Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 56 (2007) 58–67
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Effects of a carbohydrate-restricted diet with and without supplemental soluble fiber on plasma low-density lipoprotein cholesterol and other clinical markers of cardiovascular risk

Richard J. Wood[a,*], Maria Luz Fernandez[a], Matthew J. Sharman[b], Ricardo Silvestre[b], Christine M. Greene[a], Tosca L. Zern[a], Sudeep Shrestha[a], Daniel A. Judelson[b], Ana L. Gomez[b], William J. Kraemer[b], Jeff S. Volek[b]

[a]*Department of Nutritional Sciences, University of Connecticut, Storrs, CT 06269-4017, USA*
[b]*Department of Kinesiology, Human Performance Laboratory, University of Connecticut, Storrs, CT 06269, USA*

Received 26 April 2006; accepted 18 August 2006

Abstract

Carbohydrate-restricted diets (CRDs) promote weight loss, reductions in plasma triacylglycerol (TAG) levels, and increases in high-density lipoprotein cholesterol (HDL-C) levels but may cause undesirable low-density lipoprotein cholesterol (LDL-C) responses in some people. The objective of the present study was to determine the effect of adding soluble fiber to a CRD on plasma LDL-C and other traditionally measured markers of cardiovascular disease. Using a parallel-arm, double-blind, placebo-controlled design, 30 overweight and obese men (body mass index, 25-35 kg/m^2) were randomly assigned to supplement a CRD with soluble fiber (Konjac-mannan, 3g/d) (n = 15) or placebo (n = 15). Plasma lipids, anthropometrics, body composition, blood pressure, and nutrient intake were evaluated at baseline and at 6 and 12 weeks. Compliance was excellent as assessed by 7-day weighed dietary records and ketonuria. Both groups experienced decreases in ($P < .01$) body weight, percent body fat, systolic blood pressure, waist circumference, and plasma glucose levels. After 12 weeks, HDL-C and TAG improved significantly in the fiber (10% and −34%) and placebo (14%, −43%) groups. LDL-C decreased by 17.6% ($P < .01$) at week 6 and 14.1% ($P < .01$) at week 12 in the fiber group. Conversely, LDL-C reductions were significant in the placebo group only after 12 weeks (−6.0%, $P < .05$). We conclude that although clearly effective at lowering LDL-C, adding soluble fiber to a CRD during active and significant weight loss provides no additional benefits to the diet alone. Furthermore, a CRD led to clinically important positive alterations in cardiovascular disease risk factors.

1. Introduction

A significant number of studies have pointed to carbohydrate restriction as a very effective option for dieters as shown by greater weight and fat loss [1-3]. However, most professional organizations continue to discourage carbohydrate-restricted diets (CRDs) [4,5] because they are in opposition with current low-fat diet recommendations. In terms of lipoprotein metabolism, more than a dozen clinical studies have shown that CRDs outperform low-fat diets in high-density lipoprotein cholesterol (HDL-C) and triacylglycerol (TAG) responses, but low-fat diets are more effective at lowering low-density lipoprotein cholesterol (LDL-C) [6]. In our prior studies of both normal-weight and overweight men and women [7-10], we have observed a large amount of variability in the LDL-C response to CRDs [11]. One characteristic of CRDs is the relatively low fiber content, especially soluble fiber, which might contribute to the less than optimal LDL-C response. Increasing soluble fiber could reduce the variability and improve plasma LDL-C concentrations.

The incorporation of soluble fiber to a habitual diet has been consistently shown to improve fasting total cholesterol and LDL-C by interfering with cholesterol absorption and/or enhancing biliary cholesterol excretion [12]. Konjac-mannan, a natural constituent of *Amorphophallus konjac* (konjac root), is a highly viscous soluble fiber that has been

* Corresponding author. Tel.: +1 860 486 4795; fax: +1 860 486 3674.
E-mail address: woodR@dom.pitt.edu (R.J. Wood).

0026-0495/$ – see front matter © 2007 Published by Elsevier Inc.
doi:10.1016/j.metabol.2006.08.021

shown to significantly and consistently lower plasma cholesterol when provided at low doses (<4 g/d) [13,14]. Given that CRDs outperform low-fat diets in terms of TAG and HDL-C, but not LDL-C responses, and because soluble fiber specifically targets LDL-C lowering, the primary purpose of this study was to examine the effects of adding soluble fiber to a CRD on plasma lipid profiles. A secondary purpose was to examine the effects of dietary treatment on weight loss, body composition, abdominal fat, insulin, clinical chemistries, and blood pressure. We hypothesized that the addition of soluble fiber to a CRD would reduce LDL-C more than consumption of the CRD with a placebo. In addition, we hypothesized that consumption of a CRD with or without soluble fiber would improve other traditionally measured cardiovascular risk factors including plasma TAG, HDL-C, glucose, and blood pressure. We previously reported findings from this study related to dietary effects on emerging risk factors for cardiovascular disease (CVD) [15] and intravascular processing of lipoproteins [16]. Our initial findings indicated that a CRD favorably impacted lipoprotein subfractions and several emerging risk factors including C-reactive protein, tumor necrosis factor α, and lipoprotein(a) independent of fiber intake. Here we report further details of this intervention in regard to the LDL-C response and features of metabolic syndrome and present individual variation in response to fiber.

2. Subjects and methods

2.1. Materials

The glucomannan and placebo pills were provided by Nutraquest (Manasquan, NJ). Enzymatic cholesterol and TAG kits were from Boehringer-Mannheim (Indianapolis, IN). EDTA, aprotinin, sodium azide, and phenylmethylsulfonyl fluoride were obtained from Sigma Chemical (St Louis, MO). The enzyme-linked immunosorbent assay for plasma insulin determination was obtained from Diagnostic Systems Laboratory (Webster, TX).

2.2. Subjects

Overweight and obese men aged 20 to 69 years, with a body mass index (BMI) of 25 to 35 kg/m^2, were recruited between April and May of 2004. Exclusion criteria included use of lipid-lowering drugs or supplements, adherence to a CRD or weight loss greater than 2.5 kg in the past 6 months, and history of heart disease, diabetes mellitus, or thyroid disease. All subjects were educated about the purpose and risks involved with the study and provided written consent to participate. All study procedures were approved by an institutional review board.

2.3. Experimental design

This was a double-blind, placebo-controlled, parallel-arm study. All researchers administering the interventions and those assessing the outcomes were blinded to group assignment. Thirty men were matched according to BMI and age, then randomly assigned by the researchers to supplement with Konjac-mannan (fiber, n = 15) or placebo (n = 15) while consuming a CRD for 12 weeks. Data were collected at baseline and at 6 and 12 weeks to monitor weight loss, whole-body and regional composition, plasma lipids, total ketones, insulin, clinical chemistries, and blood pressure.

2.4. Diet intervention

After recruitment, all subjects attended a group meeting where registered dietitians provided instructions about how to keep diet records and how to follow a CRD similar to those used in our previous studies [9,17]. Detailed informational handouts were provided to each subject to reinforce the principles covered during the group meeting. To help motivate subjects and monitor compliance, subjects were instructed to assess ketonuria at the same time nightly by using Ketostix reagent strips (Bayer, Elkhart, IN). This test is specific to acetoacetic acid, which causes a relative color change when it reacts with nitroprusside. Adherence to a CRD containing less than 50 g carbohydrate per day generally leads to urinary ketone levels of 0.5 to 2.0 mmol/L, whereas ketoacidosis is considered to occur at levels greater than 7 mmol/L and can reach levels greater than 20 mmol/L in uncontrolled diabetic patients [18].

Design of the diet was such that approximately 60% of total energy was from fat, 30% from protein, and 10% from carbohydrate. No restrictions were given regarding type of fat or amount of dietary cholesterol to be consumed. No guidelines about energy intake were given, and food was not provided to subjects. Examples of foods consumed by the subjects included unlimited amounts of beef, poultry, fish, and eggs, moderate amounts of hard cheeses and low-carbohydrate vegetables and salad dressings, and small amounts of nuts and seeds. Subjects were instructed to restrict fruit and fruit juices, dairy products (with the exception of heavy cream and cheese), bread, pasta, cereal, and desserts. Subjects were instructed to avoid all low-carbohydrate breads and cereals and were limited to a maximum of 2 sugar alcohol–containing low-carbohydrate snacks per day. Before starting the diet, a 5-day weighed food record was completed to assess habitual intake, and 7-day weighed food records were kept during weeks 1, 6, and 12. All diet records were analyzed by using the Nutrition Data System 5.0 (Minneapolis, MN). Subjects were instructed to maintain baseline levels of physical activity throughout the intervention.

2.5. Fiber supplementation

Subjects reported to the laboratory once per week to be weighed and obtain supplement capsules that contained either 500 mg of Konjac-mannan or an equivalent amount of placebo containing maltodextrin. Capsule contents were validated by independent laboratory testing. Subjects were

instructed to take 2 capsules with 8 oz water 30 to 60 minutes before a meal, 3 times daily, for a total consumption of 3 g supplement per day similar to other studies [25,29,31]. Subjects documented consumption to assess compliance. All subjects were also given a generic multivitamin/mineral to be taken every other day to provide micronutrients at levels 100% or less of the recommended dietary allowance (RDA). After the intervention, subjects completed a questionnaire designed by the researchers to evaluate the success of supplement blinding. Subjects completed a written form that allowed them to respond whether they had been treated with fiber or placebo. In addition, subjects completed a written questionnaire to assess incidence and frequency of side effects.

2.6. Data collection

All testing was performed by the same technician in the morning after an overnight fast. Body mass was measured on a calibrated digital scale with subjects in light clothing and not wearing shoes. Whole-body and regional body composition were assessed using dual-energy x-ray absorptiometry (Prodigy, Lunar, Madison, WI). Regional analysis of the abdomen was assessed by placing a box between L1 and L4 using commercial software (enCORE version 6.00.270), which is highly reliable and accurate when compared to multislice computed tomography [19]. Waist circumference and seated blood pressure were measured by using standard procedures.

Blood was obtained from an antecubital vein and collected into tubes coated with a silicone gel and tubes with EDTA for serum and plasma isolation. Approximately 3 mL of serum was sent to a certified medical laboratory (Quest Diagnostics, Wallingford, CT) for a comprehensive metabolic screening profile that assessed serum glucose, albumin, minerals, renal function, and liver function. Plasma total cholesterol, HDL-C, and TAG levels were determined by using methods previously reported by our laboratory [20], and LDL-C level was calculated by using the Friedewald formula [21]. Our laboratory has participated in the Centers for Disease Control National Heart, Lung, and Blood Institute Lipid Standardization Program since 1989 for quality control and standardization for plasma total cholesterol, HDL-C, and triglyceride assays. Coefficients of variation assessed by the standardization program during a recent study were 0.76% to 1.42% for total cholesterol, 1.71% to 2.72% for HDL-C, and 1.64% to 2.47% for TG.

Insulin concentrations were determined in duplicate using an enzyme-linked immunosorbent assay. The intra-assay coefficient of variation was 1.6%. The homeostasis model analysis was used to calculate insulin resistance [22]. Total plasma ketones were measured by using cyclic enzymatic methodology in commercially available kits (Wako Diagnostics, Osaka, Japan).

2.7. Statistical analysis

All statistical analyses were performed with SPSS 12.0 for Windows (SPSS, Chicago, IL). All dependent variables and 21 days of diet records were analyzed by using a 2 × 3 repeated-measures analysis of variance (ANOVA) with supplement assignment as the between-groups factor and time (week 0, 6, and 12) as the within-group factor. The data are presented as mean ± SD. If a significant main effect was

Table 1
Average daily diet composition in subjects following a CRD and consuming either a soluble fiber supplement or a placebo

Variable	Habitual	Week 1	Week 6	Week 12	*P* (time effect)
Total energy (kJ/d)					
Fiber	9857 ± 2594	7468 ± 2063	6866 ± 1544	6770 ± 1966	
Placebo	9660 ± 3184	6991 ± 2481	7017 ± 2929	6824 ± 2314	<.001
% Energy from carbohydrate					
Fiber	42.6 ± 8.4	9.8 ± 4.9	12.5 ± 9.0	12.6 ± 5.7	
Placebo	45.1 ± 9.5	11.6 ± 4.7	13.3 ± 5.3	12.8 ± 5.8	<.001
% Energy from fat					
Fiber	38.6 ± 5.5	60.2 ± 6.4	60.7 ± 7.6	59.3 ± 6.3	
Placebo	37.3 ± 7.3	58.7 ± 7.8	59.6 ± 6.6	59.3 ± 7.3	<.001
% Energy from protein					
Fiber	16.5 ± 3.9	29.3 ± 4.9	28.4 ± 6.0	27.2 ± 6.4	
Placebo	17.1 ± 2.5	29.1 ± 5.6	27.1 ± 5.1	26.8 ± 4.6	<.001
Dietary cholesterol (mg/d)					
Fiber	389 ± 208	661 ± 273	635 ± 215	584 ± 233	
Placebo	368 ± 160	645 ± 242	586 ± 257	586 ± 257	<.001
Total fiber (g/d)					
Fiber	16.5 ± 7.2	11.7 ± 4.9	12.7 ± 5.9	12.7 ± 6.2	
Placebo	16.3 ± 6.8	9.4 ± 4.6	9.6 ± 4.2	9.5 ± 3.8	<.001
Soluble fiber (g/d)					
Fiber	5.9 ± 2.1	5.4 ± 1.5*	6.0 ± 1.8*	6.0 ± 2.5*	
Placebo	5.5 ± 2.3	3.1 ± 1.4	3.1 ± 1.4	3.0 ± 1.3	<.01

Values are mean ± SD for fiber (n = 14) and placebo (n = 15). Data were analyzed using repeated-measures ANOVA. *P* values are indicated for time effects. There were no significant differences between groups in any of the dietary parameters except for the soluble fiber, which was higher in the fiber group as indicated by (*).

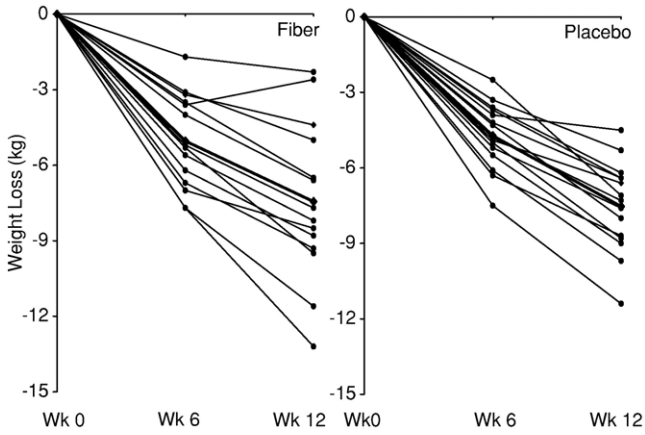

Fig. 1. Absolute weight loss for subjects who consumed a CRD with 3 g of either glucomannan (left, n = 14) or placebo (right, n = 15) per day for 12 weeks. Reduction in body weight from baseline to week 6 and week 12 was significant in the glucomannan and placebo groups ($P > .05$) but not significantly different between groups. Mean is depicted by the thick black bar.

found, subsequent post hoc analyses were completed using a Tukey test. Significance was set at a P value of .05 or less.

3. Results

3.1. Attrition and compliance

A total of 30 subjects with a mean age of 38.8 ± 14.4 years enrolled in the study. Recruited subjects had a mean body weight of 93.1 ± 14.0 kg, a mean BMI of 29.7 ± 3.46 kg/m^2, and mean total cholesterol of 178.4 ± 37.9 mg/dL. Subjects were pair-matched according to BMI and age and then randomly assigned to either the fiber or the placebo group. Twenty-nine of the 30 subjects completed the study. One subject in the fiber group was forced to discontinue because of a military obligation; his data were omitted from all analyses. At baseline, no significant differences were observed between groups in habitual diet (total energy intake, carbohydrate, fat, protein, fiber, or cholesterol intake) or physiological parameters (blood lipids, anthropometrics, body composition, glucose, or insulin).

Compliance with diet and supplementation protocols was high and not different between groups. Percent of days in ketosis as defined by a color change on the reagent strip was similar in the fiber (81.2% ± 15.1%) and placebo (83.9% ± 16.2%) group. Calculated supplement compliance was 96.7% ± 5.0% in the fiber group and 96.6% ± 4.7% in the placebo group.

3.2. Diet composition

Results from analysis of the habitual and intervention diet are presented in Table 1. From baseline, mean total energy intake at weeks 1, 6, and 12 was reduced by 24.3%, 30.3%, and 31.3% in the fiber group and 27.6%, 27.4%, and 29.4% in the placebo group. The reduction in energy intake was significant over time, but not different between groups.

Percent energy from fat increased significantly from baseline to weeks 1, 6, and 12 in both groups and was not significantly different between groups. Mean fat intake at baseline, week 1, week 6, and week 12 was 103.0, 121.5, 112.2, and 108.0 g, respectively, in the fiber group and 102.7, 111.4, 113.2, and 106.7 g, respectively, in the placebo group. Fat grams consumed did not increase significantly over time, and was not different between groups. From baseline to weeks 1, 6, and 12, energy intake from carbohydrate decreased by 83.4%, 83.1%, and 80.0%,

Table 2
Changes in anthropometrics and body composition during consumption of a CRD for 12 weeks supplemented with 3 g of either soluble fiber or a placebo per day

Variable	Baseline	Week 6	Week 12	Mean absolute change, 12 wk	P (time)
Body weight (kg)					
Fiber	93.6 ± 12.2	88.6 ± 12.9	86.2 ± 13.2	−7.4 ± 3.1	
Placebo	93.0 ± 16.0	88.3 ± 16.1	85.5 ± 15.9	−7.5 ± 1.8	<.001
Body fat (%)					
Fiber	33.0 ± 4.5	31.0 ± 4.7	29.1 ± 5.1	−3.9 ± 2.3	
Placebo	31.3 ± 4.4	28.8 ± 5.7	26.8 ± 6.4	−4.4 ± 3.0	<.001
Total fat mass (kg)					
Fiber	31.2 ± 6.1	27.8 ± 6.1	25.5 ± 6.6	−5.6 ± 2.8	
Placebo	29.6 ± 8.2	26.2 ± 9.1	23.8 ± 9.3	−5.8 ± 2.6	<.001
Lean body mass (kg)					
Fiber	59.7 ± 8.9	58.4 ± 9.3	58.2 ± 9.2	−1.4 ± 1.7	
Placebo	60.5 ± 8.8	59.4 ± 8.2	59.1 ± 8.0	−1.4 ± 2.0	<.001
Abdominal fat (kg)					
Fiber	3.67 ± 0.9	3.08 ± 0.9	2.86 ± 0.8	−0.81 ± 0.3	
Placebo	3.63 ± 1.5	3.14 ± 1.6	2.80 ± 1.5	−0.83 ± 0.3	<.001
Waist circumference (cm)					
Fiber	102.8 ± 9.9	97.9 ± 9.1	94.8 ± 9.2	−8.0 ± 4.3	
Placebo	103.0 ± 11.8	98.0 ± 11.9	95.1 ± 12.4	−8.0 ± 4.0	<.001

Values are mean ± SD. Fiber, n = 14; placebo, n = 15. Data were analyzed using repeated-measures ANOVA. P values are for time effects. There were no differences between groups in any variable reported in the table ($P > .05$).

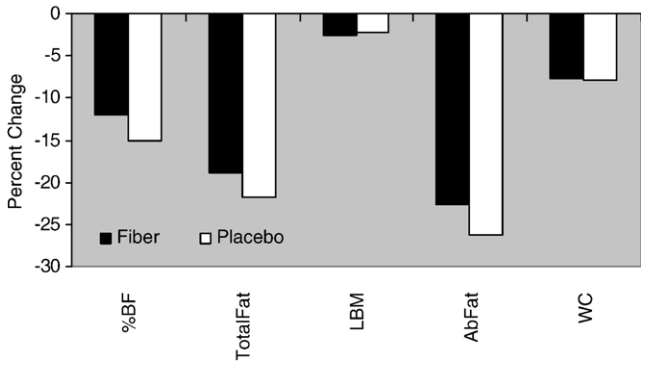

Fig. 2. Relative changes in anthropometric measures from baseline to 12 weeks in subjects who followed a CRD and consumed either a soluble fiber supplement (black bars) or a placebo (white bars). There was a significant time ($P < .05$) but not treatment ($P > .05$) effect for each parameter. BF = body fat; LBM = lean body mass; Ab = abdominal fat; WC = waist circumference.

respectively, in the fiber group and by 81.5%, 80.0%, and 79.6%, respectively, in the placebo group; there were no significant differences between groups. Protein intake increased during consumption of the diet, resulting in a significant time but not treatment effect.

Mean dietary cholesterol intake increased from baseline to weeks 1, 6, and 12 by 70.0%, 63.2%, and 50.1%, respectively, in the fiber group and by 75.2%, 59.2%, and 59.2%, respectively, in the placebo group, with no differences between groups.

Soluble fiber intake was significantly greater in the fiber group than in the placebo group. The fiber group consumed 74%, 93%, and 100% more soluble fiber than the placebo group at weeks 1, 6, and 12, respectively.

3.3. Clinical measures

All subjects lost weight, but the magnitude varied from about 2 to more than 12 kg (Fig. 1). Mean weight loss was not different between groups; subjects in the fiber and placebo groups lost 7.9% and 8.0% of body weight, respectively. Body fat was reduced by 11.8% in the fiber group and by 14% in the placebo group (Table 2). Abdominal fat was reduced by 22.0% in the fiber group and 22.8% in the placebo group from baseline to week 12. Abdominal fat had a lower contribution to total fat at week 12 compared with baseline (fiber, 11.8% [baseline] vs 11.2% [week 12]; placebo, 12.3% [baseline] vs 11.8% [week 12]; $P < .001$). BMI was reduced over time (fiber, 30.1 ± 2.8 to 27.6 ± 3.3 kg/m^2, $P < .001$; placebo, 29.3 ± 4.1 to 26.8 ± 4.2 kg/m^2, $P < .001$). Relative changes in body composition variables from baseline to week 12 are shown in Fig. 2. There were no significant differences between groups in any body composition variable.

From baseline to 12 weeks, the fiber group and placebo group experienced a significant reduction in total cholesterol (−10.0%, −6.3%), TAG (−35.0%, −42.5%), and LDL-C (−12.3%, −6.0%), as well as an increase in HDL-C (10.0%, 14.1%) (Table 3). There were no differences between groups in any plasma lipid variable; however, the fiber group experienced a significant reduction in LDL-C from baseline to 6 weeks (2.98 to 2.61 mmol/L), whereas the placebo group did not (2.89 to 2.72 mmol/L). By week 12, LDL-C remained significantly reduced in the fiber group, and the reduction in the placebo group reached significance.

There was a great deal of individual variability in plasma lipid responses in the fiber and placebo groups (Fig. 3). It is notable that all but one subject had a decrease in LDL-C at week 6 in the fiber group, whereas 6 subjects had an increase in LDL-C in the placebo group during this period. Most of the subjects increased HDL-C and decreased TAG, but the magnitude of change was quite inconsistent with little impact of fiber on this variability.

Total cholesterol/HDL-C ratio was reduced over time in both groups (fiber, 4.53 ± 1.09 to 3.81 ± 1.17, $P < .001$; placebo, 4.57 ± 1.76 to 3.71 ± 1.17, $P < .001$), with no differences between groups ($P > .05$). The TAG/HDL-C ratio was also reduced in both groups (fiber, 3.05 ± 1.42 to

Table 3
Changes in plasma lipids during a 12-week CRD supplemented with 3 g of either soluble fiber or a placebo per day

Variable	Baseline	Week 6	Week 12	Mean absolute change, 12 wk	P (time)
Total cholesterol (mmol/L)					
Fiber	4.64 ± 0.75	4.09 ± 0.60	4.18 ± 0.63	−0.47 ± 0.56	
Placebo	4.58 ± 1.18	4.38 ± 0.85	4.30 ± 0.92	−0.29 ± 0.67	<.01
TAG (mmol/L)					
Fiber	1.31 ± 0.45	0.94 ± 0.41	0.86 ± 0.39	−0.45 ± 0.43	
Placebo	1.34 ± 0.68	0.86 ± 0.47	0.77 ± 0.35	−0.57 ± 0.47	<.001
HDL-C (mmol/L)					
Fiber	1.07 ± 0.26	1.14 ± 0.27	1.17 ± 0.32	0.11 ± 0.13	
Placebo	1.08 ± 0.33	1.18 ± 0.35	1.23 ± 0.35	0.15 ± 0.18	<.01
LDL-C (mmol/L)					
Fiber	2.98 ± 0.72	2.52 ± 0.66*	2.61 ± 0.72	−0.36 ± 0.59	
Placebo	2.89 ± 1.16	2.81 ± 0.89	2.72 ± 0.95	−0.18 ± 0.59	<.05

Values are mean ± SD. Fiber, n = 14; placebo, n = 15. Data were analyzed using repeated-measures ANOVA. P values are for time effects. There were no differences between groups at any given time except for LDL at week 6.

* $P < .05$, significantly different from placebo.

1.93 ± 1.26, $P < .001$; placebo, 3.33 ± 2.46 to 1.67 ± 1.23, $P < .001$), but was not different between groups ($P > .05$).

Changes in glucose, insulin, insulin resistance, and blood pressure are shown in Table 4. There was a significant time but not treatment effect for plasma glucose and insulin resistance, with no significant time or treatment effect for insulin. Systolic blood pressure was reduced by 3.6% in the fiber group and 8.5% in the placebo group from baseline to 12 weeks. There were no differences between groups. Diastolic blood pressure remained unchanged in the fiber group, but was significantly reduced in the placebo group, with significant differences between groups.

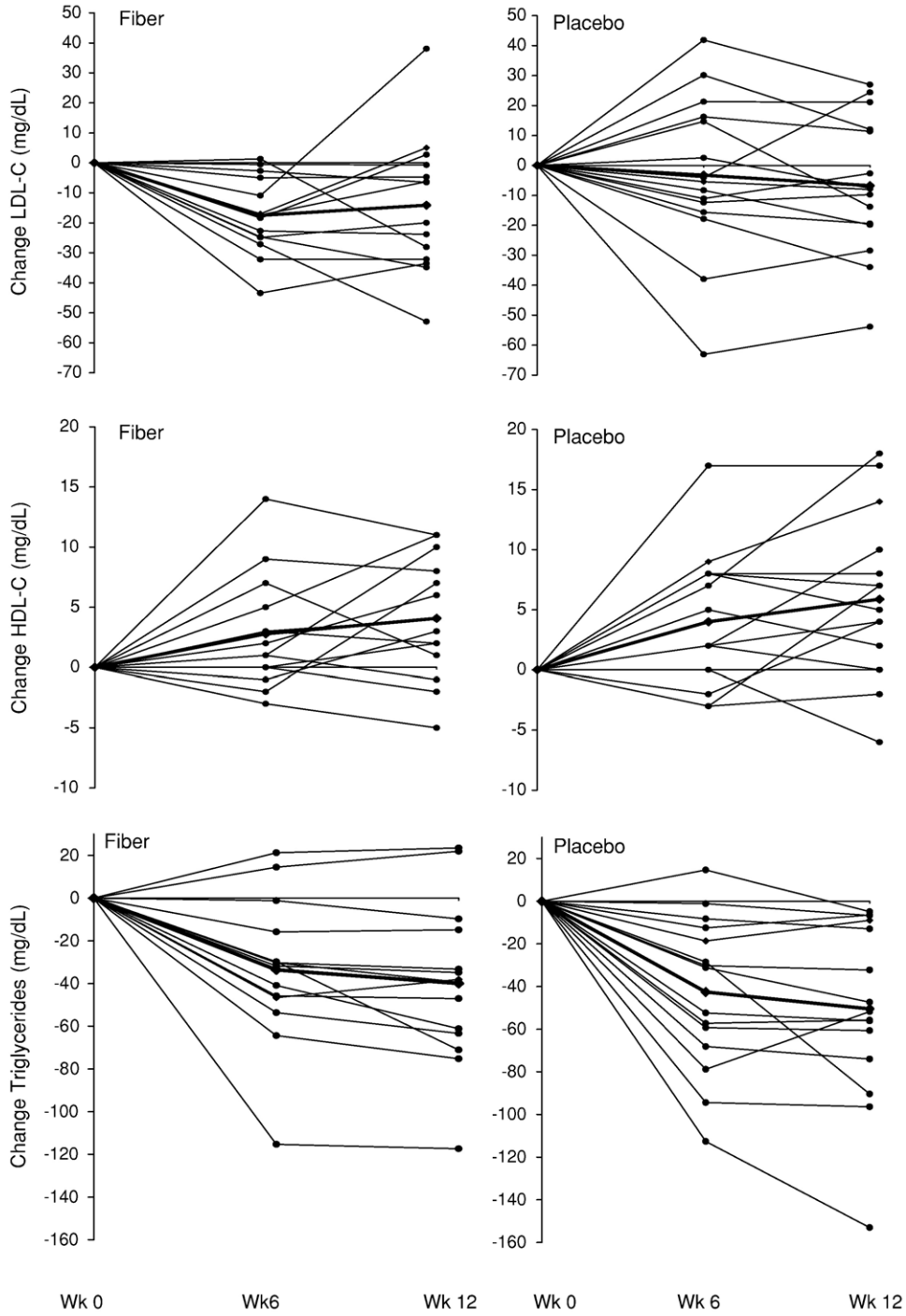

Fig. 3. Individual changes in LDL-C (top), HDL-C (middle), and TAG (bottom) for men who consumed a CRD along with 3 g of either glucomannan (left, n = 14) or placebo (right, n = 15) per day for 12 weeks. Reduction in LDL-C was significant by week 6 in the glucomannan group only ($P < .05$); by week 12, the reduction was significant in both groups, and values were not different between groups. There was a significant time ($P < .01$) but not treatment effect for both HDL-C and TAG. Means for each group are depicted by the thick black bar.

Table 4
Changes in plasma glucose, insulin, insulin resistance (homeostasis model analysis), and blood pressure during a 12-week CRD supplemented with 3 g of either soluble fiber or a placebo per day

Variable	Baseline	Week 6	Week 12	Mean absolute value change	*P* (time)
Glucose (mmol/L)					
Fiber	5.09 ± 0.83	4.55 ± 0.70	4.80 ± 0.64	−0.29 ± 0.71	
Placebo	5.15 ± 0.63	4.87 ± 0.56	5.01 ± 0.56	−0.14 ± 0.47	<.01
Insulin (pmol/L)					
Fiber	80.9 ± 36.4	79.3 ± 24.9	83.7 + 33.0	2.8 ± 38.2	
Placebo	71.1 ± 14.6	64.8 ± 11.8	77.7 ± 32.9	6.6 ± 32.0	>.05
Homeostasis model analysis of insulin resistance					
Fiber	2.3 ± 1.1[a]	2.0 ± 0.6[b]	2.3 ± 0.9[a]	N/A	
Placebo	2.6 ± 1.2[a]	2.3 ± 1.0[b]	2.6 ± 1.0[a]	N/A	<.01
Systolic blood pressure (mm Hg)					
Fiber	124.4 ± 10.6	123.3 ± 8.5	119.9 ± 7.7	−4.6 ± 10.4	
Placebo	124.3 ± 10.0	117.7 ± 8.3	113.7 ± 9.4	−10.5 ± 8.7	<.01
Diastolic blood pressure (mm Hg)					
Fiber	84.0 ± 7.7	84.9 ± 7.3	84.3 ± 7.4	0.3 ± 6.9	>.05
Placebo	85.2 ± 9.0	79.3 ± 5.7*	77.7 ± 4.6*	−7.5 ± 6.9	<.05

Values are mean ± SD. Fiber n = 14, placebo n = 15. Data were analyzed using repeated-measures ANOVA. *P* values are for time effects. Differing superscripts denote a significant time effect. N/A indicates not applicable.

* $P < .05$ (significant differences between groups).

Blood urea nitrogen and the blood urea nitrogen-creatinine ratio were increased over time ($P < .05$), but not different between groups ($P > .05$). No differences were observed over time or between groups for any other chemistry panel parameter ($P > .05$; data not shown).

In the fiber group, 11 subjects correctly identified the supplement group to which they were assigned, 2 were incorrect, whereas 1 was unsure. In the placebo group, 4 subjects correctly identified their group assignment, 6 were incorrect, and 6 were unsure. Side effects reported and the number of subjects who experienced these effects included decreased appetite (fiber = 5, placebo = 7) and increased thirst (fiber 2, placebo = 4) with no significant difference in number of reports between groups. Gastrointestinal side effects reported included diarrhea (fiber = 7, placebo = 2; $P < .05$) and constipation (fiber = 5, placebo = 1; $P > .05$). When total gastrointestinal side effects were combined (fiber, 12, vs placebo, 3), there were more side effects present in the fiber compared with the placebo group ($P < .001$).

4. Discussion

We previously reported that the beneficial effects of a CRD diet on lipoprotein metabolism and emerging risk factors for CVD were independent of fiber intake [15,16]. In this report, we extend these findings by showing that adding soluble fiber (ie, Konjac-mannan) to a CRD does not have a major impact on the response of metabolic syndrome markers. We did observe a more consistent lowering of LDL-C at week 6 when fiber was added to a CRD, but this effect was not apparent at week 12. In prior work conducted over the last 5 years, we have characterized the lipid responses to a CRD in normal-weight and overweight men and women [11]. The significant weight loss (~8.3% of initial body weight) likely overshadowed any potential beneficial effects of the glucomannan. In contrast to other studies that evaluated CRD [23-25], we had extremely low attrition and high compliance; thus, we are confident that the results reported represent the true biological adaptations to a CRD with and without supplemental soluble fiber.

4.1. Effects of a CRD with and without supplemental soluble fiber on LDL-C levels

The addition of soluble fiber resulted in a 17.6% reduction in LDL-C, whereas the placebo group experienced a 3.3% reduction in LDL-C at 6 weeks. At 6 weeks, 93% of subjects in the fiber group and 60% of subjects in the placebo group decreased LDL-C. By week 12, both the fiber and placebo groups had significantly reduced LDL-C levels, with no significant difference between groups. However, the overall changes in LDL-C appear to be more consistent in the fiber group. Because the addition of soluble fiber to habitual and intervention diets has clearly been shown to reduce LDL-C [12], we expected to see significant differences between groups at week 12. Because weight loss has been demonstrated to have a very significant effect on plasma lipids [26], it is possible that active weight loss outperformed the potential effects of Konjac-mannan in the current study. In addition, previous studies indicating the effectiveness of Konjac-mannan on LDL-C were not characterized by weight loss of the same extent as in the present study [13,14]. It is also possible that with a larger number of subjects in the Konjac-mannan group we would have been able to detect statistical differences in LDL-C even at week 12. Each kilogram of body weight lost is believed to reduce LDL-C by approximately 0.02 mmol/L [27]. In the fiber group, mean weight loss was 7.4 kg, indicating an expected LDL-C reduction of approximately 0.148 mmol/L, with an actual reduction of 0.36 mmol/L. Weight loss in the placebo group was 7.5 kg, indicating an

expected reduction in LDL-C of 0.15 mmol/L with an actual reduction of 0.18 mmol/L. Furthermore, the reductions in total and LDL-C were attained while subjects consumed 50.1% to 75.2% more dietary cholesterol in comparison to habitual diet, a finding consistent with our prior work evaluating dietary cholesterol challenges [28].

In addition to supporting a favorable LDL-C response, there were other reasons to study the addition of fiber to a CRD. A number of placebo-controlled studies have shown that small amounts of Konjac-mannan (1-4 g/d) enhance weight loss with both energy restriction and ad libitum energy consumption [29-33]. Konjac-mannan is believed to spontaneously decrease food consumption by forming a gel in the stomach, promoting satiety. Independent of its effect on weight loss, Konjac-mannan taken before or with a meal reduces the glucose and insulin response by as much as 50% [34,35] and significantly lowers cholesterol [13,14,36-39]. Most evidence indicates that Konjac-mannan interferes with cholesterol absorption or enhances cholesterol excretion through bile [37,40]. In this study, Konjac-mannan did not lead to significant improvements in weight loss, glucose, insulin, or lipids beyond those achieved by a CRD alone. This is most likely due to the powerful metabolic adaptations associated with carbohydrate restriction and/or the moderate weight loss [6,20].

4.2. Effects of a CRD on energy intake and weight loss

Subjects were not provided specific instructions regarding energy restriction, yet effectively reduced their energy intake by 705 kcal/d, equating to a 24.2% to 31.3% reduction in energy intake throughout the intervention. This is consistent with the findings of other studies showing reduced energy intake during ad libitum CRD [41]. Weight loss diets should be evaluated on their effectiveness at reducing body fat, particularly abdominal fat, and by effects on lean body mass. Despite the rapid, large reduction in body weight in the present study, the weight loss was predominantly nonlean tissue. Pooled data indicate that 76% of weight lost was fat mass. Abdominal fat was also reduced significantly during the intervention. Intra-abdominal fat is associated with all 5 of the National Cholesterol Education Program's Adult Treatment Panel III diagnostic criteria for the metabolic syndrome, and may have a pathophysiological role [42]. Our subjects lost a mean 21.6% of abdominal fat, which was reflected by a mean 8.0-cm reduction in waist circumference. Abdominal fat accounted for a smaller percentage of total fat at 12 weeks than at baseline (11.9% vs 11.3%; $P < .05$), consistent with our recent findings in overweight men of a preferential loss of fat from the abdominal region when following a CRD [17].

4.3. Effects of a CRD with and without supplemental soluble fiber on other clinical markers of CVD risk

Most health practitioners remain cautious about using CRDs because of concerns about potential adverse effects on blood lipids. Our data do not support these concerns, indicated by an overall favorable effect of CRDs on all lipoprotein fractions. Our results contribute to the growing evidence that CRDs consistently and significantly reduce fasting plasma TAG and increase HDL-C concentrations. The substantial reduction in TAG is clinically significant because elevated plasma TAG levels are an independent risk factor for CVD, principally due to their indication of higher concentrations of large, very low-density lipoprotein particles and low plasma HDL-C [43]. Cardiovascular risk was improved further through an increase in HDL-C. Of the 29 subjects, only 5 experienced reduced HDL-C from baseline to 12 weeks. Furthermore, our results suggest that CRDs significantly reduce body weight and, in addition, they improve cardiovascular risk factors that cannot be solely accounted for by weight loss. According to a meta-analysis by Dattilo and Kris-Etherton [27], each kilogram of weight loss is expected to be accompanied by a 0.015-mmol/L reduction in TAG. Considering the weight loss in the present intervention, TAG would be expected to decrease by 0.111 and 0.112 mmol/L in the fiber and placebo groups, respectively. However, TAG was reduced by 0.45 mmol/L in the fiber group and 0.57 mmol/L in the placebo group. HDL-C is expected to decrease by 0.007 mmol/L for every kilogram of body weight lost during active weight loss, and increase by 0.009 mmol/L for every kilogram of weight loss during weight stabilization [27]. Because our subjects were actively losing weight, there would be an expected reduction in HDL-C of 0.052 and 0.053 mmol/L in the fiber and placebo groups, respectively. However, the fiber group had an increase in HDL-C of 0.11 mmol/L, and the placebo group an increase in HDL-C of 0.15 mmol/L, doubling what would be expected even during stabilization of body weight after weight loss. Changes of this magnitude in TAG and HDL-C are unlikely due to weight loss alone [6,8] and were not correlated to weight loss in the current study.

The reduction in SBP was similar between groups and is similar to reductions reported previously [23,44]. The significant body weight reduction was most likely the cause of the SBP decreases, possibly due to reduced plasma renin activity [45]. An unexpected result was the significant reduction in DBP experienced by the placebo group only. The incorporation of soluble fiber to habitual diet with [30] and without [36] weight loss has resulted in unchanged DBP, whereas a CRD without supplemental soluble fiber can significantly reduce DBP [2].

Insulin resistance was significantly reduced over time, but not between groups. The improvement in insulin resistance was by virtue of the reduction in plasma glucose, as insulin was unchanged. Our laboratory has reported a similar effect on insulin resistance when overweight men followed a CRD for 6 weeks [9]. The reduction in plasma glucose may have been caused by changes in hepatic glucose production. The provision of a high-fat diet (approximately 89% of energy) in patients with mild type 2 diabetes mellitus for 14 days caused a significantly lower

rate of glycogenolysis than a diet high in carbohydrate (approximately 89% energy) without affecting gluconeogenesis [46].

Optimal dietary composition for the treatment of metabolic syndrome is a current topic of interest to the medical and research communities. Our results suggest that a CRD should be considered as a treatment option. Dramatic improvements in waist circumference and fasting TAG and HDL-C levels specifically address the needs of individuals with metabolic syndrome. At baseline, 11 subjects met the diagnostic criteria for metabolic syndrome, which was reduced to 4 and 3 at weeks 6 and 12, respectively. The high rate of retention further supports the applicability of a CRD for a moderate duration in overweight men.

The results from this study are limited to overweight and mildly obese men who are otherwise healthy and not undergoing pharmacological lipid therapy. The duration of our intervention was moderate, but carefully controlled. Particularly important is that subjects were clearly following a CRD, and changes were consistent and highly significant. We conclude that the consumption of a CRD by overweight men provides multiple improvements of cardiovascular risk profile, and LDL-C levels may be more rapidly reduced and stabilized through the addition of 3 g of soluble fiber per day.

Acknowledgment

This study was supported in part by Nutraquest and the University of Connecticut Research Foundation.

References

[1] Volek JS, Sharman MJ, Love DM, Avery NG, Gomez AL, Scheett TP, et al. Body composition and hormonal responses to a carbohydrate-restricted diet. Metabolism 2002;51:864-70.
[2] Westman EC, Yancy WS, Edman JS, Tomlin KF, Perkins CE. Effect of 6-month adherence to a very low carbohydrate diet program. Am J Med 2002;113:30-6.
[3] Yancy Jr WS, Olsen MK, Guyton JR, Bakst RP, Westman EC. A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. Ann Intern Med 2004;140:769-77.
[4] http://www.healthierus.gov/dietaryguidelines.
[5] Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.
[6] Volek JS, Sharman MJ, Forsythe CE. Modification of lipoproteins by very-low carbohydrate diets. J Nutrition 2005;135:1339-42.
[7] Sharman MJ, Kraemer WJ, Love DM, Avery NG, Gomez AL, Scheett TP, et al. A ketogenic diet favorably affects serum biomarkers for cardiovascular disease in normal-weight men. J Nutr 2002; 132:1879-85.
[8] Volek JS, Sharman MJ, Gomez AL, Scheett TP, Kraemer WJ. An isoenergetic very low carbohydrate diet improves serum HDL cholesterol and triacylglycerol concentrations, the total cholesterol to HDL cholesterol ratio and postprandial pipemic responses compared with a low fat diet in normal weight, normolipidemic women. J Nutr 2003;133:2756-61.
[9] Sharman MJ, Gomez AL, Kraemer WJ, Volek JS. Very low-carbohydrate and low-fat diets affect fasting lipids and postprandial lipemia differently in overweight men. J Nutr 2004;134:880-5.
[10] Volek JS, Sharman MJ, Gomez AL, DiPasquale C, Roti M, Pumerantz A, 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.
[11] Volek JS, Sharman MJ. Cardiovascular and hormonal aspects of very-low-carbohydrate ketogenic diets. Obes Res 2004;12(Suppl 2): 115S-23S.
[12] Fernandez ML. Soluble fiber and nondigestible carbohydrate effects on plasma lipids and cardiovascular risk. Curr Opin Lipidol 2001; 12:35-40.
[13] Chen HL, Sheu WH, Tai TS, Liaw YP, Chen YC. Konjac supplement alleviated hypercholesterolemia and hyperglycemia in type 2 diabetic subjects—a randomized double-blind trial. J Am Coll Nutr 2003;22:36-42.
[14] Vuksan V, Sievenpiper JL, Xu Z, Wong EY, Jenkins AL, Beljan-Zdravkovic U, et al. Konjac-Mannan and American ginsing: emerging alternative therapies for type 2 diabetes mellitus. J Am Coll Nutr 2001;20(5 Suppl):370S-80S [discussion 381S-383S].
[15] Wood RJ, Volek JS, Davis SR, Dell'Ova C. Effects of a carbohydrate-restricted diet on emerging plasma markers for cardiovascular disease. Nutrition & Metabolism 2006;3:19.
[16] Wood RJ, Volek JS, Liu Y, Shachter NS, Contois JH, Fernandez ML. Carbohydrate restriction alters lipoprotein metabolism by modifying VLDL, LDL, and HDL subfraction distribution and size in overweight men. J Nutr 2006;136:384-9.
[17] Volek JS, Sharman MJ, Gomez AL, Judelson DA, Rubin MR, Watson G, et al. Comparison of energy-restricted very low-carbohydrate and low-fat diets on weight loss and body composition in overweight men and women. Nutr Metab (Lond) 2004;1:13.
[18] Robinson AM, Williamson DH. Physiological roles of ketone bodies as substrates and signals in mammalian tissues. Physiol Rev 1980;60:143-87.
[19] Glickman SG, Marn CS, Supiano MA, Dengel DR. Validity and reliability of dual-energy X-ray absorptiometry for the assessment of abdominal adiposity. J Appl Physiol 2004;97:509-14.
[20] Lofgren IE, Herron KL, West KL, Zern TL, Patalay M, Koo SI, et al. Carbohydrate intake is correlated with biomarkers for coronary heart disease in a population of overweight premenopausal women. J Nutr Biochem 2005;16:245-50.
[21] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18: 499-502.
[22] 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.
[23] Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. Jama 2005;293:43-53.
[24] Foster GD, Wyatt HR, Hill JO, McGuckin BG, Brill C, Mohammed BS, et al. A randomized trial of a low-carbohydrate diet for obesity. N Engl J Med 2003;348:2082-90.
[25] Samaha FF, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, et al. A low-carbohydrate as compared with a low-fat diet in severe obesity. N Engl J Med 2003;348:2074-81.
[26] Poobalan A, Aucott L, Smith WC, Avenell A, Jung R, Broom J, et al. Effects of weight loss in overweight/obese individuals and long-term lipid outcomes—a systematic review. Obes Rev 2004;5:43-50.
[27] 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.

[28] Herron KL, Lofgren IE, Sharman M, Volek JS, Fernandez ML. High intake of cholesterol results in less atherogenic low-density lipoprotein particles in men and women independent of response classification. Metabolism 2004;53:823-30.
[29] Livieri C, Novazi F, Lorini R. [The use of highly purified glucomannan-based fibers in childhood obesity]. Pediatr Med Chir 1992;14:195-8.
[30] Biancardi G, Palmiero L, Ghirardi PE. Glucomannan in the treatment of overweight patients with osteoarthrosis. Curr Ther Res 1989;46: 908-12.
[31] Reffo GC, Ghirardi PE, Forattini C. Glucomannan in hypertensive outpatients: pilot clinical trial. Curr Ther Res 1988;44.
[32] Walsh DE, Yaghoubian V, Behforooz A. Effect of glucomannan on obese patients: a clinical study. Int J Obes 1984;8:289-93.
[33] Vita PM, Restelli A, Caspani P, Klinger R. [Chronic use of glucomannan in the dietary treatment of severe obesity]. Minerva Med 1992;83:135-9.
[34] McCarty MF. Glucomannan minimizes the postprandial insulin surge: a potential adjuvant for hepatothermic therapy. Med Hypotheses 2002;58:487-90.
[35] Doi K. Effect of konjac fibre (glucomannan) on glucose and lipids. Eur J Clin Nutr 1995;49(Suppl 3):S190-7.
[36] Arvill A, Bodin L. Effect of short-term ingestion of konjac glucomannan on serum cholesterol in healthy men. Am J Clin Nutr 1995;61:585-9.
[37] Gallaher DD, Gallaher CM, Mahrt GJ, Carr TP, Hollingshead CH, Hesslink Jr R, et al. A glucomannan and chitosan fiber supplement decreases plasma cholesterol and increases cholesterol excretion in overweight normocholesterolemic humans. J Am Coll Nutr 2002;21:428-33.
[38] Vuksan V, Jenkins DJ, Spadafora P, Sievenpiper JL, Owen R, Vidgen E, et al. Konjac-mannan (glucomannan) improves glycemia and other associated risk factors for coronary heart disease in type 2 diabetes. A randomized controlled metabolic trial. Diabetes Care 1999;22:913-9.
[39] Vuksan V, Sievenpiper JL, Owen R, Swilley JA, Spadafora P, Jenkins DJ, et al. Beneficial effects of viscous dietary fiber from Konjac-mannan in subjects with the insulin resistance syndrome: results of a controlled metabolic trial. Diabetes Care 2000;23:9-14.
[40] Gallaher CM, Munion J, Hesslink Jr R, Wise J, Gallaher DD. Cholesterol reduction by glucomannan and chitosan is mediated by changes in cholesterol absorption and bile acid and fat excretion in rats. J Nutr 2000;130:2753-9.
[41] Stern L, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, et al. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. Ann Intern Med 2004;140:778-85.
[42] Carr DB, Utzschneider KM, Hull RL, Kodama K, Retzlaff BM, Brunzell JD, et al. Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. Diabetes 2004;53:2087-94.
[43] Bradley WA, Gianturco SH. Triglyceride-rich lipoproteins and atherosclerosis: pathophysiological considerations. J Intern Med Suppl 1994;736:33-9.
[44] Meckling KA, O'Sullivan C, Saari D. Comparison of a low-fat diet to a low-carbohydrate diet on weight loss, body composition, and risk factors for diabetes and cardiovascular disease in free-living, overweight men and women. J Clin Endocrinol Metab 2004;89:2717-23.
[45] Tuck ML, Sowers J, Dornfeld L, Kledzik G, Maxwell M. The effect of weight reduction on blood pressure, plasma renin activity, and plasma aldosterone levels in obese patients. N Engl J Med 1981; 304:930-3.
[46] Allick G, Bisschop PH, Ackermans MT, Endert E, Meijer AJ, Kuipers F, et al. A low-carbohydrate/high-fat diet improves glucoregulation in type 2 diabetes mellitus by reducing postabsorptive glycogenolysis. J Clin Endocrinol Metab 2004;89:6193-7.