3-β-hydroxybutyrate (3HB—not strictly a ketone but rather a hydroxy fatty acid) and acetone (Fig. 1). The circulating levels of ketone bodies are dependent both on their rate of production (ketogenesis) and their rate of utilisation (ketolysis). AcAc and 3HB are the two main ketone bodies generated and used for fuel under low-carbohydrate conditions. Acetone is formed by spontaneous decarboxylation of AcAc [2] and gives a characteristic odour to the breath of ketotic subjects.

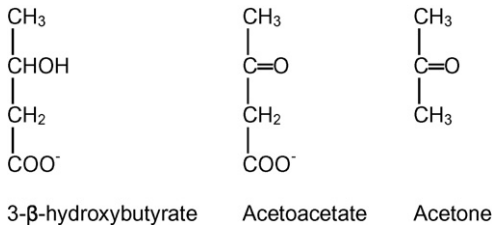


Figure 1 Structure of the three ketone bodies.

Ketone bodies are produced in the mitochondria of perivenous hepatocytes [3], mainly from the oxidation of fatty acids, and are transported to other tissues for use as an energy source. They are of key importance to the brain, which cannot derive energy from other sources when blood glucose levels are low. Ketogenic amino acids (primarily leucine and lysine) provide an independent, albeit minor, source of ketone bodies.

In healthy adults, the liver can produce 185 g of ketone bodies per day. Ketones supply 2—6% of the body's energy requirements after an overnight fast, and 30—40% after a 3-day fast [4]. Low levels of ketone bodies are also present during exercise and when a high fat diet is consumed [2], and ketosis readily develops during infancy and pregnancy. Pathological levels of ketones are found in diabetic or alcoholic ketoacidosis, salicylate poisoning and certain inborn errors of metabolism.

In 1984, Hall and colleagues found that the mean post-absorptive blood ketone level in obese subjects was threefold higher than in lean subjects (0.42 mmol/L vs. 0.12 mmol/L) [5]. More recent studies in obese subjects have found baseline fasting ketone levels of 0.06—0.09 mmol/L [6,7]. Ketogenic diets for weight loss typically result in serum ketone levels around 0.33—0.72 mmol/L [7], while those used in the treatment of paediatric epilepsy aim for levels of 2—7 mmol/L [8]. By comparison, ketone levels in diabetic ketoacidosis (DKA) may be as high as 25 mmol/L [9]. The increase in ketones following starvation or DKA is nearly all due to 3HB [5]. In their comprehensive review of ketone body metabolism, Robinson and Williamson proposed blood ketone (AcAc + 3HB) levels for defining hyperketonemia and ketoacidosis of greater than 0.2 and 7 mmol/L, respectively [10].

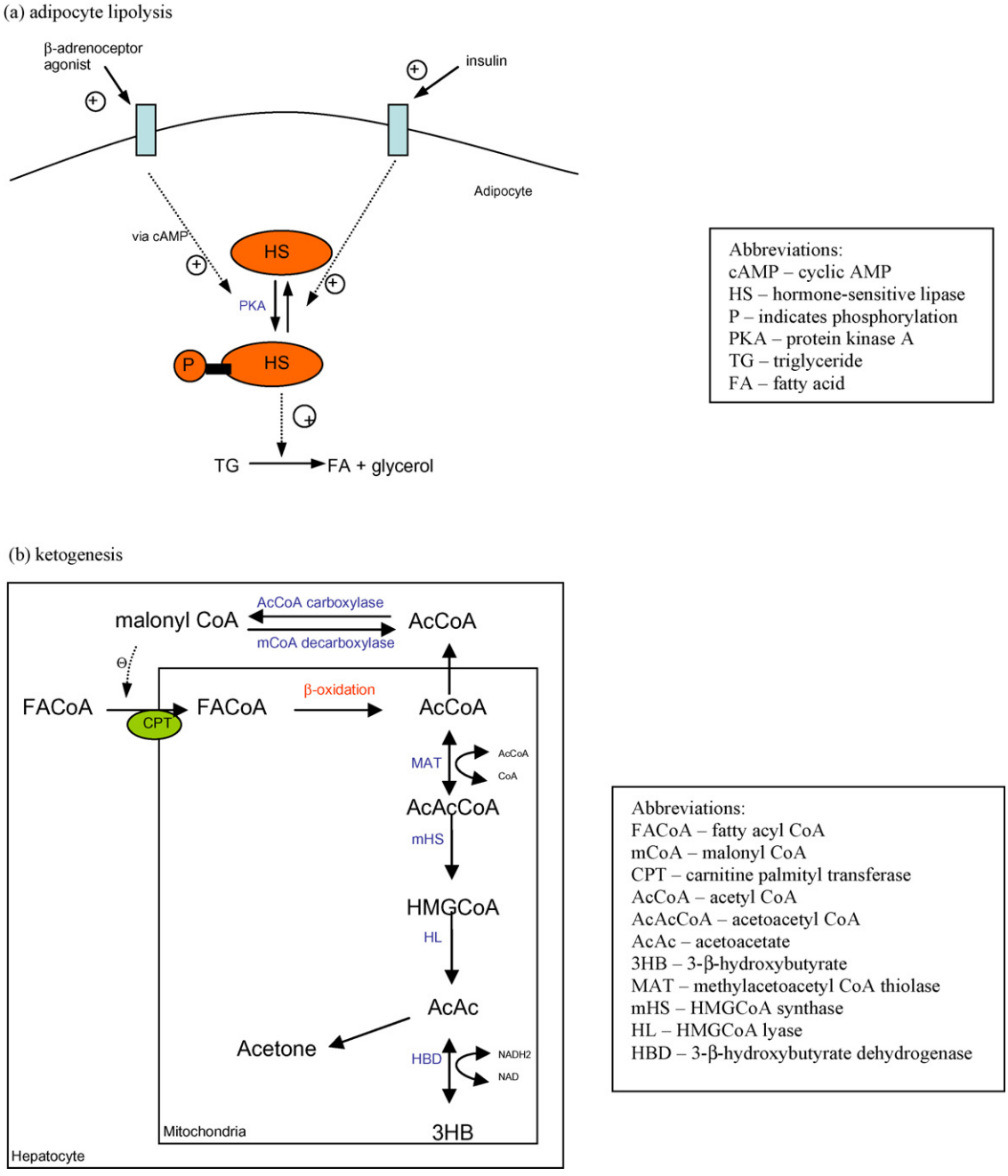


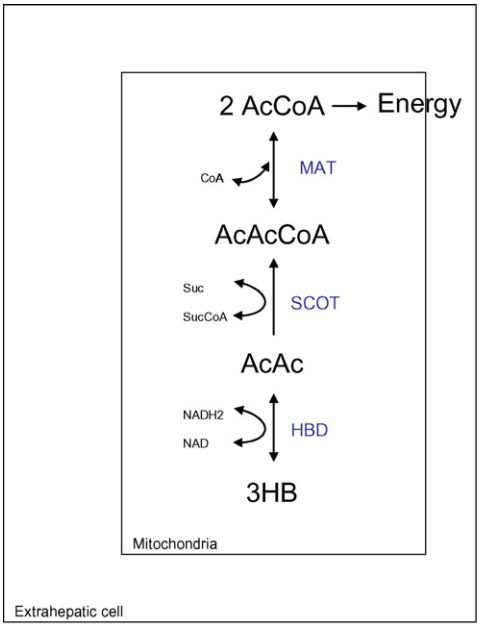
Figure 2 (a) Adipocyte lipolysis, (b) ketogenesis.

Ketogenesis

Most ketone bodies are generated from breakdown of fatty acids liberated from adipose tissue during fasting or adrenergic stress. Adipocyte lipolysis is stimulated by β-adrenergic catecholamines and glucagon, and is strongly inhibited by insulin, therefore it is most active during fasting and suppressed post-prandially (Fig. 2a).

Circulating fatty acids may also be derived from the action of lipoprotein lipase on very-low-density lipoproteins (VLDL) or chylomicrons, however this process is most active in the non-fasting state, at which time fatty acids are mainly directed towards triglyceride synthesis and storage [11].

The rate of ketone body formation is tightly regulated and depends on the activity of three key enzymes: hormone sensitive lipase (influencing the rate of adipocyte lipolysis), acetyl CoA carboxylase (which indirectly determines the rate of entry of fatty acids into the hepatocyte mitochondria), and



Abbreviations:
MAT – methylacetoacetyl CoA thiolase
SCOT – succinyl CoA-oxoacid transferase
HBD – 3-β-hydroxybutyrate dehydrogenase

Figure 3 Ketolysis.

HMG CoA synthase (which converts acetoacetyl CoA to HMG CoA) [4].

Ketolysis

Ketolysis occurs in the mitochondria of extrahepatic organs, and is the process by which ketone bodies are converted to acetyl CoA for energy production. The process involves two key steps (Fig. 3): the conversion of AcAc to acetoacetyl CoA by the enzyme succinyl CoA-oxoacid transferase (SCOT), and the subsequent creation of acetyl CoA by the enzyme methylacetoacetyl CoA thiolase (MAT). The step catalysed by SCOT determines the rate of ketolysis.

Adaptation to ketosis

During starvation, ketone body levels increase from day 3 and continue to rise to reach a plateau around 8 mmol/L after 5—6 weeks of starvation [10]. It has been suggested that down-regulation of SCOT activity accounts for this phenomenon [4]. However, while ketone body utilisation by skeletal muscle declines and free fatty acids become the muscles' principal fuel source [12], ketone body utilisation by the brain increases during prolonged starvation [10].

Measurement of ketone bodies

Standard tests for blood and urinary ketones are semi-quantitative, and reflect the presence of AcAc or acetone via a reaction with nitroprusside, which produces a complex detectable on a test strip. Ketone tests based on the nitroprusside reaction can give false positive results in the presence of drugs containing sulfhydryl groups (including captopril, *N*-acetylcysteine and penicillamine) [13,14]. False negative results may occur if test strips have been exposed to air for an extended period of time or when urine specimens are highly acidic [4].

Quantitative blood tests for 3HB have become available in recent years and can be used to detect 3HB levels in either venous or capillary samples. 3HB is not detected by the nitroprusside reaction. In DKA, the ratio of 3HB to AcAc is initially $\geq$3:1. With treatment, there is an overall reduction in the ketone level as well as a conversion of 3HB to AcAc, however the nitroprusside test will show a plateau or even an elevation in ketones [2,4], giving the misleading impression that the patient's condition is not responding to treatment.

In contrast, Coleman and Nickols-Richardson found that during the milder ketosis induced by a low-carbohydrate diet, there was a strong positive correlation between urinary ketones and serum

3HB [15]. Breath acetone has been shown to predict plasma ketones at least as well as urinary ketone testing in subjects on a ketogenic diet [16].

Ketogenic diets for weight loss

How low in carbohydrates?

The English-language literature has no clear consensus about the definition of a ''low-carbohydrate diet''. A 2003 systematic review of the efficacy and safety of low-carbohydrate diets for weight loss included diets with carbohydrate contents ranging from 0 to 263 g/day [17]. Commonly, low-carbohydrate diets are considered to contain <100 g/day or <30% of energy from carbohydrates [18—20]. Since a diet restricted in carbohydrates usually contains a relatively increased proportion of the other macronutrients, such diets have also been referred to as ''high-protein'' or ''high-fat'' diets. However, a low-carbohydrate diet may not necessarily be high in protein or fat, depending on the level of caloric restriction and the food sources used. Unlike the diets used in the treatment of paediatric epilepsy, ketogenic low-carbohydrate diets for weight loss do not have fixed macronutrient ratios.

Not all low-carbohydrate diets are ketogenic. Although there is currently no consensus as to the amount of carbohydrate restriction required to induce ketosis, the term ''ketogenic diet'' is often limited to diets containing <50 g/day carbohydrate [19,21,22]. However, elevated serum or urinary ketones have also been reported in subjects on diets with average daily carbohydrate intakes between 58 and 192 g/day [6,15,23—25]. Conversely, in a study of participants on a diet with a mean daily carbohydrate intake of 29.5 g, only 42% had urinary ketone levels of trace or greater at 24 weeks [26].

The macronutrient composition of the diet is also an important determinant of ketosis. Low-carbohydrate diets high in protein may not cause ketosis, as up to 57 g glucose can be created from 100 g dietary protein [27]. Ketogenic diets used in the treatment of paediatric epilepsy typically restrict protein as well as carbohydrates (using a ratio of fat to carbohydrate and protein of 3:1 or 4:1) [28]. According to Stock and Yudkin, a recognised formula states that ketosis will occur when fat intake exceeds twice the carbohydrate intake plus half the protein intake [29].

Klein and Wolfe evaluated the contribution of restriction of either carbohydrate or total calories to the metabolic response to fasting in five normal-weight healthy men [30]. Each subject fasted for 84 h on two occasions, during one of which lipid calories were infused intravenously to meet resting energy requirements. Plasma ketones increased to the same degree during the isocaloric lipid infusion as during complete fasting. In a 2003 study by Volek et al., all subjects consuming an isoenergetic low-carbohydrate diet (43 g/day) had detectable urinary ketones for the study duration [31]. Klein et al. showed that hypocaloric infusion of glucose (providing ≈250 kcal/day or 60 g/day glucose) reduced by sixfold the increase in plasma ketones occurring during an 84-h fast [32]. Together, these data indicate that restriction of carbohydrate is a more important determinant of ketosis than restriction of total calories.

Efficacy

In a systematic review of heterogeneous studies examining low-carbohydrate diets, Bravata et al. compared outcomes in subjects on diets with ≤60 g carbohydrate per day (for a mean of 50 days) with higher-carbohydrate diets (mean duration 73 days) [17]. The baseline weight of participants in each group was not significantly different. The authors found a mean weight loss of 16.9 kg in the ≤60 g/day group vs. 1.9 kg in the >60 g/day group. However, when only the randomised controlled and crossover trials (a more homogeneous group) were analysed, there was no difference in weight loss between the groups.

A later randomised controlled trial comparing ketogenic and non-ketogenic low-carbohydrate diets in 20 subjects over 6 weeks found no significant difference in mean weight and fat losses between groups [7].

There are numerous studies comparing *ad libitum* ketogenic low-carbohydrate (KLC) diets with low-fat (LF) diets (Table 1). In most, the diet duration was ≤6 months and the usual finding was greater weight loss on the KLC diet. There were no significant differences in baseline weights between groups. Of the studies evaluating the diets for 12 months or more, the most common finding was greater weight loss at 3—6 months on the KLC diet, with the difference no longer seen at 12 months. A 2006 meta-analysis comparing *ad libitum* KLC with LF diets confirmed this, finding a weighted mean difference of −3.3 kg (95% CI −5.3 to −1.4 kg) at 6 months in favour of the KLC diet, but no significant difference between diets at 12 months (−1.0 kg; 95% CI −3.5—1.5 kg) [33].

Although self-reported energy intake can be unreliable [34], this was similar between groups

Table 1 Weight loss: *ad libitum* ketogenic low-carbohydrate vs. low-fat diets

Authors	Diets	*N*	Age	M/F (%)	BMI	Duration (months)	Completion (%)	Weight, Δ (kg)
[45]	LC	26	44	0/100	33	6	85	8.5 ± 5.1[a]
	LF	27	43	0/100	34		74	3.9 ± 5.2
[96]	LC	33	44	36/64	34	6	73	7.0 ± 6.4[a]
	LF	30	44	27/73	34		60	3.1 ± 5.5
	LC					12	61	4.3 ± 6.6
	LF						57	2.5 ± 6.2
[87]	LC	64	53	80/20	43	6	67	5.7 ± 8.6[a]
	LF	68	54	85/15	43		53	1.8 ± 3.9
[97]	LC					12	69	5.1 ± 8.7
	LF						63	3.1 ± 8.4
[36]	LC	20	14	NA	35	3	80	9.9 ± 9.3[a]
	LF	19	15		36		74	4.1 ± 4.9
[26]	LC	59	44	25/75	35	6	76	12.0 ± 7.0[a]
	LF	60	46	22/78	34		57	6.5 ± 7.0
[6]	LC	25	45	0/100	33	4	80	9.8 ± 3.2[a]
	LF	25	41	0/100	34		80	6.1 ± 4.1
[51]	LC	13	39	0/100	31	1.5	92	6.4 ± NA[a]
	LF	15	40		30		73	4.2 ± NA
[98]	LC	77	42	0/100	32	12	88	4.7 ± 7.2
	LF	79	40		31		76	2.2 ± 6.3
[75]	LC	31	45	0/100	36	6	87	7.1 ± NA[a]
	LF	32	45		37		94	4.7 ± NA
[99]	LC	40	47	47/53	35	6		3.2 ± 4.9
	LF	40	49	57/43	35			3.6 ± 6.7
	LC					12	52	2.1 ± 4.8
	LF						50	3.3 ± 7.3

Data expressed as mean ± S.D. LC: low-carbohydrate diet. LF: low-fat diet. NA: data not available.
[a] Significantly different from LF group.

in most studies. Even when the KLC diet group reported greater energy intake, weight loss was greater than in the LF diet group [35,36].

There are fewer studies comparing energy-matched KLC and LF diets and these tend to be of relatively short duration (Table 2). No significant difference in weight loss was found between groups in the larger trials.

Studies that have examined body composition following KLC diets have generally found a reduc-

Table 2 Weight loss: energy matched ketogenic low-carbohydrate vs. low-fat diets

Authors	Diets (kcal)	*N*	Age	M/F (%)	BMI	Duration (weeks)	Completion (%)	Weight, Δ (kg)
[35]	LC 1855[a]	15	33	100/0	34	6	100	6.1 ± 2.9[a]
	LF 1562	15						3.9 ± 3.4
[77]	LC 1288	13	34	0/100	30	4	100	3.0 ± 1.5[a]
	LF 1243	13						1.1 ± 2.1
[100]	LC 1529	20	41	25/75	32	10	80	7.0 ± NA
	LF 1447	20	43	20/80	32		75	6.8 ± NA
[84]	LC 1474	24	48	17/83	33	12	86	8.0 ± 2.9
	LF 1443	22	51	23/77	33		79	6.7 ± 3.3

Data expressed as mean ± S.D.
[a] Significantly different from LF group.

tion in body fat with preservation of lean body mass [37—39].

Mechanism of effects

There have been several mechanisms proposed by which ketogenic low-carbohydrate diets may induce weight loss. Some of the initial weight loss is due to a diuresis, both as a result of glycogen depletion and ketonuria, which increases renal sodium and water loss [40]. Around 100 g of glycogen is stored in the liver, and 400 g in muscle, each gram of which is stored with approximately 2 g of water [40]. It has also been hypothesised that ketones suppress appetite [41—43], and that KLC diets may have a ''metabolic advantage'' by necessitating increased gluconeogenesis (less energy efficient than glycolytic pathways), and up-regulating mitochondrial uncoupling proteins with a resultant wasting of ATP as heat [44]. Other postulated mechanisms including limitation of food choices [41,45], reduced palatability of low-carbohydrate diets [42], the satiating effect of relatively high-protein intake [41,42,46], increased thermogenic effect of protein [47], increased adipose tissue lipolysis as a result of reduced circulating insulin levels [48], and increased fatty acid oxidation [42], apply to low-carbohydrate diets in general, not specifically those which induce ketosis.

A systematic review of low-carbohydrate diets concluded that weight loss is associated with restriction of calorie intake, longer diet duration and higher baseline body weight, but not with reduced carbohydrate content [17].

Do ketones suppress hunger?

Although it has been widely stated that ketogenic diets suppress hunger, there is conflicting evidence regarding this in the published literature.

Intracerebroventricular 3HB infusion decreases food intake in rats [49], and reduced hunger was seen in human subjects on KLC diets compared with LF diets by several groups [50,51].

In contrast, several authors have found no difference in reported hunger in subjects on KLC diets compared with baseline [52,53] or eucaloric non-ketogenic diets [7].

Two separate studies comparing KLC diets with minimally ketogenic, calorie-reduced diets also found no difference in hunger between groups [23,54]. In one study, reported hunger in all groups was significantly lower than at baseline, and the authors raised the possibility that the ketosis experienced by all groups exceeded a threshold level necessary for hunger reduction [23].

Other medical conditions

Apart from their use in the treatment of refractory paediatric epilepsy, regarding which there is a large body of literature, case reports and pilot studies have reported on the beneficial effect of KLC diets in several conditions including type 2 diabetes [55,56], polycystic ovary syndrome [57], non-alcoholic fatty liver disease [58], gastro-oesophageal reflux [59] and narcolepsy [60]. In addition, it has been hypothesised that mild ketosis may be beneficial in certain cancers and neurodegenerative conditions including Alzheimer's and Parkinson's diseases [61], and because of its effects on glucose, lipids and obesity, a KLC diet may be an ideal tool in the treatment of the metabolic syndrome [62].

Safety

Short-term

Minor adverse effects are commonly reported in studies of ketogenic diets for weight loss. In a study comparing KLC with LF diets in 119 obese adults, minor adverse effects were more common on the KLC diet. Significant differences included constipation (68% vs. 35%), headache (60% vs. 40%), halitosis (38% vs. 8%), muscle cramps (35% vs. 7%), diarrhoea (23% vs. 7%), general weakness (25% vs. 8%) and rash (13% vs. 0%) [26].

Another study found impairment in a neuropsychological test requiring higher order mental processing and flexibility in subjects on a 28-day ketogenic compared with a non-ketogenic very-low-energy diet, which was worst within the first week of the diet [63].

There have been case reports of serious adverse events occurring in adults on KLC diets including acute pancreatitis [64], exacerbation of panic disorder [65], severe metabolic acidosis [66,67], and severe hypokalaemia [68], possibly associated with sudden cardiac death in a 16-year-old dieter [69].

Studies of the ketogenic diet in children with epilepsy have found a high incidence of similar adverse effects, along with additional effects such as dehydration, electrolyte disturbances, infections, haematological disorders and hepatitis [70—72]. It is important to emphasise the different composition of the ketogenic diet for the treatment of paediatric epilepsy, and the greater frequency of ill-health, significant co-morbidities and polypharmacy in this group compared with those using a ketogenic diet for weight loss. Certain anti-epileptic medications have been reported to interact with the ketogenic diet, contributing to adverse effects [70,72].

Long-term

Most of the available information regarding long-term safety of ketogenic diets regards their use in paediatric epilepsy. Very few studies have examined the effects of ketogenic diets for greater than 12 months in adults.

Although it has been reported that low-carbohydrate diets are at risk of being nutritionally inadequate, and may lack in fibre, thiamine, folate, potassium, calcium, magnesium, iron and vitamins A, E and B6 [73], the nutritional adequacy of the diet will depend on several factors, including its overall composition, the nutrient sources, the degree of carbohydrate restriction and the diet duration. A study by Stock and Yudkin found that a 2-week low-carbohydrate diet (containing 67 g/day carbohydrates) did not result in a reduced average intake of vitamins A, C, D or B-group vitamins. Furthermore, they found that the nutrient value of the low-carbohydrate diet was generally appreciably higher than would have been achieved with a diet equivalent in calories with a restriction in all macronutrients [29]. In this study, however, the authors assumed that the subjects' carbohydrate intake would be sufficient to prevent ketosis. There are no studies which examine the nutritional adequacy of ketogenic low-carbohydrate diets specifically.

Cardiovascular risk

The effect of KLC diets on lipid profile and cardiovascular risk has been frequently studied, as there has been concern that the often increased intake of animal fats may counteract the beneficial effects of weight loss.

A 2003 systematic review found no adverse effects on any serum lipid parameters, blood pressure or fasting glucose in adults on diets containing less than 60 g/day carbohydrate [17], although the analysis was complicated by the heterogeneity and paucity of studies, particularly those evaluating the use of the diet for >90 days.

A 56-week study of a KLC diet in obese men who lost 26% of their body weight found significant decreases total cholesterol, LDL and triglycerides and an increase in HDL [74]. Beneficial changes were greater in subjects with hyperlipidaemia at baseline.

In studies comparing KLC and LF diets, it has consistently been found that KLC diets are associated with a greater reduction in triglycerides and increase (or less of a decrease) in HDL (Table 3). The differential effect on lipids appears not to be completely explained by differences in weight loss. Conversely, LF diets generally have a more beneficial effect on LDL levels than KLC diets. In a recent meta-analysis comparing *ad libitum* KLC with LF diets, the weighted mean difference in triglycerides and HDL were −0.25 and 0.12 mmol/L respectively at 6 months and −0.35 and 0.08 mmol/L at 12 months in favour of KLC diets. The difference in LDL was 0.14 mmol/L at 6 months and 0.20 mmol/L in favour of LF diets [33]. In another study, although the overall difference in LDL levels between groups did not reach statistical significance, LDL levels increased by >10% in 8/31 subjects in the KLC group compared with 4/32 in the LF group [75]. The differential effect of diet on LDL levels was particularly notable in studies in which energy intake was controlled (Table 3).

Similarly, in studies of normal-weight subjects in whom only minimal weight loss was seen, small to moderate increases in total cholesterol and LDL were seen in the KLC diet groups. These changes occurred by 3 weeks, and appeared to be returning towards baseline by 6 weeks in at least one study [76]. Significant beneficial effects on HDL and triglycerides were seen on the KLC diets but not the LF diets.

Despite their unfavourable effect on total LDL levels, several studies have found a beneficial effect of KLC diets on lipoprotein subclasses, with a reduction in VLDL [31,77], an increase in large LDL and a reduction in small LDL particles [35,76,78]. Recent evidence suggests that subjects with increased small, dense LDL particles [79,80] (''LDL pattern B'') and large VLDL particles [81] have a higher risk of coronary atherosclerosis. Studies including only female subjects have not found significant changes in LDL size with a KLC diet, which may be due to larger baseline LDL particle size in women [31,77], while a study by Seshadri et al. found generally beneficial effects on lipoprotein subclasses in subjects on both KLC and LF diets [82].

Krauss et al. recently reported that carbohydrate restriction and weight loss resulted in equivalent but non-additive improvements in atherogenic dyslipidaemia. Specifically, reduction in carbohydrate intake from 54% to 26% of energy in an isocaloric diet led to significant reductions in total cholesterol, triglycerides, apo B and total:HDL cholesterol compared with subjects remaining on the 54% carbohydrate diet [83]. Additionally, they demonstrated a linear relation of carbohydrate intake to the prevalence of LDL pattern B. In this study, the degree of carbohydrate restriction was modest, and would not be expected to result in ketosis. Noakes et al. reported no effect of a KLC diet on apo B [84].

Long-term studies of cardiovascular risk in children with epilepsy on high-fat ketogenic diets

Table 3 Effect on lipids: ketogenic low-carbohydrate vs. low-fat diets

Authors	Duration	Diet	Weight loss (kg)	TC, Δ (%)	TG, Δ (%)	HDL, Δ (%)	LDL, Δ (%)
(1) *Ad libitum* LC vs. LF diets							
[45]	6 months	LC	8.5	0	−23[a]	13	−1
		LF	3.9	−1	2	8	−5
[96]	6 months	LC	7.0	2	−15	15[a]	3
		LF	3.1	−2	−8	3	−2
	12 months	LC	4.3	0	−17[a]	11[a]	0
		LF	2.5	−3	1	2	−3
[87]	6 months	LC	5.7	−1	−20[a]	0	4
		LF	1.8	−1	−4	−2	3
[97]	12 months	LC	5.1	3	−29[a]	−3[a]	6
		LF	3.1	−4	3	−12	−3
[37]	3 months	LC	9.9	−2	−40	9	3[a]
		LF	4.1	−9	−5	4	−21
[26]	6 months	LC	12.0	−3	−47[a]	10[a]	1
		LF	6.5	−6	−14	−3	−5
[6]	4 months	LC	9.8	−3	−37	16[a]	−2
		LF	6.1	−4	−10	5	−7
[98]	12 months	LC	4.7	NA	−23	9	1
		LF	2.2	NA	−12	5	1
[75]	6 months	LC	7.1	−5	−40[a]	8[a]	−3
		LF	4.7	−10	−18	−3	−10
[99]	6 months	LC	3.2	0[a]	−7	8[a]	−2
		LF	3.6	−5	−1	−3	−8
	12 months	LC	2.1	−2	−1	7	−5
		LF	3.3	−5	3	−1	−9
(2) Energy-matched LC vs. LF diets							
[35]	6 weeks	LC	6.1	−11	−44[a]	−3	−6[a]
		LF	3.9	−15	−15	−7	−18
[77]	4 weeks	LC	3.0	1[a]	−22	2[a]	5[a]
		LF	1.1	−7	−11	−8	−5
[100]	10 weeks	LC	7.0	1[a]	−29	12[a]	0[a]
		LF	6.8	−27	−25	−15	−31
[84]	12 weeks	LC	8.0	−2	−40[a]	5[a]	5[a]
		LF	6.7	−9	−4	−5	−11
(3) Normal-weight subjects—*ad libitum* diets							
[76]	8 weeks	LC	2.2	5	−33[a]	12	4
		UD	−0.4	−3	−5	0	−5
[31]	4 weeks	LC	1.2	16[a]	−30[a]	32[a]	15[a]
		LF	0.8	−5	4	−8	−5

TC: total cholesterol. TG: triglycerides. HDL: high-density lipoprotein. LDL: low-density lipoprotein. NA: data not available. UD: usual diet.

[a] Significantly different from LF group.

have found significant elevations in total cholesterol, VLDL, LDL, triglycerides and apo B, with reductions in HDL compared to baseline values. Changes are most pronounced at 6 months, but persist at 12 and 24 months [71,85]. There have been reports of development of a prolonged QT interval and dilated cardiomyopathy in children on ketogenic diets [86]. In one patient who discontinued the diet, these cardiac changes resolved.

Some studies [77,87], but not all [35], have shown an improvement in insulin sensitivity in subjects on KLC compared with LF diets, independent of weight loss.

Renal and bone effects

Since dietary carbohydrate restriction often results in increased protein intake, it is difficult to separate the renal and bone effects of KLC diets from the effects of increased dietary protein.

High-protein diets have numerous effects on renal function and bone metabolism, including increased urinary calcium excretion, increased markers of bone resorption without a compensatory increase in markers of bone formation [88,89], increased glomerular filtration rate and renal volume [90], reduced urinary citrate, hyperuricaemia, hyperuricosuria and reduced urinary pH [40]. Many of these changes are exacerbated by dietary carbohydrate restriction [40], and promote nephrolithiasis.

The effect of ketosis independent of high-protein intake is difficult to determine. Johnston et al. found that subjects on a KLC diet had increased urinary calcium excretion at 2 weeks, but not at 6 weeks, compared with those on a non-ketogenic low-carbohydrate diet despite similar protein intake in both groups and significantly higher dietary calcium intake in the non-ketogenic diet group [7]. Many of the urinary changes noted above, as well as an increased risk of nephrolithiasis, are seen in children on ketogenic diets for epilepsy, in whom dietary protein intake is very low [91].

Ketogenic diets high in protein can result in a chronic subclinical metabolic acidosis, which promotes calcium mobilisation from bone [40]. However, compared with diets lower in protein, high-protein diets result in relatively better preservation of bone mineral content during weight loss [92]. A study by Reddy et al. found that the increased urinary calcium excretion induced by a low-carbohydrate high-protein diet was not compensated for by increased intestinal calcium absorption, and markers of bone formation were reduced [89]. Conversely, other studies have demonstrated an increase in intestinal calcium absorption with high-protein diets with no difference in measures of bone resorption, formation or balance [93,94].

A recent study by Carter et al. found no increase in bone turnover markers over 3 months in subjects on a KLC diet compared with controls, despite a significantly greater weight loss in the KLC diet group, which would be expected to increase bone resorption [95].

Conclusions

Ketogenic low-carbohydrate diets have increased in popularity over recent years, but the degree of carbohydrate restriction required to achieve ketosis remains unclear. In general, studies have shown greater weight loss at 3—6 months with KLC diets compared with LF diets, however this difference is no longer apparent at 12 months. The majority of studies have found that KLC diets are associated with favourable changes in triglyceride and HDL levels, but higher LDL levels than LF diets. The long-term effect of KLC diets on renal and bone health is unknown.

Conflicts of interest

None.

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