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The effects of a low-carbohydrate versus low-fat diet on adipocytokines in severely obese adults: three-year follow-up of a randomized trial

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Abstract. – *Background:* **Adipocytokines are associated with insulin resistance and cardiovascular disease and can be modified with weight loss. While we previously demonstrated weight loss and a reduction in leptin in obese adults who followed a low-carbohydrate diet for 6 months, the long-term effects of this diet on adipocytokines are unknown.**

Methods: **132 obese adults with a body mass index of ≥ 35 kg/m^2 were randomized to receive one year of dietary counseling to follow either a low-carbohydrate diet < 30 g/day (LC) or a caloric-restricted diet (reduced by 500 calories/day with < 30% of calories from fat) (LF). Weight, leptin, adiponectin, TNF-alpha, CRP, and insulin were measured at 0, 6, and 36 months (24 months post-counseling). Follow-up data at was collected for 53 participants who returned at 36 months.**

Results: **Mean weight change from baseline was not different between the groups at 36 months. Between 6 and 36 months weight was unchanged for LF, while LC appeared to regain weight [+ 4.84 ± 35.6 kg (+ 3.0%)]. This difference, however, was not significant (p = 0.08). Leptin was unchanged in LF at both 6 and 36 months. In LC leptin decreased by 8.49 ± 6.4 ng/mL or 22.7% at 6 months (p < 0.001) and increased by 10.68 ± 25.2 ng/mL or 41.9% between 6 and 36 months (p = 0.02). There were no differences in insulin, adiponectin, TNF-alpha, or CRP between the groups.**

Conclusions: **Favorable changes in leptin that accompany weight loss are not sustained in individuals who followed a low-carbohydrate diet for one year. A low-carbohydrate diet had no significant effect on insulin, adiponectin, TNF-alpha, or CRP compared to a low-fat diet at 36 months.**

Key Words:

Obesity, Diet, Low-carbohydrate, Adipocytokines, Leptin.

Introduction

The rise in the prevalence of obesity has resulted in an increased incidence of co-morbidities[1]. Efforts to address this growing problem include a number of dietary interventions with wide variation in macronutrient content. Low-carbohydrate diets, in particular, have risen in popularity in the last several years. Randomized studies by our group and others have shown some short-term metabolic advantages of a low-carbohydrate diet[2-5]. Specifically, these studies show decreases in insulin resistance that may be independent of weight loss compared to levels observed with conventional low-fat diets[4].

Adipocyte-derived hormones also known as adipocytokines are believed to play a role in insulin sensitivity[6]. These include leptin and TNF-alpha which are both elevated in obesity and adiponectin which is reduced in abdominal obesity[6,7]. These adipocytokines have also been associated with cardiovascular disease[8-10]. C-reactive protein (CRP) is an additional inflammatory marker that, although not produced by adipocytes, is also elevated in obesity and associated with cardiovascular disease[11,12]. Prior studies have demonstrated favorable changes in adipocytokines and CRP with weight loss[13-16]. While we previously demonstrated weight loss and a reduction only in leptin in obese adults who followed a low-carbohydrate diet for 6 months, the long-term effects of this diet on adipocytokines are unknown. In this study, we attempted to determine the trends in adipocytokines and

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CRP two years post formal education of either a low-carbohydrate or low-calorie, low-fat diet.

Methods

Subjects

The design of this study has been previously reported[4]. Briefly, 132 obese adults with a body mass index of > 35 kg/m^2 were enrolled at the Philadelphia Veterans Affairs Medical Center. 78 subjects returned for follow-up at 6 months and 88 subjects returned at 36 months. Complete adipocytokine/CRP data was available for 53 participants at 3 years (patients who presented for baseline, 6 months and 36 months visits). The study included adults 18 years of age and older with a body mass index (BMI) of > 35 kg/m^2. Individuals with serum creatinine > 1.5 mg/dL, hepatic disease, severe life-limiting medical illness, inability to self-monitor glucose levels, active participation in weight loss program or use of weight loss medications were excluded. The protocol was approved by the Institutional Review Board at the Philadelphia Veterans Affairs Medical Center, and all participants provided informed written consent.

Intervention

Participants were randomized to either a conventional low-fat diet (LF) or a low-carbohydrate diet (LC). The two groups met initially in 4 weekly dietary counseling sessions followed by 11 monthly sessions. Those in the conventional group were instructed to reduce daily caloric intake by 500 calories, with less than 30% of calories derived from fat. Participants on the low-carbohydrate diet were instructed only to restrict carbohydrate intake to < 30 g/day. Data used in this study was from the start of the study two years after completion of the intervention.

Measurements

Data collected at enrollment, 6 months, and 36 months included weight, medical history (self-reported), medication use (self-reported), fasting glucose (Beckman Coulter, Inc, Fullerton CA) and insulin (Radioimmunoassay, Laboratory Corporation of America, Raritan, NJ). Weights were measured on a single-calibrated scale (SRScales™, SR Instruments Inc., Tanawanda, NY). Insulin resistance was estimated using the Homeostasis Model Assessment (HOMA) index: [fasting insulin (μU/mL) x fasting glucose (mmol/L)]/22.5. Serum leptin concentration was measured at baseline and 6 months using an enzyme immunoassay (Cayman Chemical Co., Ann Arbor, Michigan). Leptin concentrations at 36 months were measured using a radioimmunoassay (Linco Research, St Charles, MO). Serum adiponectin was measured by radioimmunoassay (Linco Research, St. Charles, MO). TNF-alpha was measured by R&D Systems Quantikine® highly-sensitive enzyme immunoassay human kit (Minneapolis, MN). HsCRP was measured using an immunoturbidometric assay (Wako Pure Chemical Industries, Ltd., Richmond, VA) run on a Cobas Fara II analyzer (F. Hoffman-La Roche Ltd. Diagnostics, Basel Switzerland).

Data on dietary consumption were collected by interview at baseline, 6 and 36 months. These data were recorded and analyzed using Nutribase nutrition management software (CyberSoft, Inc., Phoenix, AZ).

Statistical Analysis

Statistical analysis was performed on complete adipocytokine data collected for 53 participants who returned for a visit at 36 months. Patients who were lost to follow-up were not considered as the goal of the study was to determine the effects of the diet on adipocytokine concentrations. A separate analysis of baseline measurements of body mass and glycemic indices was performed to compare these subjects to those lost to follow-up to account for any differences which may have existed. Skewness and kurtosis was determined for each variable. Nonparametric calculations were used, where the Mann-Whitney U test was used to compare variables between groups, while the Wilcoxon W was used to test for within group differences in the measurements of interest. Statistical significance was indicated by a p value of < 0.05. All analyses were performed using SPSS 12.0 (SPSS Inc., Chicago, IL).

Results

Baseline Characteristics

Data for 26 low-fat and 27 low-carbohydrate dieters were analyzed in this study. Of these individuals, 9 patients in each group reported a history of diabetes. There were 3 women in the LF group and 6 women in the LC group. The groups did not differ significantly at baseline in BMI, fasting glucose and insulin levels, HOMA-IR, or adipocyte hormones. In addition, the use of medications for treatment of diabetes and hyperlipidemia was not different between the groups at the start of the study. There were no differences in baseline BMI, fasting glucose, insulin, or HOMA between subjects who had complete adipocytokines/CRP information available and those where information was missing at 6 or 36 months.

Changes in Dietary Intake

Total caloric intake and macronutrient content were not different between the two groups at baseline (Table II). There was no change in total caloric intake within either the LF group ($p = 0.65$) or LC group ($p = 0.28$). Comparison of the change in caloric intake between the groups was not significant ($p = 0.16$). Mean change in carbohydrate calories at 36 months was –50.6 kcal for low-fat participants ($p = 0.42$) and –333.9 kcal for low-carbohydrate participants ($p = 0.04$). However, the decrease in carbohydrate calories was not significantly different between the two groups ($p = 0.23$).

Changes in absolute caloric and percentage of protein intake were not significant. While absolute caloric intake of fat did not change over 36 months, the LC group increased percentage fat intake ($p = 0.04$), but this was not significantly different than in the LF group ($p = 0.17$).

Changes in Weight, Insulin, Leptin, Adiponectin, TNF-alpha and CRP

Although we previously reported greater weight reduction at 6 months in patients who followed a LC diet as compared to a LF diet, mean weight change from baseline was not different between the groups at 36 months [136.3 ± 26 kg to 130.6 ± 29 kg for LF ($p = 0.13$)] and [131.5 ± 21 kg to 126.0 ± 23 kg for LC ($p = 0.13$)]. Between 6 and 36 months weight was unchanged for LF, while LC appeared to regain weight [+4.84 ± 36 kg (+3.0%)]. This difference, however, was not significant ($p = 0.09$) (Table III).

Insulin levels increased in both groups over 36 months. However, between group compar-

Table I. Baseline characteristics.

Characteristics	Conventional diet N = 26	Low-carbohydrate diet N = 27
Age (y)	55 ± 10	54 ± 10
Sex	23 M/3 F	21 M/6 F
BMI (kg/m2)	43.2 ± 7.2	43.4 ± 6.7
Diabetes mellitus (%)	35	33
Sulfonylurea (%)	11.5	11.1
Metformin (%)	11.5	14.8
Rosiglitazone (%)	3.8	0
Insulin (%)	3.8	7.4
Glucose (mg/dL)	125.2 ± 50.2	108.2 ± 25.8
Insulin (uIU/mL)	23.8 ± 20.2	22.1 ± 13.5
HOMA index	9.1 ± 11.6	5.7 ± 3.6
CAD (%)	11.5	11.1
Hyperlipidemia (%)	57.7	55.6
Statin (%)	46.2	40.7
Gemfibrozil (%)	3.8	3.7
Niacin (%)	3.8	3.7

There were no differences in baseline characteristics between groups.

Table II. Comparison of diet composition at 36 months.

	Low-fat			Low-carbohydrate		
	Baseline	36 months	p-value	Baseline	36 months	p-value
Total Kcal	1922 ± 827	1940 ± 885	0.65	2103 ± 1057	1940 ± 885	0.28
Kcal Protein	284 ± 134	374 ± 183	0.09	360 ± 214	347 ± 179	0.51
Kcal Carbohydrate	1007 ± 562	893 ± 522	0.42	1057 ± 619	777 ± 484	0.04
Kcal Fat	646 ± 376	658 ± 459	0.41	700 ± 491	825 ± 454	0.57
% Protein	16 ± 6	20 ± 8	0.12	17 ± 8	19 ± 8	0.24
% Carbohydrate	51 ± 14	47 ± 39	0.38	51 ± 18	39 ± 7	0.01
% Fat	33 ± 11	32 ± 13	0.95	32 ± 14	42 ± 9	0.04

P-values are for within group comparison. Between group comparisons were not significant.

ison was not significant ($p = 0.3$). TNF-alpha concentrations were decreased for both low-fat and low-carbohydrate dieters. Again, comparison of these changes between groups was not significant ($p = 0.59$). Neither group experienced a change in serum hs-CRP or adiponectin.

Despite a decrease in leptin in low-carbohydrate dieters over 6 months [32.99 ± 12.2 ng/mL to 25.50 ± 13.8 ng/mL ($p < 0.001$)], serum concentration increased from 6 to 36 months [+10.68 ± 25.2 ng/mL ($p = 0.02$)] (Figure 1). Comparison of leptin concentration at 36 months to that at baseline yielded no difference [+3.29 ± 26.2 ng/mL ($p = 0.42$)]. Leptin concentration in low-fat dieters was unchanged over both 6 months [31.72 ± 11.1 to 29.73 ± 12.9 ng/mL ($p = 0.07$)] and 36 months

Table III. Change in weight, glycemic indices, and adipocyte hormones at 36 months.

	Change from baseline		Change from 6 months	
	N = 53	P-value	N = 53	P-value
Weight (kg)				
Low-fat	-4.24 ± 12.1	0.13	-0.05 ± 10.4	0.13
Low-carbohydrate	-4.04 ± 12.7	0.14	4.84 ± 16.2	0.09
Insulin, (µU/mL)				
Low-fat	8.99 ± 30.4	0.02	3.20 ± 43.4	0.05
Low-carbohydrate	8.99 ± 17.3	0.004	15.42 ± 19.6	< 0.001
*Glucose, (mg/dL)**				
Low-fat	-15.29 ± 86.3	0.17	-5.96 ± 77.6	0.62
Low-carbohydrate	6.68 ± 34.8	0.22	18.95 ± 32.7	0.002
Adiponectin, (µg/mL)				
Low-fat	-1.10 ± 12.5	0.90	-0.61 ± 12.6	0.09
Low-carbohydrate	0.19 ± 10.4	0.89	-2.04 ± 14.7	0.87
CRP, (mg/dL)				
Low-fat	1.92 ± 5.1	0.37	2.33 ± 5.5	0.12
Low-carbohydrate	0.90 ± 5.1	0.35	1.54 ± 4.8	0.13
TNF-alpha, (pg/mL)				
Low-fat	-0.03 ± 0.6	< 0.001	-0.27 ± 0.7	0.08
Low-carbohydrate	-0.22 ± 0.8	< 0.001	-0.18 ± 0.8	0.24

P-values listed above are for within group comparisons. *Between group comparisons were not significant with the exception of change in glucose from 6 to 36 months ($p = 0.02$).

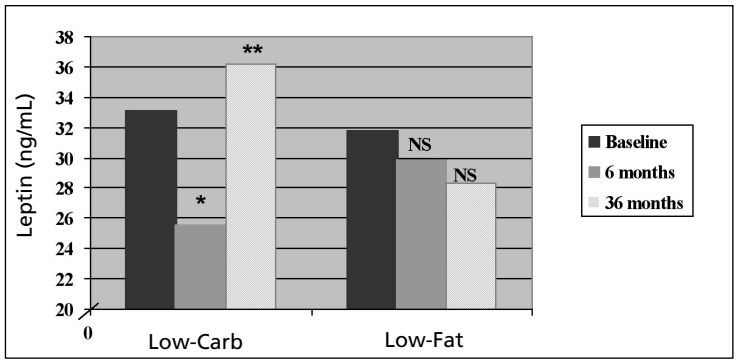

Figure 1. Mean leptin concentration over 36 months. *$P < 0.001$ for within group comparison between baseline and 6 months. **$P = 0.02$ for within group comparison between 6 and 36 months.

[–3.4 ± 12.7 ng/mL ($p = 0.27$)]. There was also no difference between 6 and 36 months [–1.38 ± 12.9 ng/mL ($p = 0.89$)] in this group. Between group comparison of changes at 36 months were not significant ($p = 0.63$).

Discussion

This is the first study to demonstrate the long-term changes in serum adipocytokines concentration due to 12 months intervention with low-fat and low- carbohydrate diets. While we have previously reported beneficial changes in leptin in patients who followed a low-carbohydrate diet for six months, our current findings suggest that these changes are short lived and are not sustained over time. The consumption of carbohydrates at 36 months continues to be reduced in LC participants as compared to their baseline intake. However, there are no differences in macronutrient content or total caloric intake when the low-carbohydrate participants are compared to their conventional diet counterparts 2 years after completion of structured counseling sessions. Similarly, patients maintained most of the weight loss that was observed within 6 months. A number of studies have demonstrated a decline in leptin levels with weight loss[16-18]. Wing et al. reported a 29% reduction in leptin in obese patients who lost 10% of initial weight after dietary intervention[17]. Wadden et al. described short term reduction in leptin due to caloric restriction and a long term decrease in the hormone due to weight loss in obese women who participated in a weight loss program[16,19]. We previously found a greater absolute decrease in leptin concentration in severely obese patients who followed a low carbohydrate diet relative to those who followed a conventional low-fat diet for 6 months even while controlling for weight loss[19].

A meta-analysis of weight loss studies found that obese individuals maintained a reduced weight of about 3% below initial body weight at 5 years[20]. Recognizing the challenge of weight loss maintenance for obese patients, it is important to know if the beneficial changes in adipocytokine levels seen in response to dietary interventions are sustained over time. Few investigators have explored longitudinal changes in leptin with weight regain. Lazzer et al. followed a small group of obese adolescents enrolled in a 9-month multidisciplinary weight reduction program and reported a 70% decline in leptin levels immediately after intervention[15]. Leptin levels increased, but did not return to baseline during the 4-month follow-up period. Mavri et al. reported a reduction in leptin levels with weight loss after a 12-week dietary intervention and an increase in those who regained weight 5 months later[21]. A third study evaluated leptin concentrations pre-diet and at 5 years in overweight adults who had experienced significant weight loss[22]. Both weight and leptin were similar at baseline and 5 years. The change in leptin at the time of weight loss, however, was not reported.

Our results are able to uniquely trace the changes in adipocytokine levels over time in response to 2 different short-term dietary interventions. While short-term beneficial changes in leptin were seen with weight loss in patients who followed a low-carbohydrate diet, it does not appear that these changes are sustained as patients regain weight over time

following the intervention. These findings provide important information about the role of low-carbohydrate diets in modifying certain cardiovascular risk factors. The West of Scotland Prevention Study (WOSCOPS) has shown that higher leptin concentrations are an independent risk factor for coronary artery disease[23], and the early reduction in leptin levels previously reported was thought to be advantageous[19]. Our current findings suggest that this benefit does not persist as patients are followed over time.

Adiponectin, TNF-alpha, and C-reactive protein are also associated with cardiovascular disease[9,11,24,25], and favorably modified with weight loss[14,25-27]. We previously found no improvement in adiponectin or TNF-alpha at 6 months with either diet[19]. We did, however, report a modest decrease in CRP with both diets[28]. There was no significant improvement in adiponectin or CRP for either low-carbohydrate diet or conventional low-fat diet participants at 36 months. There was a very slight improvement in TNF-alpha for both groups of dieters, although the magnitude of the change is very small and the clinical significance of this finding is uncertain. In addition, there was no difference in TNF-alpha between the groups over time. Other investigators who have explored the effects of weight loss on adipocytokines and CRP have had variable results. Favorable increases in adiponectin levels have been demonstrated with weight loss[14]. Obese subjects who lose more than 10% of their BMI are known to increase their adiponectin to a significant extent[7]. There is no known relationship, however, between adiponectin and macronutrient content[29]. Other investigators who have explored the effects of weight loss on adipocytokines and CRP have had variable results. Favorable decreases in CRP without changes in TNF-alpha have been reported in obese patients who underwent bariatric surgery[30,31]. Similar results were reported in obese postmenopausal women who lost weight after 6 months of diet and exercise[32]. In a lengthier study, Marfella et al. reported reductions in both CRP and TNF-alpha in obese premenopausal women who lost weight after one year of multidisciplinary intervention[33].

Our study has several limitations. The generalizability of the results is limited by the predominantly male subject population. A large proportion of patients was lost to follow-up. While 132 subjects were initially randomized, only 88 patients returned for follow-up at 36 months. Of these patients, baseline, 6 month, and 36 month serum was available for only 53 participants. This high dropout rate is commonly seen in studies of dietary intervention. However, there were no baseline differences in terms of BMI, insulin and other clinical parameters between subjects who returned for follow-up and those who did not. We also could not account for the presence of comorbidities, particularly inflammatory conditions, which may have influenced the concentrations of the markers we examined.

In conclusion, we have shown that although severely obese individuals following a low-carbohydrate diet for one year substantially lower serum leptin concentration at 6 months, they are unable to maintain this beneficial change over time. With weight regain leptin levels return to baseline at 36 months. In addition, we found no changes in other adipocyte-derived inflammatory markers including adiponectin, TNF-alpha, and hs-CRP which are associated with cardiovascular disease. Future studies that compare the effect of low-carbohydrate and conventional low-fat diets on cardiovascular outcomes may provide additional valuable information about their impact on obesity-associated morbidity.

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