Effect of a low-carbohydrate, ketogenic diet program compared to a low-fat diet on fasting lipoprotein subclasses ☆

Eric C. Westman [a,*], William S. Yancy Jr.[a,b], Maren K. Olsen [b,c], Tara Dudley [b], John R. Guyton [a]

[a] *Department of Medicine, Duke University Medical Center, Durham, NC, USA*
[b] *Center for Health Services Research in Primary Care, Department of Veterans' Affairs Medical Center, Durham, NC, USA*
[c] *Department of Biostatistics and Bioinformatics, Duke University Medical Center, Durham, NC, USA*

Abstract

Background: Low-carbohydrate, ketogenic diets (LCKD) are effective for weight loss, but concerns remain regarding cardiovascular risk. The purpose of this study was to determine the effect of an LCKD program on serum lipoprotein subclasses.
Methods: This was a randomized, two-arm clinical trial in an outpatient research clinic involving overweight, hyperlipidemic community volunteers motivated to lose weight. Subjects were randomized to either an LCKD ($n = 59$) and nutritional supplementation (including fish, borage and flaxseed oil), or a low-fat, reduced-calorie diet (LFD, $n = 60$). The main outcomes were fasting serum lipoprotein subclasses determined by nuclear magnetic resonance analysis.
Results: The mean age of subjects was 44.9 years, the mean BMI was 34.4 kg/m^2, and 76% were women. Comparing baseline to 6 months, the LCKD group had significant changes in large VLDL (-78%), medium VLDL (-60%), small VLDL (-57%), LDL particle size ($+2\%$), large LDL ($+54\%$), medium LDL (-42%), small LDL (-78%), HDL particle size ($+5\%$), large HDL ($+21\%$), and LDL particle concentration (-11%). Compared with the LFD group, the LCKD group had greater reductions in medium VLDL ($p = 0.01$), small VLDL ($p = 0.01$) and medium LDL ($p = 0.02$), and greater increases in VLDL particle size ($p = 0.01$), large LDL ($p = 0.004$), and HDL particle size ($p = 0.05$).
Conclusions: The LCKD with nutritional supplementation led to beneficial changes in serum lipid subclasses during weight loss. While the LCKD did not lower total LDL cholesterol, it did result in a shift from small, dense LDL to large, buoyant LDL, which could lower cardiovascular disease risk.
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1. Introduction

Recent research implicates dietary carbohydrates, especially refined carbohydrates, as a risk factor for cardiovascular disease [1]. In recent studies, a low-carbohydrate, ketogenic diet (LCKD) led to weight loss and improvements in high-density lipoprotein cholesterol (HDL-C) and serum triglyceride over a 6- to 12-month period [2–5]. Because obesity, low HDL-C, and elevated triglyceride are recognized as cardiovascular risk factors, and can be made worse by a low-fat/high-carbohydrate diet [6–8], an LCKD might be a candidate treatment for these conditions.

However, the LCKD does not uniformly reduce low-density lipoprotein cholesterol (LDL-C) [9,10], the principal target in treatment guidelines for atherosclerosis prevention [11]. A more detailed cardiovascular risk assessment can be made by lipoprotein subclass analysis. Recent evidence suggests that small, dense LDL particles and large very low-

* Corresponding author. Duke University Medical Center, Box 50, Suite 200-B Wing, 2200 West Main Street, Durham, NC 27705, USA. Tel.: +1 919 416 5242; fax: +1 919 286 6758.
E-mail address: ewestman@duke.edu (E.C. Westman).

density lipoprotein cholesterol (VLDL) particles correlate with atherosclerotic diseases [12–15]. The relationship between large VLDL and small LDL may explain why elevated serum triglyceride is predictive of coronary heart disease [8].

This paper reports the changes in lipoprotein subclasses in subjects enrolled in a randomized trial comparing an LCKD program to a low-fat, low-calorie diet (LFD) for weight loss over a 6-month period.

2. Materials and methods

The main results from this study have been published previously [16]. In brief, healthy individuals motivated to lose weight were recruited from the community for a study of dietary treatments for obesity and hyperlipidemia. Subjects were required to be aged 18–65 years, have a body mass index from 30 to 60 kg/m^2, have LDL-C >130 mg/dl or triglyceride >200 mg/dl, and have no serious medical condition. One hundred and nineteen subjects were randomized to a low-carbohydrate, ketogenic diet (initially <20 g of carbohydrate/day) and nutritional supplements, or a low-fat, low-calorie diet [17,18]. Subjects returned for group meetings on a bi-weekly basis for 3 months, then monthly for 3 months.

After fasting overnight, blood was collected at baseline, then 6, 12, and 24 weeks after starting the diet for serum total cholesterol, HDL-C, and triglyceride by standard automated enzymatic methods [19]. LDL-C was calculated if the triglyceride was not higher than 400 mg/dl [20].

Plasma samples were collected in EDTA tubes for the lipoprotein subclass analysis. Samples were refrigerated a maximum of four days and sent for nuclear magnetic resonance (NMR) assay testing (LipoScience, Inc., Raleigh, NC). This assay measures the distinctive NMR signals broadcast by lipoprotein subclass particles of different size [21]. The measured amplitudes of these signals give the subclass concentrations. The following subclasses, with subpopulation designation and estimated diameter ranges, were quantified: large VLDL (V6, V5; 60–200 nm), medium VLDL (V4, V3; 35–60 nm), small VLDL (V2, V1; 27–35 nm), intermediate density lipoprotein (23–26.9 nm), large LDL (L3; 21.3–23 nm), medium LDL (L2; 19.8–21.2 nm), small LDL (L1; 18.3–19.7 nm), large HDL (H5, H4, H3; 8.2–13 nm), small HDL (H2, H1; 7.3–8.1 nm). From the initial 15 subclass concentrations, weighted-average VLDL, LDL, HDL particle sizes (nm) and LDL particle concentration (nmol/L) were calculated.

All available data, including from subjects who discontinued the study early, were used for analyses by employing linear mixed-effects models [22]. The models included fixed and random effects to calculate expected mean values at each time point and to test hypotheses of group differences. The time-by-group interaction was treated as a categorical variable while an unstructured covariance accounted for the

within-patient correlation over time. A p value of <0.05 was considered statistically significant. Analyses were performed using SAS Statistical Software, Version 9.1 (SAS Institute Inc., Cary, NC). Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Duke University Health System human research committee. Duke University investigators conducted the trial and retained exclusive control of the data, analyses, and manuscript.

3. Results

Of the original 119 participants, 118 had lipoprotein subclass testing performed at least once and were included in these analyses. Baseline characteristics were similar between groups, while weight loss at 6 months was greater in the LCKD group than in the LFD group (Table 1). In a sample of LCKD subjects ($n=13$), the estimated daily diet composition was 1475 kcal, 97.4 g fat, 36.5 g saturated fat, 14.8 g polyunsaturated fat, 34.4 g monounsaturated fat. In a sample of LFD subjects ($n=9$), the estimated daily diet composition was 1590 kcal, 54.3 g fat, 16.6 g saturated fat, 11.2 g polyunsaturated fat, 17.9 g monounsaturated fat.

3.1. Enzymatically determined lipids

Analysis of within-group changes from baseline to 6 months revealed that the LCKD led to a reduction in triglyceride and an increase in HDL-C, whereas the LFD led to reductions in fasting serum total cholesterol and triglyceride (Table 2). In comparisons between groups, the LCKD group had statistically greater improvements in triglyceride and HDL-C ($p<0.05$).

3.2. NMR-determined lipoprotein subclasses

Within-group comparisons from baseline to 6 months showed significant changes in fasting lipoprotein subclasses

Table 1
Baseline subject characteristics

Characteristic	Low-carbohydrate ketogenic diet program ($n=59$)	Low-fat diet ($n=60$)
Age (years)	44.2 (10.1)	45.6 (9.0)
Gender, female	75%	78%
Race		
Caucasian	75%	78%
African-American	22%	18%
College degree	56%	63%
BMI (kg/m^2)	34.6 (4.9)	34.1 (5.1)
Body weight (kg)	97.8 (15.0)	96.8 (19.2)
Weight loss at 6 months (kg)	− 12.0 (0.9)	− 6.5 (0.9)

Values are observed means (S.D.) except weight loss, which is the expected mean (S.E.) determined by a linear mixed-effects model.

Table 2
Mean fasting lipid and lipoprotein levels

Test	Low-carbohydrate ketogenic diet program ($n=59$)					Low-fat diet ($n=60$)					Between group
	Week 0	Week 6	Week 12	Week 24	Difference 0–24	Week 0	Week 6	Week 12	Week 24	Difference 0–24	P value
Enzymatically determined lipids											
Total cholesterol (mg/dl)	244.5	215.7	231.1	236.4	− 8.1	239.9	216.0	228.6	226.2	− 13.7*	0.4
Triglyceride (mg/dl)	157.8	86.4	86.8	83.6	− 74.2**	190.7	171.5	181.8	162.7	− 27.9*	*0.004*
LDL-C (mg/dl)	157.2	143.5	156.2	158.8	1.6	148.0	135.2	139.4	140.6	− 7.4	0.2
HDL-C (mg/dl)	55.4	54.5	57.3	60.9	5.5**	54.1	48.1	50.1	52.5	− 1.6	*<0.001*
NMR-determined lipoprotein subclasses											
VLDL particle size (nm)	49.0	47.8	51.2	56.0	7.0	52.4	51.3	49.9	45.8	− 6.6	*0.01*
Large VLDL (mg/dl)	44.3	5.3	7.9	9.7	− 34.6**	61.8	49.7	44.2	39.2	− 22.6*	0.3
Medium VLDL (mg/dl)	43.4	16.2	16.3	17.3	− 26.1**	51.4	53.1	52.9	43.9	− 7.5	*0.01*
Small VLDL (mg/dl)	31.3	16.3	13.9	13.6	− 17.7**	25.9	21.3	21.9	20.2	− 5.7	*0.01*
Intermediate DL (mg/dl)	1.8	0.4	0.2	0.6	− 1.2	3.6	2.8	1.6	2.3	− 1.3	1.0
LDL particle size (nm)	21.0	21.3	21.5	21.5	0.5**	20.9	20.9	21.1	21.2	0.3*	0.1
LDL particle concentration (nmol/l)	1745	1556	1611	1554	− 192*	1759	1568	1527	1500	− 258**	0.44
Large LDL (mg/dl)	78.2	89.1	123.7	120.1	41.9**	79.5	69.6	78.3	81.2	1.7	*0.004*
Medium LDL (mg/dl)	59.9	62.8	40.2	34.9	− 25.0**	49.4	50.6	49.4	49.5	0.2	*0.02*
Small LDL (mg/dl)	22.3	3.1	3.8	4.9	− 17.4*	28.9	21.6	15.0	9.7	− 19.2**	0.8
HDL particle size (nm)	8.6	8.9	8.9	9.0	0.4*	8.6	8.6	8.7	8.8	0.2**	*0.05*
Large HDL (mg/dl)	23.2	23.5	25.1	28.1	4.9*	21.7	21.0	22.4	25.8	4.1*	0.7
Small HDL (mg/dl)	21.5	22.3	22.1	23.3	1.8*	21.8	21.6	21.9	22.7	0.9	0.4

Values are expected means by linear mixed-effects models analysis. For the low-fat diet group, $n=59$ for the NMR-determined lipid subclass analyses because one subject had no data to contribute to the models.

VLDL = very low density lipoprotein, LDL = low-density lipoprotein cholesterol, HDL = high-density lipoprotein cholesterol.

To convert to SI units, multiply total cholesterol, LDL-cholesterol, HDL-cholesterol (mg/dl) × 0.0259 = mmol/l; multiply triglyceride (mg/dl) × 0.0113 = mmol/l.

* $p < 0.05$, within-group changes from baseline to 6 months.

** $p < 0.001$, within-group changes from baseline to 6 months.

for both groups (Table 2). For the LCKD group, there were changes in large VLDL (− 78%), medium VLDL (− 60%), small VLDL (− 57%), LDL particle size (+2%), LDL particle concentration (− 11%), large LDL (+54%), medium LDL (− 42%), small LDL (− 78%), HDL particle size (+5%), large HDL (+21%), and small HDL (+8%). For the LFD group, there were significant changes from baseline to 6 months in large VLDL (− 37%), LDL particle size (+1%), LDL particle concentration (− 15%), small LDL (− 66%), HDL particle size (+2%), and large HDL (+19%).

Between-group comparisons showed differences in VLDL subclasses and LDL subclasses, but not HDL subclasses, LDL particle concentration, or LDL particle size. While both groups showed a reduction in overall triglyceride (VLDL) by the enzymatic determination, the reduction was greater in the LCKD group. Moreover, using NMR determination, the LCKD group had significantly greater reductions in medium VLDL ($p=0.01$) and small VLDL ($p=0.01$) concentrations, and an increase in VLDL particle size ($p=0.01$) as compared with the LFD group (Table 2). For LDL, there were significant differences between groups for large LDL and medium LDL, but not for small LDL. The large LDL increased 54% in the LCKD group, but did not change significantly in the LFD group (between-group comparison: $p=0.004$). The medium LDL decreased 42% in the LCKD group, but did not

change in the LFD group (between-group comparison: $p=0.02$).

4. Discussion

In this controlled trial over a 6-month period, an LCKD with nutritional supplementation led to greater reductions in serum triglyceride and associated VLDL subclass levels, and a greater increase in HDL-C compared with an LFD. There were similar reductions between the two diets in small LDL subclass levels and LDL particle concentrations, although the LCKD led to a comparatively greater increase in large LDL and a greater decrease in medium LDL. The effects of both diets appeared favorable.

The reduction in VLDL particles is consistent with the decrease in serum triglyceride levels observed in previous studies of an LCKD [2–5,23–25]. In other studies of the LCKD to examine lipoprotein subclasses, a similar reduction in VLDL subclasses and small LDL, and elevation of large LDL was seen [26–29]. While the LCKD appears effective for treating hypertriglyceridemia, individuals with fasting chylomicronemia (serum triglyceride usually >800 mg/dl) should be treated with a low-fat diet [30].

The LCKD group also experienced an increase in HDL-C, occurring concurrently with weight loss. With low-fat,

reduced-calorie diets, HDL-C generally decreases during active weight loss, and then increases again during weight stabilization [31]. As we did not follow participants beyond the period of active weight loss, it is uncertain how HDL-C, or other lipoprotein classes, would be affected when body weight is stable. However, one other study suggests that an elevation in HDL-C and reduction in triglyceride and small LDL subclasses may occur on an LCKD after only mild weight loss (−2.2 kg) [28].

Several studies have shown the small LDL subclass level and the LDL particle concentration to be highly predictive of progression of coronary artery disease [32–36]. In one study, a small LDL level >30 mg/dl was associated with a nine-fold increased risk of CAD progression. While there is general agreement that a reduction in small LDL is favorable, it is not yet known if a shift from small to large LDL, as was seen on the LCKD, is entirely favorable [15]. However, niacin therapy, which has had beneficial effects in outcomes studies, also has led to a shift from small to large LDL [37].

Triglyceride is increasingly thought to be important in the pathogenesis of atherosclerosis, and treatments that lower triglyceride and raise HDL-cholesterol have been shown to reduce major coronary events [38,39]. High triglyceride levels promote the formation of small LDL by a process of cholesterol ester/triglyceride exchange and subsequent lipase action on triglyceride-enriched LDL [40]. Small HDL appear to be formed by a similar process and are then cleared from the circulation more rapidly than large HDL [41]. Based on the findings of this study, the reduction of dietary carbohydrate should be evaluated as a treatment for hypertriglyceridemia, low HDL-C, and ultimately atherosclerosis.

It is possible that the nutritional supplements given only to the LCKD group enhanced compliance or improved the metabolic effects of the LCKD. While the supplements contained omega-3 fatty acids, which are known to lower triglyceride and slightly raise HDL-C and LDL-C, the amount in the supplements (1200 mg each per day of flaxseed oil and fish oil) was lower than the doses recommended for triglyceride-lowering purposes (3000–9000 mg) [42].

We conclude that an LCKD with nutritional supplementation led to greater reductions in triglyceride and VLDL subclass levels, and greater increases in HDL-C and large LDL level compared with a low-fat, reduced calorie diet over a 6-month period. Because these changes in cardiovascular risk factors appear favorable on balance, the LCKD merits further evaluation in longer-term outcome studies.

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