Cardiovascular and Hormonal Aspects of Very-Low-Carbohydrate Ketogenic Diets

Article *in* Obesity Research · December 2004

DOI: 10.1038/oby.2004.276 · Source: PubMed

CITATIONS
43

READS
654

2 authors:

Jeff S Volek
The Ohio State University
507 PUBLICATIONS **21,723** CITATIONS
SEE PROFILE

Matthew J Sharman
University of Tasmania
150 PUBLICATIONS **4,763** CITATIONS
SEE PROFILE

Cardiovascular and Hormonal Aspects of Very-Low-Carbohydrate Ketogenic Diets

Jeff S. Volek and Matthew J. Sharman

Abstract

VOLEK, JEFF S. AND MATTHEW J. SHARMAN. Cardiovascular and hormonal aspects of very-low-carbohydrate ketogenic diets. *Obes Res.* 2004;12: 115S–123S.

In recent years, restriction of carbohydrate intake for weight loss has become widespread. Our research group began studying physiological responses to very-low-carbohydrate ketogenic diets (VLCKDs) in the late 1990s because we felt there was a significant void in the literature and limited understanding of metabolic responses to VLCKDs. This launched us into a line of research examining the physiological effects of VLCKDs. In this paper, we briefly overview nine studies we have published on isoenergetic and hypoenergetic VLCKDs in men and women. These studies have focused on blood lipid responses to VLCKDs, but we have also addressed changes in body weight, body composition, and hormones. Compared with low-fat diets, short-term VLCKDs consistently result in improvements in fat loss, fasting and postprandial triacylglycerols, high-density lipoprotein-cholesterol, the distribution of low-density lipoprotein-cholesterol subclasses, and insulin resistance. These are the key metabolic abnormalities of metabolic syndrome, a problem of epidemic proportions in the United States. There is substantial variability in total cholesterol and low-density lipoprotein-cholesterol responses to VLCKD. The factors responsible for this variability are not known, and studies designed to identify methods to predict blood lipid responses to VLCKD and other dietary approaches represent critical areas for nutrition researchers. Further research is warranted to validate the physiological effects of VLCKD over longer periods of time, including studies that modify the quality of macronutrients (i.e., the type of fat and protein) and the interaction with other interventions (e.g., exercise, dietary supplements, drugs).

Key words: very-low-carbohydrate diet, blood lipids, ketogenic diet, triglycerides, hormones

Introduction

The popularity of weight-loss diets that limit intake of carbohydrates has increased dramatically in recent years. Very-low-carbohydrate diets (i.e., <50 g/d) result in a metabolic state of ketosis, and these diets are commonly referred to as "ketogenic" diets. Very-low-carbohydrate "ketogenic" diets (VLCKDs)[1] are dramatically different from standard recommendations that focus on restriction of dietary fat and emphasize carbohydrates. A common criticism of VLCKDs has been related to the high total fat, saturated fat, and cholesterol content, and thus, the potential adverse effects on blood lipoproteins and other risk factors for cardiovascular disease and diabetes (1). Although frequently criticized on these grounds, there is little research to support these concerns. Our research group began studying blood lipid and hormonal responses to VLCKDs ~6 years ago because we felt there was a significant void in the literature and widespread misunderstanding with respect to basic physiological adaptations to carbohydrate restriction. This launched us into a line of research examining the physiological effects of VLCKDs, with a focus on how such diets affect weight loss, body composition, hormones, blood lipoproteins, and other risk factors for cardiovascular disease.

This article overviews results from several studies we have conducted in healthy normal weight and overweight men and women. A primary purpose is to provide nutrition scientists, clinicians, and other health professionals with accurate information regarding the expected metabolic, hormonal, and lipoprotein responses to a VLCKD. We hope

Human Performance Laboratory, Department of Kinesiology, University of Connecticut, Storrs, Connecticut.

Address correspondence to Jeff S. Volek, Department of Kinesiology, 2095 Hillside Road, Unit 1110, University of Connecticut, Storrs, CT 06269-1110.

E-mail: jeff.volek@uconn.edu

[1] Nonstandard abbreviations: VLCKD, very-low-carbohydrate ketogenic diet; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; TAG, triacylglycerol; AUC, area under the curve; REE, resting energy expenditure; HOMA, homeostatic model assessment.

Table 1. Daily nutrient intakes in subjects consuming a VLCKD

Nutrient	Study 1/2	Study 3/4	Study 5	Study 6/9	Study 7	Study 8
Energy (kcal)	2112	2335	1793	1855	1288	1542
Protein (g)	147	176	128	130	88	108
Protein (%)	28	30	29	28	28	29
Carbohydrate (g)	39	46	43	36	29	32
Carbohydrate (%)	7	8	10	8	9	9
Fat (g)	151	157	118	130	88	106
Fat (%)	64	61	60	63	63	62
SFA (g)	37	56	41	46	34	38
MUFA (g)	70	57	35	48	29	38
PUFA (g)	24	24	20	20	12	16
Cholesterol (mg)	397	741	650	731	470	593
Alcohol (%)	1	1	1	1	0	0

Studies 1 through 9 refer to those described in the Results section.
SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

this overview of VLCKDs provides a background on which to formulate ideas and testable hypotheses and stimulate further research in this area.

Research Methods and Procedures

With respect to the studies conducted by our research group described in the next section, there are some common elements related to our experimental approach and the nature of the VLCKD intervention used in these studies. The VLCKD was designed to restrict carbohydrates to a level that induces ketosis. To ensure appropriate carbohydrate restriction, subjects monitored their level of ketosis daily using urine reagent strips that produce a relative color change in the presence of one of the primary ketones, acetoacetic acid. We have found this to be a very sensitive indicator of carbohydrate restriction and compliance to the VLCKD. On this basis, all subjects in our studies assigned to the VLCKD were in ketosis for the majority of the experimental period. The macronutrient distribution goals of the VLCKD as a percentage of total energy were ~30% protein, ~60% fat, and <10% carbohydrate. There were no restrictions on the type of fat from saturated and unsaturated sources or cholesterol levels (with the exception of our first experiment described in Study 1). Foods commonly consumed were beef (e.g., hamburger, steak), poultry (e.g., chicken, turkey), fish, vegetable oils, various nuts/seeds and peanut butter, moderate amounts of vegetables, salads with low-carbohydrate dressing, moderate amounts of cheese, eggs, protein powder, and water or low-carbohydrate diet drinks, etc. All subjects received extensive initial instruction (including detailed diet packets) and weekly follow-up dietetic education. Subjects received thorough instructions for completing detailed weighed food records during baseline and various phases of the VLCKD. These food records were subsequently analyzed using regularly updated nutrient analysis software. The actual nutrient composition of the VLCKD consumed in our various studies are presented in Table 1. In each case, carbohydrate intake was <50 g/d and <10% of total energy. Protein intake ranged from 28% to 30% and fat from 60% to 64% of total energy. Energy levels were either assigned to the nearest 837kJ (200 kcal) increment based on resting energy expenditure obtained using indirect calorimetry (for Studies 3 to 9) or the Harris–Benedict equation (for Studies 1 and 2) at the start of the study and appropriate activity factors.

We have implemented experimental measures to control some of the variability that often confounds individual lipoprotein responses to a change in diet composition. In all our studies, by performing blood draws on two separate occasions at each time-point, we controlled day-to-day variability in blood lipids. Physical activity patterns were controlled before and during the experimental period. We obtained blood measures in a fully postabsorptive (fasting) state after a 12-hour overnight fast. All testing for premenopausal women was performed between days 2 and 4 of the follicular phase. In addition to studying fasting blood lipids and hormones, we have also examined postprandial lipid and hormone responses to a fat-rich meal before and after a VLCKD. These oral meal-tolerance tests were conducted after an overnight fast and involved subjects consuming a standardized fat-rich meal, while blood samples were taken at 60-minute intervals for a total of 8 hours after the meal to

assess the level of postprandial lipemia and other metabolites and hormones. Significance was set at $p < 0.05$ for all studies. Following is a brief overview of nine studies we have published or submitted that examined cardiovascular and hormonal aspects of VLCKD.

Results

Study 1: Lipoprotein and Triacylglycerol Responses to a Low-Saturated-Fat VLCKD

Our initial interest was to determine the effects of a VLCKD on blood lipids. Although VLCKDs have been used predominantly for weight-loss purposes, in 2000 we chose to study a group of 10 normal weight, normolipidemic men to isolate the effects of the diet independently of weight loss (2). We also made some modifications to the diet intervention to optimize the lipid responses. In addition to being very low in carbohydrates, we counseled subjects to restrict saturated fat and cholesterol levels and to emphasize monounsaturated fat through generous consumption of olive oil, canola oil, almonds, and lean meats. Subjects were also provided with 2.5 grams of ω3-fatty acids as eicosapentaenoic acid and docosahexaenoic acid. The diet intervention was 8 weeks in duration, and two blood draws were obtained on different days for determination of fasting lipids at 2-week intervals. An oral fat tolerance test was done before and after the VLCKD.

Carbohydrate intake was 7% of total energy, and subjects were successful in keeping saturated fat low (~15% of total energy) despite total fat being very high (64% total energy). We have found it very difficult to counsel subjects to eat enough calories to maintain body weight, presumably because of the inhibitory effects of ketones on appetite (3). Subsequently, there was a gradual loss in body weight over the 8 weeks, averaging ~0.5 kg/wk. Fasting total cholesterol and low-density lipoprotein-cholesterol (LDL-C) transiently increased, peaking at 4 weeks and declining to values not significantly different from baseline after 8 weeks. There was a trend for increased high-density lipoprotein-cholesterol (HDL-C) after 8 weeks ($p = 0.077$). The most consistent effect was a remarkable decrease in fasting triacylglycerols (TAGs), which declined 55% after 8 weeks of the VLCKD. There was a similar decline of 48% in the area under the curve (AUC) for postprandial TAG response to the oral fat tolerance test. These lipid responses were not explained by changes in body weight. This study has shown rather potent TAG-lowering effects of a VLCKD without significant adverse effects on other lipoproteins. However, the independent or combined effects of carbohydrate restriction, the quantity or quality of dietary fat, and the ω3-fatty acid supplementation could not be determined.

Study 2: VLCKD Effects on Testosterone and Insulin

Using the data from the same study, we have reported fasting and postprandial hormonal responses to a VLCKD rich in monounsaturated fat and supplemented with ω3-fatty acids (4). Fasting and postprandial total testosterone, free testosterone, cortisol, leptin, and insulin responses to an oral fat tolerance test were determined before and after the 8-week VLCKD. There were no significant changes in fasting total testosterone, free testosterone, and cortisol, but there were significant decreases in insulin (−28%) and leptin (−64%) concentration after the VLCKD. Postprandial insulin responses immediately after the fat-rich meal were significantly lower after the VLCKD.

Study 3: Serum Biomarkers for Cardiovascular Disease with No Restriction on Saturated Fat Intake

The results of these initial studies stimulated our interest to study further the effects of VLCKDs on blood lipids and hormones. We have conducted another study to validate these findings in a similar group of 12 normal weight, normolipidemic men and 8 control subjects who consumed their normal diet (5). We used the same diet intervention over a 6-week period, except there were no restrictions on the type of fat, and there was no ω3-fatty acid supplementation. Thus, our main dietary aim was to study a free-living VLCKD without any other dietary restrictions. The VLCKD resulted in a similar carbohydrate intake (8% of total energy) and total fat content (61% of total energy) as our initial study, but higher saturated fat (~25% of total energy). We had better success in achieving an isoenergetic diet, but there was still a slight weight loss after 6 weeks (−2.2 kg), again highlighting the difficulty in attaining a true weight-maintenance VLCKD under free-living conditions in healthy normal weight men.

We observed very similar responses in fasting lipids with small but nonsignificant increases in total cholesterol and LDL-C, a strong trend for increased HDL-C ($p = 0.066$), and highly significant decreases in fasting TAGs (−33%) and postprandial lipemia after the fat-rich meal (−29%). Because an increase in LDL-C is generally considered atherogenic, we decided to measure LDL particle size distribution using a polyacrylamide gel electrophoresis procedure. Smaller LDL particles are more atherogenic and associated with higher risk for cardiovascular disease. Individuals with a predominance of smaller LDL particles are classified as pattern B, whereas those with larger particles are pattern A. We observed that, in subjects who started with the smaller pattern B profile, there was a significant increase in mean and peak LDL particle size after the VLCKD. This study has provided evidence that carbohydrate restriction was the driving force behind our lipid results in Study 1 (2) and not the type of fat or the ω3-fatty acid supplementation. This was also the first of our studies to report a beneficial shift in LDL particle size.

Study 4: Body Composition and Hormonal Responses to VLKCD

The few studies that have examined body composition after a VLCKD have reported enhanced fat loss and preservation of lean body mass (6–8). Because insulin and leptin were significantly reduced on a VLCKD and these hormones have a role in regulation of protein and triacylglycerol balance (4), we have decided to look at the effects of VLKCDs on testosterone, cortisol, insulin, leptin, glucagon, thyroid, and insulin-like growth factor-1. The objective was to see whether a VLCKD could alter the hormonal environment and affect protein and lipid kinetics, which over time could lead to decreased fat mass or increased lean body mass.

We have examined the effects of an isoenergetic VLCKD on body composition (assessed using DXA) and fasting hormone concentrations (9). Twelve healthy normal weight men switched from their habitual diet (48% carbohydrate) to a VLCKD for 6 weeks, and eight men served as controls, consuming their normal diet. Body composition and fasting blood samples were assessed before and after the VLCKD. If active, subjects maintained their normal level of physical activity.

Fat mass was significantly decreased (−3.4 kg), and lean body mass was significantly increased (+1.1 kg) after the VLCKD. There was a significant decrease in serum insulin (−34%), and an increase in total thyroxine (+11%) and the free thyroxine index (+13%). Approximately 70% of the variability in fat loss on the VLCKD was accounted for by the decrease in serum insulin concentrations. There were no significant changes in glucagon, total or free testosterone, sex hormone binding globulin, insulin-like growth factor-I, cortisol, or triiodothyronine uptake. Thus, a VLCKD resulted in a significant reduction in fat mass and a concomitant increase in lean body mass in normal weight men, which may be partially mediated by the reduction in circulating insulin concentrations.

Study 5: Improved Lipid Levels with VLCKD Compared with Low-Fat Diet

We have previously reported that a VLCKD favorably affected fasting and postprandial TAGs, LDL subclasses, and HDL-C in normal weight, normolipidemic men (2,5). Whether women experience similar lipid responses was uncertain at that time. Therefore, similar to our studies in normal weight men, we have conducted a VLCKD study in normal weight women to investigate the effects on blood lipids independent of weight loss (10). The experimental approach was a balanced, randomized, two-period, crossover study design. Subjects were 10 healthy, normolipidemic women who consumed two isoenergetic diets: a low-fat (<30% fat) and a VLCKD for 4 weeks each. A 4-week washout period, during which time women consumed their habitual diet, separated the two experimental diets. Two blood draws were performed on separate days at 0, 2, and 4 weeks and an oral fat tolerance test was performed at baseline and after each feeding period. In addition to measuring blood lipids, we also assessed several biomarkers of inflammation in fasting blood.

Compared with the low-fat diet, the VLCKD resulted in significant increases in fasting serum total cholesterol (16%), LDL-C (15%), and HDL-C (33%), and significant decreases in serum TAGs (−30%), total cholesterol to HDL-C ratio (−13%), and postprandial lipemia (−16%). These responses were similar in direction to our studies in normal weight men but higher in magnitude. Unlike our response in men, there were no significant changes in LDL size, but this was likely because of the larger LDL particle sizes in these women at the start of the diet. There were no significant changes in serum oxidized LDL or markers of inflammation (i.e., C-reactive protein, interleukin-6, tumor necrosis factor-α) after either the low-fat diet or the VLCKD. We also measured several hormones including insulin, glucagon, free thyroxine, free triiodothyronine, cortisol, and insulin-like growth factor-1 (unpublished results). The only hormone to be significantly affected by the VLCKD was glucagon, which was raised by 16%.

Study 6: Lipids and Lipemic Response in Overweight Men

Our work up to this point had attempted to determine blood lipid responses to isoenergetic VLCKDs in normal weight men and women to control for the confounding effect of weight loss on these measures. Because most people initially try VLCKDs with the goal of weight loss, we next examined the effects of hypoenergetic VLCKDs in overweight men. We studied 15 overweight/obese men who consumed two experimental hypoenergetic (a deficit of 500 kcal/d) diets for 6-week periods: a VLCKD and a low-fat (<30% fat) diet (11). The diets were consumed in a balanced and randomized fashion. Two fasting blood draws were performed on separate days, and an oral fat tolerance test was performed at baseline and after each diet period.

The VLCKD and low-fat diet had the same effect on total cholesterol (−11% and −15%, respectively) and HDL-C (−3% and −7%, respectively). The VLCKD resulted in a greater decrease in TAGs (−44%) than the low-fat diet (−15%). Serum LDL-C was significantly reduced only after the low-fat diet (−18%), but there was no difference in oxidized LDLs after either diet. Postprandial lipemia was significantly reduced on both diets compared with baseline, but the reduction was significantly greater after the VLCKD (−38%) compared with the low-fat diet (−19%). Mean and peak LDL particle size increased only after the VLCKD; 75% of the subjects classified as pattern B switched to pattern A after the VLCKD.

Study 7: VLCKD Effects on Lipids, LDL Subclasses, and Insulin Resistance in Overweight Women

Using the same experimental approach as Study 6, we have compared the effects of a VLCKD and a low-fat diet on fasting blood lipids, LDL subclasses, postprandial lipemia, and insulin resistance in overweight/obese women. We have studied 13 moderately overweight women who consumed both a hypoenergetic (deficit of 500 kcal/d) VLCKD and a low-fat (<30% fat) diet in a balanced and randomized fashion (12). The diets were ~4 weeks in duration, so that blood draws could be performed at the same time of the menstrual phase. Two fasting blood draws were performed on separate days, and an oral fat tolerance test was performed at baseline and after each diet.

The low-fat diet significantly reduced total cholesterol, LDL-C, and HDL-C compared with the VLCKD. The VLCKD was more effective than the low-fat diet at lowering fasting TAGs (−23 vs. −11%) and postprandial lipemia (−29 vs. −24%), but these were not statistically significant. There were no significant differences in oxidized LDL responses, nor were there any differences in LDL subclass distribution, although all but one subject was classified as pattern A at baseline. Fasting glucose, insulin, and insulin resistance were all significantly lower after the VLCKD compared with the low-fat diet.

Study 8: Weight Loss, Regional Body Composition, and Hormonal Responses in Overweight Men and Women

Although controversial, a number of studies have shown that VLCKDs are associated with greater weight loss than low-fat diets (13). An equally important question also relates to the composition of weight loss on a VLCKD. Our prior study in normal weight men (9) has provided some indication of a preferential loss of fat that might be related to hormonal changes, in particular, insulin. We therefore have conducted a study to compare the effects of energy-restricted VLCKDs and low-fat diets on weight loss, body composition, trunk fat mass, and hormonal responses in overweight men and women (14,15). The design was a parallel, randomized, clinical intervention study of an energy-restricted (deficit of 500 kcal/d) VLCKD and low-fat diet (<30% total energy from fat) in 29 healthy overweight/obese men and premenopausal women. We assessed weight loss, whole body and regional composition (by DXA), resting energy expenditure (REE; using indirect calorimetry), and fasting hormone profiles before and after the diet interventions.

Compared with the low-fat diet, the VLCKD diet resulted in significantly greater weight loss (−675 and −1091 g/wk, respectively), total fat loss (−384 and −775 g/wk, respectively), and trunk fat loss (−157 and −505 g/wk, respectively) despite similar energy deficits between diets. There were no significant changes in fasting glucagon, free triiodothyronine, cortisol, or insulin-like growth factor-1. Insulin was significantly ($p < 0.05$) decreased on the VLCKD (−29%) and low-fat diet (−12%). Free thyroxine concentrations significantly ($p < 0.05$) decreased on the VLCKD (−14%) and low-fat diet (−7%). There were greater reductions in leptin after the VLCKD (−50%) than the low-fat diet (−17%). The ratio of leptin/total fat mass also decreased more after the VLCKD (−45%) than the low-fat diet (−21%). REE (kilojoules per day) was significantly decreased after the VLCKD (−4.2%) and low-fat diet (−9.0%). Expressed relative to body mass (kilojoules per kilogram), REE was not significantly affected by the VLCKD (2.3%) or low-fat diet (−5.7%). This study has shown that, compared with a low-fat diet, a VLCKD resulted in 2-fold greater losses in body mass and whole body fat mass and 3-fold greater losses in trunk fat. There were also differences in insulin and leptin responses that were related to the changes in body composition.

Study 9: Weight Loss and Inflammatory Biomarkers in Overweight Men

In recent years, it has become apparent that low-grade vascular inflammation plays a key role in all stages of the pathogenesis of atherosclerosis (15). Weight loss has been shown to improve blood inflammatory markers (17,18); however, it is unknown whether weight-loss diets varying in macronutrient composition differentially affect inflammatory responses. Therefore, the primary purpose of this study was to compare a VLCKD and a low-fat weight-loss diet on inflammatory biomarkers in overweight men (16). In a randomized cross-over design, 15 overweight/obese men consumed two experimental weight-loss diets for two consecutive 6-week periods: a VLCKD and a low-fat (<30% energy fat) diet. There were significant reductions in high-sensitivity tumor necrosis factor-α, high-sensitivity interleukin-6, high-sensitivity C-reactive protein, and soluble intracellular adhesion molecule-1 after the VLCKD (−45%, −51%, −55%, and −18%, respectively) and low-fat diet (−42%, −46%, −48%, and −20%, respectively). There were no significant changes in soluble P-selectin after either diet. These data indicate that weight loss is the driving force underlying the reduction in inflammatory markers and not the composition of the diet.

Discussion

The effects of VLCKDs on blood lipids have been reviewed previously (13,19). Here we emphasize the studies we have conducted and make some general conclusions based on these responses (Table 2). The majority of VLCKD studies have been in subjects who lost weight, and the general response is a minimal reduction in total cholesterol and LDL-C, which has probably been driven primarily by the beneficial effect of weight loss on these lipoproteins (20), because our studies with minimal weight loss show a

Table 2. Description of studies we have conducted examining the effects of VLCKDs on fasting blood lipids and postprandial lipemia

Study	Subjects	Duration (weeks)	Diet	Age (years)	TC (%)	LDL (%)	HDL (%)	TAG (%)	PP TAG (%)
1	Normal weight men	8	VLCKD (MUFA-rich)	26	1.8	10.3	10.0	−54.9	48
3	Normal weight men	6	VLCKD	37	4.7	4.2	11.5	−33.0	29
5	Normal weight women	4	VLCKD	26	15.8*	14.6*	32.0*	30.2*	16.0*
			Low-fat	26	−5.2	−4.8	−7.7	3.8	9.6
6	Overweight men	6	VLCKD	33	−10.9	−6.2*	−3.3	−44.1*	−37.6*
			Low-fat		−14.8	−17.4	−6.6	−15.0	−19.5
7	Overweight women	4	VLCKD	34	1.1*	4.6*	1.3*	−23.0	−28.9
			Low-fat		−7.1	−5.7	−8.6	−11.2	−24.5

*$p = 0.05$ from corresponding change on low-fat diet.
TC, total cholesterol; PP TAG, postprandial TAG AUC; MUFA, monounsaturated fatty acids.

small-to-moderate increase in LDL-C. The increases in total cholesterol and LDL-C on a VLCKD in the absence of weight loss may be transient, with concentrations peaking after 2 to 4 weeks and gradually returning toward baseline levels after 6 to 8 weeks. It should also be noted that a great deal of intersubject variability in total cholesterol responses exist, as shown in Figure 1. The underlying genetic and physiological basis for this variability is unclear, and future research should be directed at understanding these biological factors.

While LDL-C may increase in some people, this must be considered in the context of other changes in lipoproteins and cardiovascular risk factors. The majority of VLCKD studies have shown an increase in HDL-C and improvement in the total cholesterol/HDL-C ratio (13). The response is particularly evident in studies that have reported minimal weight loss. This is probably because active weight loss has been associated with significant reductions in HDL-C (20), at least if induced by a low-fat diet, whereas VLCKDs tend to prevent this decrease.

The most consistent response to a VLCKD is a reduction in TAGs, which is independent of weight loss. The largest reduction in TAGs (−55%) has been seen in healthy men who consumed a VLCKD supplemented with fish oils (2), indicating supplementation may work in concert with carbohydrate restriction to maximize TAG-lowering. Although nearly all subjects experience a reduction in TAGs, those with higher levels seemed to experience the greatest reductions (Figure 2). The TAG response to a meal (i.e., postprandial lipemia) may be more important than fasting TAG levels in terms of risk status (21). In all our studies, we have shown that a VLCKD decreased postprandial lipemia on the order of one-third to one-half with or without weight loss. Again, individuals who exhibit exaggerated postprandial lipemia have the largest improvements after a VLCKD (Figure 3).

Although the significant reductions in fasting and postprandial TAGs and the increases in HDL-C in response to VLCKDs are favorable in terms of coronary artery disease risk, the moderate increases in LDL-C in some people could be interpreted as unfavorable. However, there appear to be changes in the size and composition of LDL-C that may counteract any adverse effects. Distinct LDL subclasses can be separated out based on their diameter, which range in size from ~21.8 nm for the small dense LDL particles to 27.8 nm for the larger more buoyant LDL particles (22). Individuals with a predominance of large buoyant LDL-C have been classified as pattern A, whereas those with a predominance of small dense LDL particles are termed pattern B. The latter pattern is associated with a >3-fold risk of coronary artery disease (23). We have shown that a VLCKD results in increased peak LDL size and shifts in particle distribution from pattern B to pattern A in men. We did not report the same effect in women, but this was likely due to the larger starting particle sizes in the women. Similar to our results with fasting TAG and postprandial lipemia, there was an inverse correlation between baseline LDL size and the change in LDL size in response to a VLCKD (Figure 4), indicating that both men and women who have smaller more atherogenic LDL particles shift to a larger particle distribution in response to a VLCKD. This is supported by the study by Hays et al, who have shown that a VLCKD results in significantly increased mean LDL size

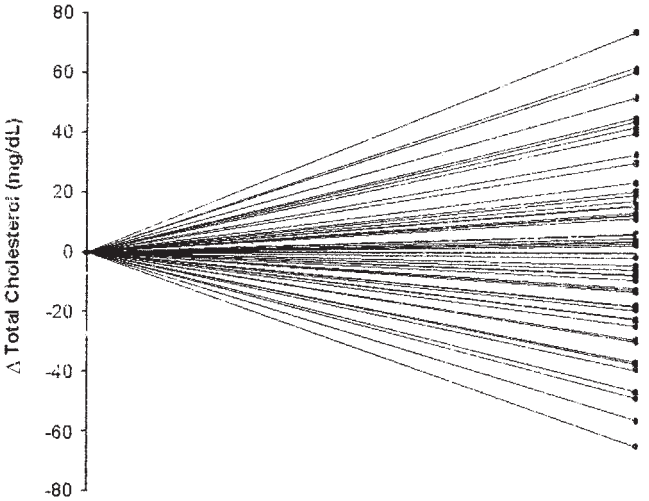

Figure 1: Individual total cholesterol responses to a VLCKD. Subjects include normal weight men [1,3], normal weight women [5], overweight men [6], and overweight women [7].

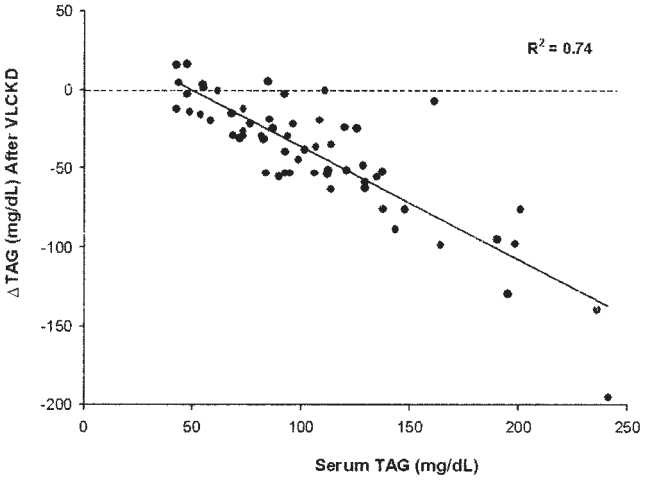

Figure 2: Relationship between baseline fasting serum TAGs and the change in TAGs in response to a VLCKD. Subjects include normal weight men [1,3], normal weight women [5], overweight men [6], and overweight women [7].

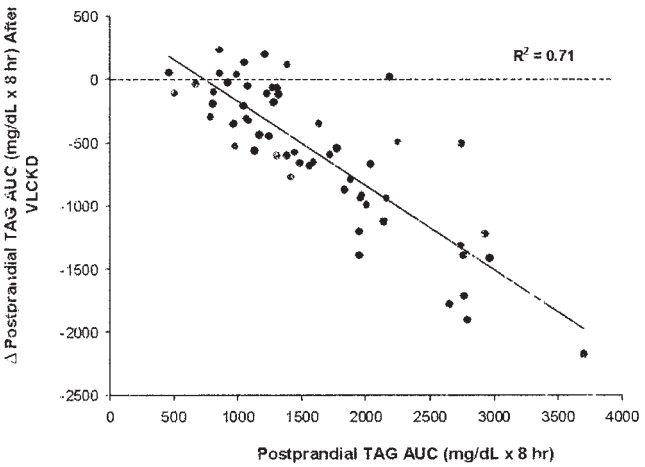

Figure 3: Relationship between baseline postprandial TAGs AUC to an oral fat tolerance test and the change in postprandial TAGs AUC in response to a VLCKD. Values represent the integrated area under the 8-hour serum TAG curve. Subjects include normal weight men [1,3], normal weight women [5], overweight men [6], and overweight women [7].

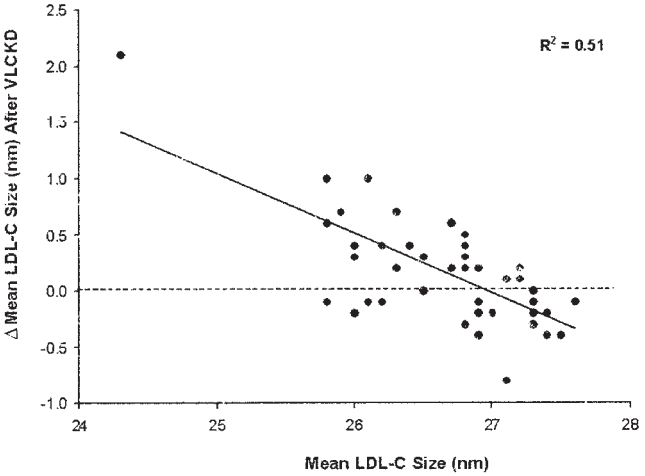

Figure 4: Relationship between baseline mean LDL-C size and the change in mean LDL-C size in response to a VLCKD. Subjects include normal weight men [3], normal weight women [5], overweight men [6], and overweight women [7].

in patients with cardiovascular disease and a high prevalence of metabolic syndrome (24).

Another consistent effect we have seen in our studies is a reduction in fasting glucose and insulin, which can be used to calculate the level of insulin resistance using the homeostatic model assessment (HOMA) technique (25). In our studies, insulin resistance assessed using HOMA has tended to improve with the VLCKD, especially in those who exhibited low levels of insulin sensitivity (Figure 5). This is consistent with other work examining VLCKDs using the insulin-clamp technique (26). Thus, the concern that VLCKDs might induce insulin resistance because of the high saturated fat content has not been supported by published data; in fact, the research supports a possible beneficial effect (26,27).

The greater reduction in body mass and fat mass we have observed during a VLCKD (12) is consistent with several recent clinical studies (13,19). Although the reason for this beneficial effect is speculative, our research has indicated that hormonal adaptations may play a role, in particular the reduction in insulin. Adipose tissue lipolysis is exquisitely sensitive to insulin at physiological concentrations (28). Small-to-moderate decreases in insulin can increase lipoly-

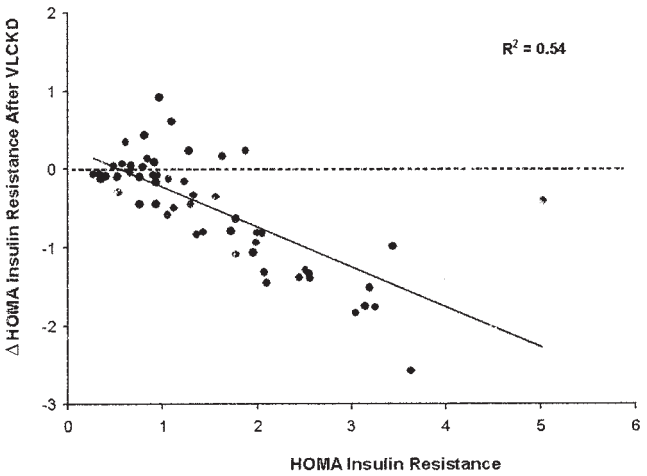

Figure 5: Relationship between baseline insulin resistance and the change in insulin resistance in response to a VLCKD. Insulin resistance was calculated by the HOMA using the formula: glucose (mmol/liter) + [insulin (mU/liter)/22.5] [17]. Subjects include normal weight men [2,4], normal weight women [5], overweight men [6], and overweight women [7].

sis several-fold, the response being virtually immediate. Insulin also stimulates lipogenesis by increasing glucose uptake and activating lipogenic and glycolytic enzymes (29).

As seen in Figures 2 to 5, people with elevated fasting TAGs, exaggerated postprandial lipemia, a predominance of small LDL-C, and a tendency toward insulin resistance respond in a positive manner to a VLCKD. These are the primary metabolic problems characteristic of the metabolic syndrome, which is a highly prevalent multifaceted clustering of cardiovascular disease risk factors, with key features of insulin resistance and dyslipidemia (increased TAGs, decreased HDL-C, and predominance of small LDL-C) (30). Ironically, low-fat diets tend to worsen many of the features of metabolic syndrome, which has prompted concern regarding the value of low-fat diets for people with these characteristics (31,32). Other features of metabolic syndrome include central obesity and chronic inflammation (33). Our data has shown that VLCKD enhance total fat loss and may preferentially target central fat stores when compared with low-fat diets. We have also shown inflammatory markers improve with weight loss. Thus, we propose that VLCKD may be particularly suitable for preventing and treating metabolic syndrome, which currently is estimated to afflict one-quarter of adults >20 years of age and 40% of subjects >40 years of age in the United States (34).

The duration of our interventions was short (4 to 8 weeks), and it is unknown whether the changes in lipids and other outcomes would persists over longer periods of time. The studies were also conducted on relatively small samples of healthy volunteers. Although we have assessed a large number of risk factors related to CHD and diabetes, we have not assessed other important clinical end-points, such as renal function or bone health. We encourage further work to address a broad spectrum of clinical end-points in diverse healthy and clinical populations for longer periods of time.

In summary, as the number of people following a VLCKD increases, there is a greater need to understand the underlying cardiovascular and metabolic aspects of these diets. Our work over the last 5 years has indicated that short-term VLCKDs are associated with improvements in a number of cardiovascular disease risk factors, in particular, those associated with the metabolic syndrome. These have included favorable affects on whole body and central fat loss, fasting and postprandial TAGs, HDL-C, LDL-C subclass distribution, and insulin resistance, suggesting that carbohydrate restriction could be a viable approach for preventing and treating the metabolic syndrome. We are currently pursuing the effects of VLCKDs on many standard and novel risk factors for cardiovascular disease in men and women with the metabolic syndrome in our laboratory.

Acknowledgments

Dr. Volek has received research support from the Robert C. Atkins Foundation.

References

1. **Blackburn GL, Phillips JC, Morreale S.** Physician's guide to popular low-carbohydrate weight-loss diets. *Cleve Clin J Med.* 2001;68:761–74.
2. **Volek JS, Gómez AL, Kraemer WJ.** Fasting and postprandial lipoprotein responses to a low-carbohydrate diet supplemented with ω-3 fatty acids. *J Am Coll Nutr*. 2000;19:383–91.
3. **Arase K, Fisler JS, Shargill NS, York DA, Bray GA.** Intracerebroventricular infusions of 3-OHB and insulin in a rat model of dietary obesity. *Am J Physiol*. 1988;255:R974–81.
4. **Volek JS, Gómez AL, Love DM, Avery NG, Sharman MJ, Kraemer WJ.** Effects of a high-fat diet on postabsorptive and postprandial testosterone responses to a fat-rich meal. *Metabolism*. 2001;50:1351–5.
5. **Sharman MJ, Kraemer WJ, Love DM, et al.** A ketogenic diet favorably affects serum biomarkers for cardiovascular disease in normal-weight men. *J Nutr*. 2002;132:1879–85.
6. **Young CM, Scanlan SS, Im HS, Lutwak L.** Effect on body composition and other parameters in obese young men of carbohydrate level of reduction diet. *Am J Clin Nutr*. 1971; 24:290–6.
7. **Benoit FL, Martin RL, Watten RH.** Changes in body composition during weight reduction in obesity. *Ann Intern Med*. 1965;63:604–12.
8. **Willi SM, Oexmann MJ, Wright NM, Collop NA, Lyndon L.** The effects of a high-protein, low-fat, ketogenic diet on adolescents with morbid obesity: body composition, blood

chemistries, and sleep abnormalities. *Pediatrics*. 1998;101: 61–7.
9. **Volek JS, Sharman MJ, Love DM, et al.** Body composition and hormonal responses to a carbohydrate-restricted diet. *Metabolism*. 2002;51:864–70.
10. **Volek JS, Sharman MJ, Gómez AL, Scheett TP, Kraemer WJ.** An isoenergetic very low-carbohydrate diet is associated with improved serum high-density lipoprotein cholesterol (HDL-C), total cholesterol to HDL-C ratio, triacylglycerols, and postprandial lipemic responses compared to a low-fat diet in normal weight, normolipidemic women. *J Nutr*. 2003;133: 2756–61.
11. **Sharman MJ, Gómez AL, Kraemer WJ, Volek JS.** Comparison of a very low-carbohydrate and a low-fat diet on fasting lipids and postprandial lipemic responses in overweight men. *Metabolism*. 2004;134:880–5.
12. **Volek JS, Sharman MJ, Gómez AL, et al.** Comparison of a very low-carbohydrate and low-fat diet on fasting lipids, LDL subclasses, insulin resistance, and postprandial lipemic responses in overweight women. *J Am Coll Nutr*. 2004;23:177–84.
13. **Volek JS, Westman EC.** Low carbohydrate weight-loss diets revisited. *Cleve Clin J Med*. 2002;69:849–62.
14. **Volek JS, Sharman MJ, Gómez AL, et al.** Comparison of an energy-restricted very low-carbohydrate and low-fat diet on weight loss, regional body composition and hormonal responses in overweight men and women. *Nutr Metab.* (in press).
15. **Blake GJ, Ridker PM.** Inflammatory bio-markers and cardiovascular risk prediction. *J Intern Med*. 2002;252:283–94.
16. **Sharman MJ, Volek JS.** Weight loss leads to reductions in inflammatory biomarkers independent of diet composition in overweight men. *Clin Sci.* 2004;107:365–9.
17. **Heilbronn LK, Noakes M, Clifton PM.** Energy restriction and weight loss on very-low-fat diets reduce C-reactive protein concentrations in obese, healthy women. *Arterioscler Thromb Vasc Biol*. 2001;21:968–70.
18. **Ito H, Ohshima A, Inoue M, et al.** Weight reduction decreases soluble cellular adhesion molecules in obese women. *Clin Exp Pharmacol Physiol*. 2002;29:399–404.
19. **Westman EC, Mavropoulos J, Yancy WS, Volek JS.** A review of low carbohydrate ketogenic diets. *Curr Atherosclerosis Rep*. 2003;5:476–83.
20. **Dattilo AM, Kris-Etherton PM.** Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. *Am J Clin Nutr*. 1992;56:320–8.
21. **Patsch JR, Miesenbock G, Hopferwieser T, et al.** Relation of triglyceride metabolism and coronary artery disease: studies in the postprandial state. *Thrombosis*. 1992;12:1336–45.
22. **Krauss RM, Burke DJ.** Identification of multiple subclasses of plasma low density lipoproteins in normal humans. *J Lipid Res*. 1982;23:97–104.
23. **Austin MA, King MC, Vranizan KM, Krauss RM.** Atherogenic lipoprotein phenotype. A proposed genetic marker of coronary heart disease risk. *Circulation*. 1990;82:495–506.
24. **Hays JH, DiSabatino A, Gorman RT, Vincent S, Stillabower ME.** Effect of a high saturated fat and no-starch diet on serum lipid subfractions in patients with documented atherosclerotic cardiovascular disease. *Mayo Clin Proc*. 2003;78: 1331–6.
25. **Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC.** Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28:412–9.
26. **Bisschop PH, de Metz J, Ackermans MT, et al.** Dietary fat content alters insulin-mediated glucose metabolism in healthy men. *Am J Clin Nutr.* 2001;73:554–559.
27. **Cutler DL, Gray CG, Park SW, Hickman MG, Bell JM, Kolterman OG.** Low-carbohydrate diet alters intracellular glucose metabolism but not overall glucose disposal in exercise-trained subjects. *Metabolism*. 1995;44:1264–70.
28. **Jensen MD, Caruso M, Heiling VJ, Miles JM.** Insulin regulation of lipolysis in nondiabetic and IDDM subjects. *Diabetes*. 1989;38:1595–601.
29. **Kersten S.** Mechanisms of nutritional and hormonal regulation of lipogenesis. *EMBO Rep*. 2001;2:282–6.
30. **Haffner S, Taegtmeyer H.** Epidemic obesity and the metabolic syndrome. *Circulation*. 2003;108:1541–5.
31. **Katan MB, Grundy SM, Willet WC.** Should a low-fat, high-carbohydrate diet be recommended for everyone? Beyond low-fat diets. *N Engl J Med*. 1997;337:563–6.
32. **Kris-Etherton PM, Taylor DS, Zhao G.** Is there an optimal diet for the hypertriglyceridemic patient? *J Cardiovasc Risk*. 2000;7:333–7.
33. **Sakkinen PA, Wahl P, Cushman M, Lewis MR, Tracy RP.** Clustering of procoagulation, inflammation, and fibrinolysis variables with metabolic factors in insulin resistance syndrome. *Am J Epidemiol*. 2000;152:897–907.
34. **Ford ES, Giles WH, Dietz WH.** Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA*. 2002;287: 356–9.