Original Article

Effect of a High Saturated Fat and No-Starch Diet on Serum Lipid Subfractions in Patients With Documented Atherosclerotic Cardiovascular Disease

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- ***Objective*: To determine whether a diet of high saturated fat and avoidance of starch (HSF-SA) results in weight loss without adverse effects on serum lipids in obese nondiabetic patients.**
- ***Patients and Methods*: Twenty-three patients with atherosclerotic cardiovascular disease participated in a prospective 6-week trial at the Christiana Care Medical Center in Newark, Del, between August 2000 and September 2001. All patients were obese (mean ± SD body mass index [BMI], 39.0±7.3 kg/m^2) and had been treated with statins before entry in the trial. Fifteen obese patients with polycystic ovary syndrome (BMI, 36.1±9.7 kg/m^2) and 8 obese patients with reactive hypoglycemia (BMI, 46.8±10 kg/m^2) were monitored during an HSF-SA diet for 24 and 52 weeks, respectively, between 1997 and 2000.**
- ***Results*: In patients with atherosclerotic cardiovascular disease, mean ± SD total body weight (TBW) decreased 5.2%±2.5% (*P*<.001) as did body fat percentage (*P*=.02). Nuclear magnetic resonance spectroscopic analysis of lipids showed decreases in total triglycerides (*P*<.001), very low-density lipoprotein (VLDL) triglycerides (*P*<.001), VLDL size (*P*<.001), large VLDL concentration (*P*<.001), and medium VLDL concentration (*P*<.001). High-density lipoprotein (HDL) and LDL concentrations were unchanged, but HDL size (*P*=.01) and LDL size (*P*=.02) increased. Patients with polycystic ovary syndrome lost 14.3%±20.3% of TBW (*P*=.008) and patients with reactive hypoglycemia lost 19.9%±8.7% of TBW (*P*<.001) at 24 and 52 weeks, respectively, without adverse effects on serum lipids.**
- ***Conclusion*: An HSF-SA diet results in weight loss after 6 weeks without adverse effects on serum lipid levels verified by nuclear magnetic resonance, and further weight loss with a lipid-neutral effect may persist for up to 52 weeks.**

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ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; BOHB = β-hydroxybutyrate; CRP = C-reactive protein; HDL = high-density lipoprotein; HSF-SA = high saturated fat and avoidance of starch; LDL = low-density lipoprotein; NMR = nuclear magnetic resonance; PCOS = polycystic ovary syndrome; RH = reactive hypoglycemia; TBW = total body weight; TG = triglyceride; VLDL = very low-density lipoprotein

Obesity has reached epidemic proportions in the United States, affecting more than 30% of the adult population.[1] Hundreds of thousands of deaths and billions of dollars in health care costs are directly related to obesity and its complications.[2] Obesity often coexists with atherosclerotic cardiovascular disease (ASCVD).

Statin therapy reduces but does not eliminate the incidence of ASCVD, and obese patients who are treated to goal low-density lipoprotein (LDL) cholesterol levels may still have limited exercise capacity, hyperinsulinemia, hypertension, and hyperglycemia. The "metabolic syndrome,"[3] a triad of hypertriglyceridemia, low high-density lipoprotein (HDL) levels, and insulin resistance associated with increased risk of atherosclerosis, also appears to include abnormalities in lipid subfractions.[4] Weight loss and its accompanied improvement in insulin sensitivity could be expected to benefit these patients.

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A diet of high saturated fat and avoidance of starch (HSF-SA) appeared to result in weight loss without adverse effects on serum lipid levels in a group of patients with type 2 diabetes.[5] These observations were difficult to interpret because of the use of multiple hypoglycemic and lipid-lowering drugs, which were changed on the basis of clinical judgment.[4] In our study, patients with polycystic ovary syndrome (PCOS) and reactive hypoglycemia (RH) also appeared to have sustained weight loss without significant changes in serum lipid levels despite taking no lipid-lowering medications. However, there was concern about adverse effects on serum lipid subfractions not revealed by routine monitoring. We describe nuclear magnetic reso-

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nance (NMR) spectroscopic analysis of lipid subfractions in a group of markedly obese nondiabetic patients with documented ASCVD treated with statins to goal LDL levels before study entry.

PATIENTS AND METHODS

Atherosclerotic Cardiovascular Disease

Twenty-three patients (17 men and 6 women) were referred by their cardiologists for participation in a prospective study as approved by the Christiana Care Corporation Institutional Review Board. Patient recruitment began in August 2000, and the study was completed in September 2001. All patients were obese (mean ± SD body mass index [BMI], 39.0±7.3 kg/m^2; range, 30.5-62.7 kg/m^2), and all had been treated with statins to goal LDL levels. Patients took various statins, but no changes were made in dose or brand. Ten patients had coronary artery bypass grafting, and 16 had undergone percutaneous coronary intervention. Left ventricular ejection fractions were not measured, but all participants were judged not to have overt congestive heart failure during the study. Three patients had concomitant peripheral vascular disease, but no patients had cerebrovascular disease. Every patient had documented ASCVD, but none had had an acute event in the 6 months before study entry. Patients with diabetes mellitus and those receiving hypoglycemic therapy were excluded. Baseline laboratory values for patients with ASCVD were as follows (ranges shown in parentheses): mean age, 61 years (53-73 years); systolic blood pressure level, 129.2 mm Hg (104-180 mm Hg); diastolic blood pressure level, 76.5 mm Hg (60-100 mm Hg); serum creatinine, 0.93 mg/dL (0.8-1.4 mg/dL); alanine aminotransferase, 30.9 U/L (15-58 U/L); aspartate aminotransferase, 25.0 U/L (18-25 U/L); and alkaline phosphatase, 86.1 U/L (64-141 U/L). After we obtained informed patient consent, initial fasting blood and urine samples were obtained, and patients were prescribed an HSF-SA diet. During weekly follow-up visits at the cardiology research center, patients were weighed, body measurements were taken, fasting urine specimens were analyzed for ketones, and diet logs were reviewed. Final fasting blood and urine samples were obtained after patients were on the diet for 6 weeks.

Polycystic Ovary Syndrome

Fifteen women were referred by gynecologists or reproductive endocrinologists to an endocrinologist for various symptoms of PCOS during 1998 and 1999: 8 desired fertility, 4 were concerned primarily with hirsutism, and 3 had oligoamenorrhea as their primary symptom. Initial evaluation revealed the following (ranges shown in parentheses): mean age, 33.9 years (21-43 years); BMI, 36.1±9.7 kg/m^2 (33-39 kg/m^2); testosterone, 61.5 ng/dL (21-196 ng/dL); free testosterone, 22 ng/dL (5.0-61.0 ng/dL); and sex hormone binding globulin, 58 nmol/L (13-171 nmol/L). At time of referral, 3 patients were treated with metformin in doses of 500 mg twice daily. No changes in dose of metformin were made, and no other insulin-sensitizing medications were given. These women were prescribed the HSF-SA diet because previous studies indicated that patients with PCOS benefit from interventions that improve insulin sensitivity[6,7]; they were then monitored for 24 weeks.

Reactive Hypoglycemia

Reactive hypoglycemia is a poorly defined clinical syndrome in which patients present with postprandial dysphoria revealed by caloric intake. A carbohydrate-restricted diet has been suggested for these patients.[8] Repeated episodes of postprandial dysphoria relieved by food were considered sufficient for clinical diagnosis, even in the absence of documented hypoglycemia. In 1997, 116 patients with RH were referred to an endocrinologist at our institution. Dietary intervention resulted in symptomatic improvement in most patients, but few reported long-term dietary compliance. A small group of 8 morbidly obese women (mean age, 45.2 years [30-56 years]) (BMI, 46.8±10 kg/m^2 [39.9-65.3 kg/m^2]) persisted on the diet for 1 year, primarily to lose weight. Previously, 6 of the 8 women had taken prescription medication for weight loss, but none had taken such medication for 6 months before observation. No patient in this group took lipid-lowering or insulin-sensitizing medications.

Diet

An HSF-SA diet was prescribed for all patients; they were instructed to attempt to consume one half of all calories as saturated fat, primarily as red meat and cheese. Eggs and other low-fat forms of protein were allowed, regardless of cholesterol content. Fresh fruit and nonstarchy vegetables were prescribed in restricted amounts at each meal. Starch was forbidden. Dietary logs were used to encourage compliance with the intake of saturated fat and restriction of carbohydrates in all patients.

Serum Analysis

Lipid fractions were determined by NMR spectroscopic analysis assay (LipoScience, Inc, Raleigh, NC). Information regarding details of these assays, including normal ranges, are available at www.lipoprofile.com. Analyses of plasma homocysteine concentrations, sensitive assay of C-reactive protein (CRP), and β-hydroxybutyrate (BOHB) were performed (Quest Diagnostics, Horsham, Pa). Glucose, insulin, and bicarbonate levels were determined in our clinical laboratories.

Statistical Analyses

Sample size for the prospective study in patients with ASCVD was determined to achieve 80% power for detecting whether an HSF-SA diet results in weight loss without adversely affecting serum lipids. Patients with PCOS and RH were observed in clinical practice; sample size was determined by the willingness of these patients to continue the diet and follow-up. Patients with ASCVD had serum studies only at baseline and 6 weeks later, whereas measurements of body dimensions and fasting urinary ketones were repeated weekly. Patients with PCOS and RH had repeated measures of body weight and serum studies taken approximately every 3 months during observation. Serum data from patients with ASCVD were evaluated by analysis of variance using each patient's initial value as a baseline. Inclusion of repeated weights and body measurements in patients with ASCVD and repeated weights and serum studies in patients with PCOS and RH were evaluated by repeated measures analysis of variance, again using the individual patient's initial value as a baseline. Inclusion of these intervening values did not change the statistical significance of changes in any measured outcome vs a paired *t* test comparing only the baseline and last-observed measure. Therefore, Table 1, Table 2,[9] and Table 3 represent comparisons of only the first and last measurements. Values in the text are mean ± SD differences of change between the first and last measurements.

RESULTS

Diet

Diet logs indicated uniform compliance with consumption of one half pound of red meat (precooked weight) or equivalent and starch avoidance at each meal. Unfortunately, accurate measurements of fruits and vegetables were not required; therefore, exact caloric consumption could not be calculated. Patients reported satiety, but the mean ± SD total number of feedings per day decreased only slightly, from 2.9±0.6 to 2.7±0.7 (P=.18). Assuming the patients consumed only the mandatory amount of saturated fat and prescribed portions of fruits and vegetables, each meal would contain at least 600 kcal, resulting in approximately 7500 kJ/d (1800 kcal/d). If previous estimates of caloric expenditure for men[10] and women[11] are extrapolated, almost all weight loss would be due to decreased caloric intake. All patients entered the study with negative fasting urinary ketones and normal fasting serum BOHB levels. In each of the subsequent weekly urine samples from 5 male patients, fasting ketonuria was noted, and all 5 were positive for both elevated fasting urinary ketones and elevated levels of serum BOHB in the sixth-week samples of blood and urine. No patients with normal serum BOHB measurements had ketonuria, and all ketonuric patients had elevated serum BOHB levels.

Table 1. **Changes in Body Measurements in Patients With Atherosclerotic Cardiovascular Disease (N=23) During 6-Week Trial***

Study	Baseline	Final	*P* value
TBW (%)	100	94.8±2.5	<.001
Weight (kg)	113.0±19.5	107.5±18.9	<.001
BMI (kg/m^2)	39.0±7.3	36.8±6.9	<.001
Neck (in)	16.9±1.2	16.5±1.1	<.001
Waist (in)	48.4±5.1	46.2±4.7	<.001
Hip (in)	50.4±6.3	47.8±6.3	<.001
Body fat (%)†	37.3±5.9	36.6±6.3	.02

*All values are mean ± SD. BMI = body mass index; TBW = total body weight, 100% at baseline by definition.
†Calculated.

Changes in Body Measurements in Patients With ASCVD

Mean ± SD body weight decreased 5.5±2.1 kg (P<.001), representing a loss of 5.2%±2.5% of total body weight (TBW) (P<.001). Mean ± SD BMI dropped 2.2±0.7 kg/m^2 (P<.001). Mean ± SD neck size decreased 0.4±0.3 in

Table 2. **Serum Studies in Patients With Atherosclerotic Cardiovascular Disease (N=23) During 6-Week Trial*†**

Study	Baseline	Final	*P* value
Glucose (mg/dL)	106.1±17.7	98.3±9.3	.04
Insulin (μIU/mL)	21.3±13.2	14.8±5.7	.006
Triglycerides (mg/dL)	146.2±82.6	87.8±41.4	<.001
VLDL			
Size (nm)	54.6±6.6	45.6±7.3	<.001
TG (mg/dL)	113.5±81.2	57.4±43.9	<.001
Large (mg/dL)	51.2±45.5	13.6±20.5	<.001
Medium (mg/dL)	40.2±38.6	23.6±19.3	<.001
Small (mg/dL)	17.6±11.0	15.4±13.3	.54
Cholesterol (mg/dL)	167.9±84.9	161.1±41.4	.48
HDL			
Total (mg/dL)	44.1±11.8	42.8±12.8	.34
Size (nm)	8.61±0.39	8.77±0.42	.01
Large (mg/dL)	19.9±12.2	19.5±12.0	.76
Small (mg/dL)	23.5±4.4	22.6±3.8	.26
LDL			
Total (mg/dL)	100.5±27.3	103.6±38.9	.64
Size (nm)	20.6±0.9	21.0±0.7	.02
Medium (mg/dL)	37.9±26.4	30.5±22.0	.26
Small (mg/dL)	35.4±39.5	26.6±27.9	.31
Number (nmol/L)	1156.0±340.9	1122.9±368.2	.68
Homocysteine (μmol/L)‡	9.5±3.0	10.6±2.7	.002
CRP (mg/dL)§	0.21±0.6	0.44±0.7	.17

*All values are mean ± SD. CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein.
†Nuclear magnetic resonance spectroscopic analysis of serum lipids.
‡Homocysteine levels of 5.0 to 15.0 μmol/L are considered low risk.
§CRP levels <0.80 mg/dL are considered low risk.

Table 3. **Weight and Serum Studies in Patients With Polycystic Ovary Syndrome and Reactive Hypoglycemia*†**

	PCOS (24-wk monitoring; n=15)			RH (52-wk monitoring; n=8)		
Study	Baseline	Final	*P* value	Baseline	Final	*P* value
BMI	36.1±9.7	32.4±8.9	<.001	46.8±10.0	37.2±7.5	<.001
TBW (%)	100	85.7±20.3	.008	100	80.1±8.7	<.001
Glucose (mg/dL)‡	90.0±11.3	95.1±86.0	.43	NA	NA	NA
Insulin (mg/dL)‡	24.2±11.8	12.2±5.0	.005	NA	NA	NA
Total cholesterol (mg/dL)	215.3±46.4	205.3±38.9	.16	221.8±41.6	208.5±16.8	.34
Triglycerides (mg/dL)	121.4±63.0	99.0±43.1	.12	137.4±79.1	95.0±30.9	.20
Total HDL (mg/dL)	54.4±15.7	54.6±12.3	.93	46.4±14.7	48.0±8.3	.67
Total LDL (mg/dL)	136.8±43.1	128.7±39.2	.22	144.3±44.8	140.5±18.7	.82

*All values are mean ± SD. BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not available; PCOS = polycystic ovary syndrome; RH = reactive hypoglycemia; TBW = total body weight, 100% at baseline by definition.

†All patients had measurements of weight and fasting serum lipids every 6 to 12 weeks during the observation time. Inclusion of these intervening values did not change the significance of the analysis of data compared with a *t* test between baseline and final value for each study. All patients had no fasting ketonuria detected at the time of serum studies (data not shown).

‡Levels were measured in only 2 patients with RH.

(*P*<.001); mean ± SD waist size decreased 2.2±1.0 in (*P*<.001); and mean ± SD hip size decreased 2.6±0.9 in (*P*<.001). These measurements were used to calculate a 0.7%±1.8% decrease in total body fat (*P*=.02).[12] Changes in body measurements in patients with ASCVD are shown in Table 1.

Serum Studies in Patients With ASCVD

Weight loss appeared to be associated with improvements in insulin sensitivity. Mean ± SD fasting glucose levels decreased 7.8±10.4 mg/dL (*P*=.04), and this was accompanied by a decrease in mean ± SD fasting insulin level of 6.5±8.4 μIU/mL (*P*=.006). The mean ± SD total triglyceride (TG) levels decreased 58.4±42.6 mg/dL (*P*<.001). Decreases in mean ± SD very low-density lipoprotein (VLDL) TG levels (56.1±55.3 mg/dL [*P*<.001]) were revealed by NMR spectroscopic analysis, as were decreases in mean ± SD concentrations of large VLDL (37.6±42.2 mg/dL [*P*<.001]) and medium VLDL (16.6±25.7 mg/dL [*P*<.001]). Small VLDL concentrations were unaffected. Overall, there was a decrease in VLDL size of 9.0±11.4 nm (*P*<.001).

These patients previously had followed a diet restricted in saturated fat and cholesterol as instructed by their cardiologist and reinforced by a registered dietitian. Their diet logs, kept for 1 week before study entry, indicated red meat 1 to 3 times per week and no more than 2 eggs per week. Their diet logs during the study indicated uniform compliance with 1 to 1½ pounds of red meat and 2 to 4 eggs per day, representing increases of approximately 24 g of saturated fat per day and 1000 mg of cholesterol per day. Despite this massive increase in dietary intake, NMR spectroscopic analysis revealed that total cholesterol and HDL cholesterol levels were unchanged. There was an increase in mean ± SD HDL size of 0.16±0.27 nm (*P*=.01). Total LDL cholesterol and its subfractions were unchanged. The mean ± SD LDL size increased 0.4±0.7 nm (*P*=.02). Lipoprotein traits of the metabolic syndrome profile include LDL particle numbers of greater than 1400 nmol/L and 1 or more of the following: LDL size less than 20.5 nm, large HDL concentrations of less than 11 mg/dL, or large VLDL levels of greater than 27 mg/dL.[4] Using these criteria, 10 of 23 patients had a metabolic syndrome profile at baseline despite treatment with statins to goal total LDL levels. At the end of the study, 8 of these 10 patients had changed to a low-risk profile, 2 remained in the high-risk category, and 1 low-risk patient developed a metabolic syndrome profile. Mean ± SD plasma homocysteine levels increased 1.1±1.4 μmol/L (*P*=.002), but CRP levels were unchanged. Serum studies in patients with ASCVD appear in Table 2.

Weight and Serum Studies in Patients With PCOS and RH

Patients with PCOS and RH were monitored for 24 weeks and 52 weeks, respectively, on the HSF-SA diet. Patients with PCOS lost 14.3%±20.3% of TBW (*P*<.008); patients with RH lost 19.9%±8.7% of TBW (*P*<.001) at last observation. There were no significant changes in serum lipid levels in either group. Fasting urinary ketones measured at 6- to 12-week intervals were repeatedly not detected in both groups. Weight and serum studies in patients with PCOS and RH are shown in Table 3.

DISCUSSION

The HSF-SA diet resulted in decreases in body weight and calculated body fat in patients with ASCVD. These de-

creases were accompanied by decreased fasting serum glucose, insulin, and TG levels. An NMR spectroscopic assay of serum lipids showed no effect on total cholesterol level or the LDL and HDL subfractions in these patients who were treated with statins throughout the observation time. Patients with PCOS and RH monitored in clinical practice for longer periods also lost weight and had no changes in serum lipid levels despite receiving no lipid-lowering drug therapy.

Overwhelming evidence shows that addition of saturated fat to an otherwise low-fat diet will adversely affect serum markers of ASCVD.[13-15] Because such effects were so strongly anticipated in this study, only patients treated with statins to goal LDL levels who were also believed to be unable to exercise sufficiently to lose weight were referred for participation. However, some evidence indicated that there may not be a simple relationship between increasing dietary intake of saturated fat and cholesterol and the serum levels of markers of ASCVD. Some humans can adapt to increased intake of dietary cholesterol by decreasing absorption and increasing excretion.[16] Stearic acid has been substituted for monounsaturated fat without adverse effects on serum lipid levels.[17] Westman et al[18] reported decreases in total cholesterol and total TG levels and increases in HDL concentrations in patients prescribed a different ketogenic high saturated fat diet. This is the first report of NMR analysis of lipid subfractions in patients who ingested a high saturated fat diet along with substantial carbohydrate restriction. Of note, despite statin therapy to goal LDL levels of 100 mg/dL, 10 of 23 patients had lipoprotein traits consistent with the "high-risk metabolic profile"[4] before study entry.

Taken together, decreases in weight[19] and levels of glucose,[20,21] insulin,[22] and TG[23] could be considered to improve risks of ASCVD. Decreases in VLDL size and increases in LDL and HDL size[24] may also improve risks, but we know of no studies linking these changes to improved clinical outcome. Plasma homocysteine levels (Table 2) have also been correlated with future coronary events, and although the changes seen appeared not to result in movement to a higher risk quartile,[25] the negative trend is concerning. Finally, CRP levels (Table 2), which also predict future coronary events, were not significantly changed, even when analyzed by nonparametric paired *t* test (*P*=.14), and means of both plasma homocysteine levels and CRP levels remained in the lowest quintile of risk.[26]

The presence or absence of ketosis and its potential role in weight loss is of interest. Patients with type 2 diabetes,[5] PCOS, and RH (Table 3) treated in clinical practice had negative fasting urinary ketones, but only patients in this study had measurable levels of fasting serum BOHB. All 5 men who had elevated levels of BOHB also had detectable ketonuria, suggesting that urinary monitoring may be sufficient to avoid unintended ketosis; why these men became ketotic is unclear. Diet logs and personal interviews indicated compliance with fruit and vegetable intake equal to that of patients with ASCVD. It is difficult to completely exclude ethanol intake in an outpatient study, but all 5 men reported no ethanol intake, as they had been instructed. It is possible that these men misinterpreted their diet prescription and followed a high saturated fat ketogenic diet, as has been prescribed by Atkins.[9] The Westman et al[18] study used this diet; investigators documented ketonuria and saw a significant drop in serum bicarbonate levels associated with a 10% decrease in TBW within 6 months. The mean ± SD serum bicarbonate levels of our patients with ASCVD changed from 27.6±1.94 mEq/L to 26.9±2.57 mEq/L (*P*=.13); of note, the ketotic patients lost no more weight than did their nonketotic cohorts (TBW loss in patients with ketosis [6.77%±2.50%] vs TBW loss in nonketotic patients [4.67%±2.50%]; *P*=.09). A previous study of metabolism showed that when total caloric intake was limited to levels of approximately 1000 kcal/d, patients given high fat contents became ketotic but lost no more weight than when they were given equally caloric-restricted but nonketogenic liquid diets.[27] Thus, ketosis may be unnecessary to induce weight loss and may add little to caloric restriction per se. It may be possible that an HSF-SA diet can result in satiety without ketosis. This is relevant because any dietary therapy for obesity must be maintained, presumably, for life. Of note, however, the sample sizes in all groups were small, and the NMR spectroscopic lipid analysis was done only in patients with ASCVD after a relatively short time. It remains to be shown whether the lack of effect on LDL and HDL particle size and distribution is maintained.

CONCLUSION

The serum lipid measurements in patients with PCOS and RH suggest, but by no means prove, that long-term compliance with an HSF-SA diet can result in continued weight loss without adverse effects on serum lipid levels. Long-term studies, including NMR spectroscopic analysis of lipids, serum homocysteine, sensitive CRP, and other ASCVD markers, appear warranted. Ultimately, all these matters would need to correlate with clinical outcomes, regardless of their direction or degree of change.

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