Lipoprotein Response to a National Cholesterol Education Program Step II Diet With and Without Energy Restriction

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This study examined the efficacy of a National Cholesterol Education Program (NCEP) step II diet (25% fat with <7% saturated fat [SFA]) with and without moderate energy restriction. We tested the hypothesis that moderate energy restriction would improve the lipid profile resulting from an isoweight NCEP step II diet. Twenty hypercholesterolemic subjects (10 men and 10 postmenopausal women) consumed the following three controlled diets, each of 4 weeks' duration, as outpatients: (1) high-fat, high–saturated-fat diet to establish baseline lipids and isoweight energy requirements, (2) NCEP step II diet at isoweight energy, and (3) NCEP step II diet with an energy level 15% less than isoweight. The NCEP step II diet at isoweight energy reduced total cholesterol (TC) by 4% ($P = .015$), high-density lipoprotein cholesterol (HDL-c) by 13% ($P < .0001$), and HDL2-c by 40% ($P < .0001$). The TC:HDL-c ratio increased from 4.9 to 5.5 ($P < .0001$) and was increased in 19 of 20 subjects. Apolipoprotein B (apo B)–containing lipoproteins changed reciprocally: low-density lipoprotein cholesterol (LDL-c) decreased 4% ($P = .008$) and very–low-density lipoprotein cholesterol (VLDL-c) increased 29% ($P < .0001$). Apo B levels did not change. Compared with the NCEP isoweight diet, the NCEP hypocaloric diet significantly reduced VLDL-c (−9%, $P = .014$) and apo B (−5%, $P = .015$). There was an additional reduction in TC (−4%, $P = .073$) and LDL-c (−4%, $P = .126$) with no change in HDL-c ($P = .807$). These data indicate that a NCEP step II diet with energy restriction produces a more desirable lipoprotein response than a NCEP step II isoweight diet. Neither NCEP step II diet improved the TC:HDL-c ratio.

THE AMERICAN HEART Association (AHA)[1] and National Cholesterol Education Program (NCEP)[2] recommend diets with no more than 30% total fat, 10% saturated fat (SFA), and 300 mg/d cholesterol for all persons over 2 years of age. Individuals with total cholesterol (TC) greater than 200 mg/dL who do not show lower blood cholesterol in response to this diet are advised to further restrict their intake of SFA and cholesterol.[3] Both the AHA[1] and NCEP[2,3] advise that dietary carbohydrate should replace the eliminated fat energy. Compared with a diet containing 17% SFA, the second NCEP report[3] predicts a 14% reduction in TC after a step I diet (≤30% fat with <10% SFA). An additional 3% to 7% decrease in TC is predicted after the step II diet (≤30% fat with <7% SFA).

Numerous studies have examined the efficacy of low-fat diets in improving the lipid profile. Studies of low-fat diets either have been controlled, with all food provided, or self-selected, with the subjects responsible for making the appropriate diet choices. Controlled diets containing less than 30% fat generally decrease TC and low-density lipoprotein cholesterol (LDL-c) in hyperlipidemic patients.[4,5] The higher dietary carbohydrate content often increases triglycerides and decreases high-density lipoprotein cholesterol (HDL-c).[4,5] It is hypothesized that the increase in triglycerides is directly responsible for decreased HDL-c.[6] In contrast, self-selected low-fat diets typically produce a more favorable lipid profile without an increase in triglycerides,[7-11] and HDL-c levels may actually increase.[9,10]

Differences in energy intake between controlled and self-selected low-fat diets may account for the observed lipid responses. Controlled diets provide food in quantities to maintain baseline body weight (isoweight energy). In contrast, the energy content of a self-selected low-fat diet may be unintentionally reduced, as decreasing the dietary fat intake often requires an increase in the quantity of food to maintain the energy level of the higher-fat diet. The NCEP states that a reduction in dietary fat may help overweight patients lose weight,[3] but energy restriction is not the primary recommendation of the NCEP reports. The contribution of dietary energy restriction to lipid decreases, apart from clinically significant weight loss, has not been formally tested.

The present study examined in hypercholesterolemic subjects the effects of a NCEP step II diet provided in both isoweight and hypocaloric quantities as controlled diets. We tested the hypothesis that moderate energy restriction would improve the lipid profile resulting from an isoweight NCEP step II diet.

SUBJECTS AND METHODS

Study Subjects

Subjects were men or postmenopausal women not receiving oral estrogen replacement therapy who met the following criteria: age 20 to 70 years, TC 200 to 300 mg/dL and fasting triglycerides less than 200 mg/dL, healthy and free of known coronary heart disease, no regular medications, nonsmoker, aerobic exercise less than three times per week for less than 30 minutes, and body mass index between 20.0 and 27.8 kg/m^2.

Subjects were screened using a health questionnaire. Three blood samples at least 7 days apart after a minimum 12-hour fast were averaged to establish eligibility. Alcohol consumption was proscribed during the lipid screening period. Subjects who met all study criteria provided written informed consent as approved by the Institutional Review Board of The Miriam Hospital. Subjects entered a cohort (four cohorts total) as they were recruited.

Study Diets

Two controlled diets were used in this study, (1) a diet high in both total fat (40%) and SFA (18%) (HFSF baseline diet) and (2) a NCEP step II diet. The overall diet composition is listed in Table 1 and the fatty acid composition of the diets in Table 2. The step II diet was provided

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Table 1. Composition of Controlled Study Diets

Component	HFSF	NCEP Step II
Protein (%TE)	17	15
Lipid, total (%TE)	40	25
SFA	18	6.8
MFA	16	10
PFA	6	8
CHO, total (%TE)	43	60
Sucrose (% of CHO)	8	9
Total dietary fiber (g/1,000 kcal)	8	11
Cholesterol (mg/1,000 kcal)*	194	69

NOTE. Sucrose and total sugar values are from *Sugar Content of Selected Food: Individual and Total Sugar. USDA Home Economic Research Report #48* (1987). Fiber values are from *Provisional Table on the Dietary Fiber Content of Selected Foods and USDA Agriculture Handbook #8.*

Abbreviations: %TE, % total energy; SFA, saturated fat. MFA, monounsaturated fat; PFA, polyunsaturated fat; CHO, carbohydrate.

*Average of 7 days.

for two separate diet periods. During one diet period, the step II diet was provided at the energy level determined in the HFSF diet (isoweight energy). During the other diet period, the subject received the step II diet at an energy level that was 15% less than their isoweight energy (hypocaloric diet). Diet composition was calculated using the Nutripractor program (Practorcare, San Diego, CA).

Diets were developed for a range of baseline energy levels (1,500, 1,800, 2,100, 2,400, and 2,800 calories). Supplemental muffins were formulated to contain the same energy distribution as the diets and provided additional energy for intake between the two baseline energy levels. An energy intake range for each subject was initially estimated with the Practorcare computer program, which uses the Harris-Benedict equation to estimate energy needs. Subjects were weighed Monday through Friday during the controlled diets. Any subject experiencing weight loss during the HFSF baseline period was given additional energy. Subjects kept light clothing at the Nutrition Center for weight measurement to avoid possible influences of seasonal dress on body weight.

All study subjects were free-living. Breakfast was consumed at the Nutrition Center Monday through Friday, with lunch and dinner meals provided to take home. Weekend food was provided on Fridays. All take-out food was provided completely prepared. Subjects were instructed not to consume any other foods or energy-containing beverages during the controlled diets, including no alcoholic beverages. The empty food containers from the previous day were returned each morning and examined by the staff. The only medication permitted was acetaminophen as needed. An anonymous questionnaire for diet compliance was administered after the controlled diets.

Table 2. Fatty Acid Composition of the Controlled Diets (% total energy)

Fatty Acid	HFSF	NCEP Step II
Total SFA	17.69	6.63
4:0	0.78	0.2
6:0	0.44	0.12
8:0	0.27	0.07
10:0	0.59	0.16
12:0	0.66	0.18
14:0	2.49	0.68
16:0	8.21	3.41
18:0	3.62	1.63
Total MFA	12.68	8.14
16:1	0.70	0.2
18:1	11.58	7.8
Total PFA	5.30	7.81
18:2	4.54	7.46
18:3	0.69	0.35

Abbreviations: SFA, saturated fat. MFA, monounsaturated fat; PFA, polyunsaturated fat.

Protocol

The study involved three 28-day controlled diet periods that were each separated by 6 weeks. All subjects first consumed the HFSF diet to establish both the isoweight energy level and baseline lipids to assess the low-fat diet response. Isoweight energy was the mean energy intake that maintained baseline body weight during the HFSF diet. During the second and third diet periods, the NCEP diet was provided as either (1) isoweight or (2) 15% less than isoweight (hypocaloric) energy. The order in which the subjects received the NCEP diets was randomly assigned. During the 6 weeks between each diet, subjects followed their usual diet at home and were encouraged to maintain their baseline body weight. Subjects were weighed during the NCEP diet periods, but the estimated isoweight energy level established with the HFSF diet was not adjusted even if body weight changed. Physical activity was constant, limited to no more than three 30-minute sessions per week and verified by questionnaire during each controlled diet period.

Blood samples after a 12-hour fast were obtained on days 22, 25, and 29 of each controlled diet period. Subjects were asked to refrain from exercise during the fast.

Lipid, Lipoprotein, and Apolipoprotein Analysis

Cholesterol[12] and triglycerides[13] were determined on a Beckman CX 4 (Beckman Instruments, Brea, CA). HDL-c and HDL3-c levels were determined by the method of Gidez et al.[14] HDL2-c was determined by subtracting HDL3-c from total HDL-c after correcting for dilution. LDL-c was calculated using the Friedewald equation.[15] The lipid laboratory at The Miriam Hospital has been a Centers for Disease Control Lipid Standardization Program since 1977, and is currently in the monitoring phase III.

Apolipoprotein A-I (apo A-I), apo A-II, and apo B were assayed by nephelometry on a Behring Nephelometer 100 (Behring Diagnostics, Somerville, NJ) using antisera raised in goats to purified apo A-I and apo A-II and to intact LDL for apo B. Secondary standard pools were prepared for apo A-I and apo B using as primary standards serum samples supplied by the Lipid Standardization Laboratory of the Centers for Disease Control. Purified apo A-II, quantified by amino acid analysis, was used to prepare a secondary serum standard for apo A-II. Interassay coefficients of variation for apo A-I, apo A-II, and apo B were 2.6%, 5.0%, and 1.8%, respectively. Serum was stored at −70°C. All lipid and lipoprotein samples from an individual subject were analyzed in a single autoanalyzer determination at the completion of the study.

Statistical Analysis

The averages of lipid, lipoprotein, and apolipoprotein values from days 22, 25, and 29 of each controlled diet were used in statistical analyses. The study was designed to test the response of lipids to the recommended NCEP step II diet (comparison of HFSF to NCEP isoweight) and to test the contribution of energy restriction to a low-fat diet (comparison of NCEP isoweight to NCEP hypocaloric). Differences among study diets were first tested for statistical significance with repeated-measures ANOVA. When an overall ANOVA was statistically significant, differences between diets were further assessed with paired *t* tests and Bonferroni adjustment for multiple comparisons. Values are reported as the mean ± SD. The data were also analyzed by comparing the absolute changes in lipid, lipoprotein, and apolipoprotein levels between the baseline HFSF and isoweight NCEP step II diets and

between the isoweight and hypocaloric NCEP step II diets using Wilcoxon signed-rank tests. All statistical analyses were performed with SPSS (Chicago, IL).

RESULTS

Approximately 150 people responded to advertisements describing the study, and 43 satisfied the health history criteria. Twenty-two subjects met the lipid criteria. Ten men and 10 women completed the study. One subject decided not to participate in the study, and one withdrew after 4 weeks due to a change in work schedule. The mean lipid and lipoprotein values at the time of recruitment were as follows: TC, 239 ± 25 mg/dL; LDL-c, 167 ± 24 mg/dL; HDL-c, 52 ± 9 mg/dL; and triglycerides, 101 ± 36 mg/dL. The women, selected to be postmenopausal, were older (mean, 58 ± 6 years; range, 47 to 67) than the men (men, 42 ± 14; range, 25 to 65; $P = .006$).

Compliance with the controlled diet was high based on inspection of empty food containers and responses to the anonymous questionnaires. In two of the total 12 controlled diet periods, one subject admitted to consuming a food that was not provided. The mean energy intake (calories) was as follows: isoweight: women, 1,869 ± 80; men, 2,745 ± 325; hypocaloric: women, 1,590 ± 69; men, 2,335 ± 276. There was no difference in the change in body weight observed during the HFSF baseline diet relative to the NCEP step II isoweight diet (HFSF, −0.4 ± 0.9 kg; NCEP isoweight, −0.6 ± 0.8 kg). The weight change during the NCEP hypocaloric diet (−1.9 ± 1.0 kg) was statistically greater than the weight change during the NCEP isoweight diet ($P < .0001$). There were no statistical differences between the weights on day 1 for each of the diets.

Response to the NCEP Diet

Lipid, lipoprotein, and apolipoprotein values after the controlled diets are presented in Table 3. All NCEP isoweight diet changes are compared with the values obtained after the HFSF baseline diet. All NCEP hypocaloric diet changes are compared with the NCEP isoweight diet. The NCEP isoweight diet significantly reduced TC ($P = .015$), although it decreased by only 4%. Only three subjects had TC decreases greater than 10%, and 10 subjects had less than a 5% decrease. Reductions in LDL-c (−4%, $P = .008$) were also small and associated with significant increases in VLDL-c (29%, $P < .0001$) and no change in apo B ($P = .868$). Twelve subjects had a baseline LDL-c greater than 160 mg/dL, and neither NCEP diet decreased the LDL-c to less than 160 mg/dL. The NCEP hypocaloric diet compared with the NCEP isoweight diet reduced both apo B (−5%, $P = .015$) and VLDL-c (−9%, $P = .014$), but LDL-c did not change ($P = .126$). The NCEP isoweight diet increased triglycerides by 30% ($P < .0001$). Increases occurred in 19 of 20 subjects (range, 0% to 95%). The NCEP hypocaloric diet reduced triglycerides by 10% relative to isoweight values ($P = .014$), with 17 subjects showing reductions in triglycerides with the hypocaloric diet (range, +20% to −37%).

The NCEP isoweight diet reduced HDL-c by 13% ($P < .0001$). Eighteen of 20 subjects had reductions in HDL-c (range, 0% to −36%). Decreases in HDL-c were due to decreases in the HDL2-c subfraction, and all subjects had reductions in HDL2-c after the NCEP isoweight diet (range, −14% to −65%, $P < .0001$). The hypocaloric diet did not further change either HDL-c or HDL2-c. The large reductions in HDL-c after the NCEP isoweight diet were primarily responsible for the 11% increase in the TC:HDL-c ratio ($P < .0001$). The hypocaloric diet reduced this ratio by 3% ($P = .056$), with 12 of 20 subjects showing reductions, but the mean TC:HDL-c ratio still remained higher than on the HFSF diet. Nonparametric analyses produced similar results.

Table 3. Lipid, Lipoprotein, and Apolipoprotein Values After the Controlled Diet Periods (N = 20)

	NCEP Step II Diet				
Parameter	HFSF	Iso	Iso *v* HFSF *P*	Hypo	Hypo *v* Iso *P*
Cholesterol (mg/dL)					
Total	245 ± 41	233 ± 34	.015	224 ± 38	.073
LDL	177 ± 32	168 ± 29	.008	161 ± 32	.126
HDL	50 ± 12	43 ± 8	<.0001	43 ± 8	.807
HDL2	16 ± 8	10 ± 5	<.0001	10 ± 5	.309
HDL3	34 ± 6	33 ± 4	.307	33 ± 5	.389
VLDL	17 ± 4	22 ± 6	<.0001	19 ± 6	.014
Triglyceride (mg/dL)	86 ± 23	109 ± 30	<.0001	98 ± 28	.014
TC/HDL ratio	4.9 ± 0.8	5.5 ± 0.9	<.0001	5.3 ± 0.9	.056
Apolipoprotein (mg/dL)					
B	139 ± 17	138 ± 16	.868	131 ± 19	.015
A-I	148 ± 19	136 ± 14	<.0001	134 ± 15	.306
A-II	34 ± 4	36 ± 4	.0006	35 ± 4	.025

NOTE. Values are the mean ± SD. *P* values were determined by paired *t* tests.

Abbreviations: Iso, NCEP diet at isoweight energy; Hypo, NCEP diet with energy 15% less than isoweight energy.

DISCUSSION

This study assessed the more restrictive NCEP diet (step II) at isoweight energy, as well as combined with energy restriction (NCEP hypocaloric), to determine the contribution of energy restriction to the lipid profile response. The results support the hypothesis that differences in energy intake affect the lipid response to low-fat diets. The mean decrease (−4%) in TC after the NCEP isoweight diet compared with the HFSF baseline diet was considerably less than the 17% to 24% reduction predicted by the NCEP.[3] This is of particular note because the baseline diet composition (40% total fat with 18% SFA) was selected to maximize the NCEP diet response.

The NCEP isoweight diet decreased HDL-c by 7 mg/dL, and most of this decrease occurred in the HDL2-c subfraction. As a consequence of the decrease in HDL-c, the TC:HDL-c ratio increased from 4.9 to 5.5 with the NCEP isoweight diet. The small decreases in TC and LDL-c combined with the decreases in HDL-c and HDL2-c and no change in apo B indicate that the NCEP isoweight diet did not improve the overall lipid profile in these hyperlipidemic men and women.

A reduction in HDL-c when carbohydrate is substituted for SFA is not unexpected.[16-20] Substitution of polyunsaturated fat for SFA may[21,22] or may not[23,24] reduce HDL-c. Substitution of monounsaturated fat for SFA, in contrast, has minimal effects on HDL-c.[16-20]

The hypocaloric low-fat diet was designed to mimic a patient self-selecting a prescribed low-fat diet. Energy intake of

self-selected low-fat diets in a research setting has been shown to be unintentionally hypocaloric compared with the energy intake in diets containing higher amounts of dietary fat.[25,26] The hypocaloric diet period of the present study tested the contribution of energy restriction combined with dietary fat restriction to lipid reduction. The hypocaloric low-fat diet period in the present study reduced VLDL-c and apo B compared with the low-fat isoweight diet. Although the additional decrease in TC after the hypocaloric diet was not statistically significant, the reduction resulted from nonsignificant decreases in LDL-c and VLDL-c without further decreases in HDL-c.

The overall lipid profile after the hypocaloric NCEP step II diet improved compared with the lipid profile after the NCEP step II diet at isoweight energy. However, neither NCEP step II diet resulted in a healthy TC/HDL-c level. The lipid results after the hypocaloric NCEP diet suggest that the lipid improvement ascribed to reduced fat intake in self-selected low-fat diet studies may actually be due in part to the contribution of energy restriction and not solely to the reduction in dietary fat intake. Energy restriction of the step II diet was required to decrease apo B and triglycerides, although clinically meaningful weight loss did not occur in this 4-week study (mean, -1.9 ± 1.0 kg). Low-fat diet studies that specifically allow weight loss have suggested that lipid changes are enhanced with weight loss.[4,5,10,11,27,28] Indeed, Lichtenstein et al[4] concluded that weight loss is essential for lipid improvement with a low-fat diet, although weight loss alone can improve the lipid profile.[29]

Schaefer et al[30] also evaluated the effect of a controlled NCEP step II diet in hypercholesterolemic men and women. Subjects in that study had baseline lipids comparable to our subjects but showed four times the reduction in LDL-c that we observed (-18% *v* -4%). Since our baseline diet contained more SFA (18% *v* 14%), one would have predicted larger effects in our study. The greater lipid reductions found in their study relative to our study are not readily explained. They may be partly due to an unrecognized energy difference between the high-fat and low-fat diets used by these investigators. In our study, the energy intake was kept constant for comparison of the HFSF baseline diet and NCEP isoweight diet, and we attempted to maintain body weight during the baseline HFSF diet. Their study allowed adjustments in energy intake and stable weight was defined as ± 1 kg; therefore, direct comparisons between the two studies are difficult.

The equations of Keys et al[31] and Hegsted et al[32] predict that changing from a high-fat, high–saturated-fat diet to the NCEP step II diet will reduce TC by 30 to 50 mg/dL. We observed much smaller cholesterol changes (mean, -11 mg/dL). More recently published studies of a NCEP step II diet[33,34] showed lipid responses that were similar to the lipid changes we observed. Since these studies[33,34] were outpatient diet studies and subjects, on average, lost weight, these small changes in lipids are intriguing. The Dietary Effects on Lipoprotein and Thrombogenic Activity (DELTA) Study,[35] which was a controlled-diet study, produced slightly greater lipid reductions than observed either in our study or in previous studies.[33,34] However, the DELTA Study results were also less than the prediction equations.

The NCEP diet in isoweight or hypocaloric quantities increased triglycerides by 15% to 29% relative to baseline values. This phenomenon has been reported in numerous studies of low-fat diets. Early diet studies using formula diets with extreme amounts of carbohydrate and negligible fat content produced marked elevations in triglycerides (>100%) in normolipidemic subjects.[36-38] Diets with moderate levels of fat (20% to 25%) will also produce triglyceride elevations.[39-41] In contrast, diets providing approximately 30% or greater energy from fat do not generally increase triglycerides or decrease HDL-c.[42,43] Low-fat diets with large amounts of dietary fiber also prevent carbohydrate-induced triglyceride elevations.[44,45] The significance of this "carbohydrate induction" of plasma triglycerides has been debated for more than three decades. Previous studies suggested that triglyceride elevations were transient,[46,47] but more recent investigations showed unabated effects after 12 months.[39,48] Moreover, virtually all diets substituting carbohydrate for fat markedly decrease HDL-c.[18-20]

In summary, dietary advice for blood lipid improvement should emphasize the restriction of both SFA and total diet energy, especially for overweight patients. As the current diet guidelines do not specify a lower limit on the recommendation for the percentage of dietary fat, advice to reduce dietary fat should caution that restriction of dietary fat calories without energy restriction may worsen blood lipids. The results of the current study indicate that replacing dietary fat with carbohydrate may not improve the lipid profile of hypercholesterolemic patients. Restricting SFA and not replacing the eliminated fat energy is an alternative that may be more efficacious for lipid reduction. Although the 15% reduction in energy in the present study did not produce meaningful weight loss during the 4 weeks of the study, this moderate energy reduction improved the overall lipoprotein profile. Moreover, increases in physical activity, as suggested by the NCEP reports, may ameliorate the effects of carbohydrate-enriched diets on blood lipids.

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