

Modification of Lipoproteins by Very Low-Carbohydrate Diets¹

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ABSTRACT Very low-carbohydrate diets (VLCDs) are popular, but remain controversial. This review summarizes the latest studies that have examined the effects of VLCDs on lipoproteins and related risk factors for cardiovascular disease. Prospective studies indicate that VLCDs improve the lipoprotein profile independently of weight loss. Although not as effective at lowering LDL cholesterol (LDL-C), VLCDs consistently improve postabsorptive and postprandial triacylglycerols (TAGs), HDL cholesterol (HDL-C), and the distribution of LDL-C subfractions to a greater extent than low-fat diets. VLCDs also improve proinflammatory markers when associated with weight loss. Studies usually report mean lipid responses, but individual data indicate a large degree of variability in the magnitude and in some cases the direction (e.g., LDL-C) of lipoprotein responses to both low-fat and VLCDs. Such variability makes it hard to defend a single diet recommendation, especially considering the potential for low-fat/high-carbohydrate diets to exacerbate TAG, HDL-C, and other characteristics of the metabolic syndrome. Considering the effectiveness of VLCDs in promoting fat loss and improving the metabolic syndrome, discounting or condemning their use is unjustified. We encourage a more unbiased, balanced appraisal of VLCDs. *J. Nutr.* 135: 1339–1342, 2005.

KEY WORDS: • cholesterol • low-carbohydrate diet
• ketogenic • triglycerides • lipoproteins

The aim of this review is to acquaint the reader with the resurgence of scientific papers published recently examining the effects of very low-carbohydrate diets (VLCDS)³ on blood lipoproteins and cardiovascular disease (CVD) risk factors. Despite the number of papers and the consistency of the results, most health practitioners including dietitians are unaware or misinformed on the topic and remain cautious about using VLCDs. VLCDs are discouraged by most professional

organizations (1,2) because they contradict low-fat diets. This review will address whether it is reasonable to consider VLCDs as a dietary option with respect to outcomes related to CVD risk.

Despite government and medical disapproval of carbohydrate restriction, physicians personally use VLCDs at least as much as low-fat diets (3). Surveys indicate that millions of Americans are attempting to limit carbohydrate intake and the best-selling lay diet books have consistently focused on carbohydrate restriction. Interest in VLCDs among the scientific community has lagged behind the public. No formal definition of VLCDs exists, but arbitrary levels are defined as <50 g carbohydrate/d or <10% of total energy (4). Most VLCD studies do not control the amount of cholesterol, fiber, or quality of nutrients (e.g., type of fat). This is important because the effects could be enhanced further if, for example, a VLCD were combined with exercise or fiber-rich foods. Food choices compatible with this level of carbohydrate restriction (e.g., vegetables, beef, poultry, fish, oils, nuts/seeds, salads, cheese) generally result in an intake of ~60–65% fat and 20–25% protein. Nearly all VLCD studies are among free-living subjects; thus actual intakes are variable and dependent on subject preference and compliance. A major point is that VLCDs differ dramatically from current recommendations, and this fact has unnerved many people in the nutrition community.

Single-arm studies in normal-weight men and overweight/obese men and women evaluating the effects of VLCDs on blood lipids have ranged in duration from 1 to 12 mo (5–16). These studies show variable responses in total and LDL cholesterol (LDL-C) that are not explained by weight loss, suggesting a possible genetic explanation. There is a more consistent increase in HDL cholesterol (HDL-C) and decrease in triacylglycerol (TAG), although the magnitude of change is variable across studies. The greatest absolute and relative reductions in TAG occurred when a VLCD was combined with fish-oil supplementation (10,13) or in subjects with elevated TAG (>2.4 mmol/L) (14,16).

More recent prospective studies measured plasma lipid responses in subjects assigned to a VLCD or a low-fat diet (17–32). With 1 exception (22), experimental diets were *hypoenergetic*, involving overweight/obese men and women and ranging in duration from 1 to 12 mo. A common objective was to compare the effects of strict dietary carbohydrate restriction (i.e., Atkins diet) to a more conventional low-fat diet. Because of the free-living nature and lack of quality dietary education and follow-up, the degree of dietary compliance was poor in many studies, particularly as a function of time adhering to the diet intervention. Nevertheless, in all cases, the VLCD was still significantly lower in carbohydrate and higher in fat than the comparison low-fat diet and several studies did indeed achieve levels of carbohydrate < 50 g/d (17,19,22–24,28).

Although the magnitude of lipid responses varied, a notable degree of replication is evident across studies (Fig. 1). In all cases, the VLCD led to greater increases in total cholesterol,

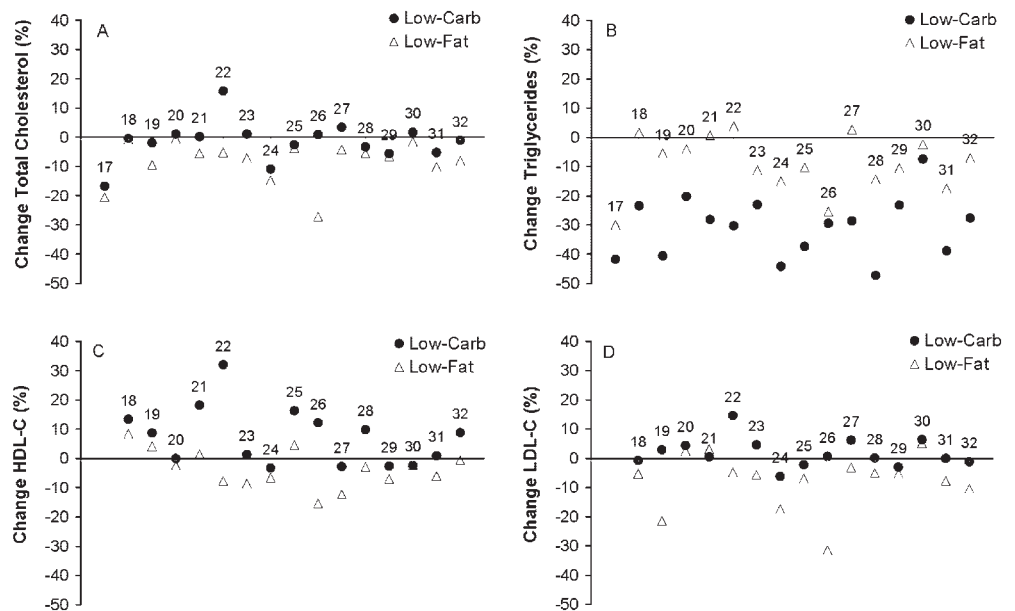
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³ Abbreviations used: apo, apolipoprotein; CETP, cholesterol ester transfer protein; CVD, cardiovascular disease; FA, fatty acid; HDL-C, HDL cholesterol; HL, hepatic lipase; hsCRP, high-sensitivity C-reactive protein; hsIL-6, high-sensitivity interleukin-6; hsTNF- α , high-sensitivity tumor necrosis factor- α ; HSL, hormone-sensitive lipase; LDL-C, LDL cholesterol; LPL, lipoprotein lipase; PL, phospholipids; sICAM-1, soluble intracellular adhesion molecule-1; TAG, triacylglycerol; VLCD, very low-carbohydrate diet.

FIGURE 1 Relative changes in total cholesterol (A), TAG (B), HDL-C (C), and LDL-C (D) in prospective studies comparing VLCDs and low-fat diets. Numbers correspond to studies in the reference list.



LDL-C, and HDL-C, and decreases in TAG. The mean difference between the relative changes in diets was greatest for TAG (22%) followed by HDL-C (11%), LDL-C (9%), and total cholesterol (7%). Although the low-fat diet was better at reducing total and LDL-C, the VLCD did not have a significant adverse effect on LDL-C in any study (defined as <7% increase) with the exception of a 15% increase in a carefully controlled study of normal-weight women who consumed isoenergetic (no change in body weight) VLCDs and low-fat diets in a crossover design (22). Interestingly, the increase in HDL-C with consumption of the VLCD was proportionally larger (+32%), thus lowering the total cholesterol/HDL-C ratio (22). The total cholesterol/HDL-C ratio tends to improve with weight loss; the decrease with consumption of a low-fat diet is driven by a reduction in LDL-C, whereas with consumption of a VLCD, it is due to an increase in HDL-C. The relative benefits of decreasing LDL over increasing HDL-C on mortality are debatable and are influenced by diet-induced modifications of other “emerging” CVD risk factors (i.e., fasting and postprandial TAG, LDL size distribution, LDL oxidation, and inflammatory markers).

The most consistent and predictable lipid change with consumption of a VLCD is a reduction in TAG. The most dramatic reductions are seen in those with moderate hypertriglyceridemia. A remarkable 79% of the variability in TAG response to a VLCD is explained by baseline (prediet) fasting TAG values (Fig. 2) independently of weight loss (10,11,22). Low-fat diets reduce TAG to a small extent during active weight loss, but increase TAG when not associated with significant weight loss or combined with exercise (33).

There is concern that repeated high-fat meals that occur when a VLCD is consumed will lead to enhanced postprandial lipemia (34), which is associated with promotion of an atherogenic environment. However, the degree of postprandial lipemia in response to a fat-rich meal is decreased dramatically after consumption of a VLCD (10,11,22–24,34). We hypothesize that a VLCD, by virtue of lower postprandial lipemia, would prevent postprandial neutral lipid exchange among lipoproteins, formation of small HDL-C particles (removed quickly), small LDL particles that are prone to oxidative modification, and proinflammatory cytokines. We are currently assessing these markers including endothelial function

in ongoing studies in our laboratory in men and women with metabolic syndrome.

There is limited information on the effects of VLCDs on lipoprotein subfractions, oxidative LDL, and inflammatory markers. A predominance of smaller LDL particles has greater atherogenic potential (35). Using a nongradient PAGE procedure to separate LDL-C, we showed repeatedly that a VLCD shifts the particle distribution to a larger size, resulting in significant increases in peak and mean LDL diameter and decreases in the proportion of small, dense LDL particles (11,22,24). This effect is most evident in men and women who start with a predominance of smaller LDL particles (i.e., pattern B). Other studies in patients with CVD and a high prevalence of metabolic syndrome showed similar results using gradient gel electrophoresis (29) and NMR spectroscopy (15,30). A VLCD also increases the distribution of larger HDL particles (15,30), which is believed to be the cardioprotective fraction (36).

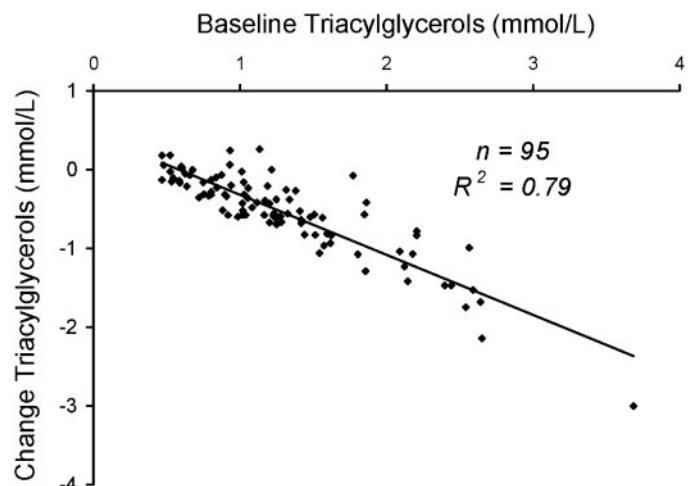


FIGURE 2 Relation between baseline fasting serum TAG and the change in response to a VLCD. Data are from 95 men and women studied in our laboratory.

Based on the lipoprotein findings presented in the above-mentioned studies, we propose a model to explain the modifications in lipoprotein metabolism on a VLCD (Fig. 3). Repeated ingestion of a VLCD initially increases circulating TAG-rich chylomicrons, which are cleared rapidly by lipoprotein lipase (LPL) bound to the luminal surface of capillary endothelial cells in skeletal muscle and adipose tissue. Although speculative, we suggest that a VLCD increases muscle LPL, enhancing TAG clearance. A VLCD leads to lower glucose and insulin levels, which decrease LPL and increase hormone-sensitive lipase (HSL), promoting TAG hydrolysis and increasing fatty acid (FA) rate of appearance. LPL-mediated lipolysis of chylomicrons results in release of FA that is either taken up by the underlying tissue or escapes into the circulation. Any increase in FA delivery to skeletal muscle is balanced by an increase in fat oxidation as evident from the postabsorptive respiratory exchange ratios near 0.7. Circulating FAs are taken up by the liver and preferentially diverted away from esterification to TAG and toward mitochondrial oxidation to acetyl CoA. Accumulation of acetyl CoA exceeding the capacity for mitochondrial oxidation results in the formation of ketones. Reduced hepatic production of TAG results in less VLDL synthesis and secretion into the circulation. LPL-mediated lipolysis of VLDL results in transfer of unesterified cholesterol, phospholipid (PL), apolipoprotein (apo)E, apoC-II, and apoC-III to form mature HDL-C. The remaining remnant particles are either taken up by the liver or converted to LDL. Decreased circulating VLDL, particularly in the postprandial period, results in less cholesterol ester transfer protein (CETP)-mediated neutral lipid exchange with LDL-C. A reduction in hepatic lipase (HL) prevents larger LDL-C from being delipidated to smaller, dense (atherogenic) LDL, resulting in a predominance of larger LDL particles.

A few studies have measured inflammatory markers during consumption of a VLCD. After 24 wk of consuming hypoenergetic diets either low in carbohydrate (Atkins), low in fat, or moderate in protein (Zone), C-reactive protein (CRP) levels fell by 35, 13, and 15%, respectively (31). After a 1-y comparison of 4 popular weight loss diets characterized by low-carbohydrate (Atkins), low-fat (Weight Watchers), ultra low-

fat (Ornish), and moderate-protein (Zone), CRP levels were decreased by 30, 24, 40, and 24%, respectively (32). We reported significant reductions in inflammatory markers after consumption of a VLCD in overweight men (37) and women (unpublished). The changes in high-sensitivity tumor necrosis factor- α (hsTNF- α), interleukin-6 (hsIL-6), CRP, and soluble intracellular adhesion molecule-1 (sICAM-1) after consumption of a hypoenergetic VLCD (-45, -51, -55, and -18%, respectively) did not differ from the low-fat diet (-42, -46, -48, and -20%, respectively) (37). In normal-weight women who consumed an isoenergetic VLCD diet, there were no changes in CRP, IL-6, and TNF- α (22). In a 6-mo weight loss study, CRP levels decreased to a similar extent with consumption of a VLCD (13%) and low-fat diet (7%), but subjects with CRP >30 mg/L at baseline demonstrated a significantly greater decrease with consumption of the VLCD independently of weight loss (30). These data indicate that weight loss is the driving force underlying the reduction in inflammatory markers and not the composition of the diet. A VLCD may be more effective at lowering CRP in high-risk individuals, but this must be confirmed in additional studies.

In conclusion, VLCDs consistently improve postabsorptive and postprandial TAG, HDL-C, and the distribution of LDL-C subclasses (i.e., the dyslipidemia of metabolic syndrome). There is an urgent need for innovative measures to address metabolic syndrome as a growing medical, societal, and economic problem. A primary problem with low-fat/high-carbohydrate diets is that they contribute to carbohydrate-induced hypertriglyceridemia (38), a major problem underlying the metabolic syndrome, challenging the appropriateness of current diet recommendations (39,40). Promotion of a single diet is not justified, given the known variability in response to the same diet. Considering the favorable and consistent outcomes in many carbohydrate-restricted diet studies, we encourage a more unbiased and dispassionate discussion of the relative merits of VLCD by the nutrition and medical communities.

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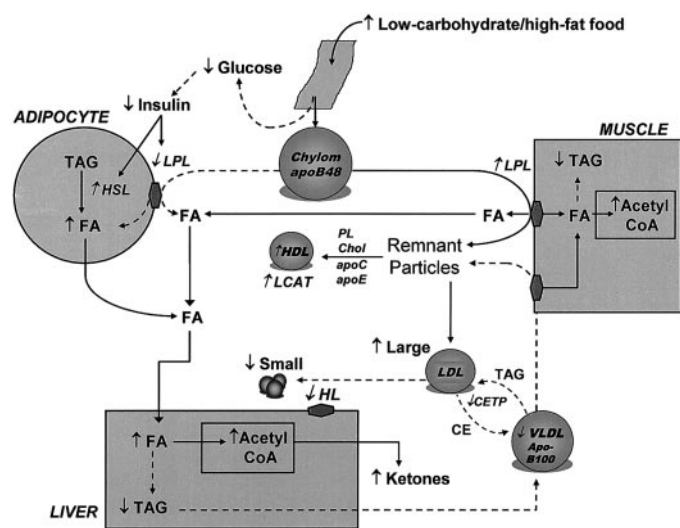


FIGURE 3 Proposed model of lipoprotein metabolism with consumption of a VLCD that explains the observed decrease in TAG, increase in HDL-C, and redistribution of LDL to a larger particle size. Paths upregulated during consumption of a VLCD are represented by solid lines and those downregulated by dashed lines.

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