EFFECT OF CHOLESTEROL-LOWERING DIETS ON INDICES OF DEPRESSION AND HOSTILITY[1]

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ABSTRACT

Increased injury deaths have been reported among treatment groups in cholesterol lowering trials, leading to speculation that lipid lowering may result in behavioral disorders. We investigated this in 319 men enrolled in a 2-year trial of lipid lowering diets who completed measures of depression and hostility at entry and 24 months later. Mean Beck Depression Inventory (BDI) scores were lower after 24 months (3.8 versus 3.3, $p < 0.05$) and Symptom Checklist 90-Revised (SCL-90) depression and hostility scores were unchanged. After adjustment for potential confounding, 24-month hostility and BDI scores were unrelated to lipid changes. A small inverse association of borderline statistical significance ($B = 0.034$, $p = 0.08$) was noted between 24-month SCL-90 depression scores and lipid changes. Lipid lowering diets had no significant adverse effect on psychological function and are consistent with current dietary recommendations.

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INTRODUCTION

Early trials of the primary prevention of coronary artery disease showed reductions in coronary heart disease (CHD) but not total mortality (1–3). Several early trials reported increased but not statistically significant risk of traumatic death among treated individuals (e.g. 4–6). Meta-analyses of these trials reported excess mortality from trauma in treatment versus control groups comparable in magnitude to the reduction in CHD deaths and higher than population levels of trauma death (7,8). Odds ratios were nearly identical for injury deaths in the treatment groups of both dietary (OR = 1.76) and drug trials (OR = 1.75) (7).

It has been speculated that the excess injury-associated mortality in lipid lowering trials results from increased psychopathology associated with lipid lowering (7–11). Several cross-sectional studies have reported associations between low lipid levels and psychiatric or behavioral disorders (12–16), while others have reported mixed findings (17) or no association (18,19). In one study (20), self-reported dietary change among participants was associated with decreases in depression and hostility, but the amount of cholesterol lowering was small and participants were not randomly assigned to dietary interventions. Mechanisms by which low or lowered cholesterol might lead to psychopathology have not been extensively investigated (21–25). There is some evidence from primates that low-fat diets may be associated with increased aggression (26,27). One small human study suggested that, in women, cholesterol lowering diets may be associated with reduced levels of tryptophan and alteration of serotonin, which, in turn, may lead to altered mood states (28). The mechanisms for any causal relationships among low or lowered lipid levels, psychopathology, and traumatic death continue to be debated (23,24,29).

We examined data from the Dietary Alternatives Study (DAS) (30,31), a 2-year trial of four lipid lowering diets, to explore the relationship between lipid lowering and psychological well-being. Participants had elevated cholesterol levels at baseline, achieved clinically meaningful lipid lowering, and completed depression and hostility measures both prior to the dietary intervention and after 24 months. Therefore, it was possible to examine changes in hostility and depression in relation to clinically meaningful reductions in plasma cholesterol levels.

METHODS

Subjects

The DAS investigated the efficacy of fat- and cholesterol-restricted diets among hypercholesterolemic and combined hyperlipidemic men and was conducted at a large Puget Sound, Washington, area worksite by the Northwest Lipid Research Clinic (NWLRC) from 1985 to 1989 (30,31). To be eligible, men were required to have fasting low-density lipoprotein cholesterol (LDL-C) levels at or above the age-specific 75th percentile and not using lipid altering medication, have triglyceride under 12.9 mmol/L, be 21 or older, be free of medical conditions known to induce secondary hyperlipidemia, not be maintaining a fat-restricted diet, and have a spouse or partner willing to participate by attending dietary instruction (31).

For the present analyses, participants were required to have blood cholesterol data at baseline and 24-month follow-up and to have completed baseline and 24-month administrations of two measures of psychological distress, the Hopkins Symptom Checklist-90-R (SCL-90) (32) and the Beck Depression Inventory (BDI) (33). Of 508 subjects enrolled in diet classes, 417 (82%) completed the 24-month trial, and 319 of these (76%) were eligible for the current analyses.

Procedure

Prior to diet instruction, participants completed the SCL-90 and BDI. Fasting blood samples were collected for lipid analysis. Subjects were randomly assigned to diets targeted to contain 30%, 26%, 22%, or 18% of calories from fat. Diet instruction took place in eight weekly group sessions. Instructional methods, diet composition, and study methods have been detailed elsewhere (32,34). At

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24 months, participants completed both the BDI and the SCL-90 and had blood drawn for lipid analyses.

Measures

Beck Depression Inventory (BDI): The 21-item Beck Depression Inventory is a widely-used clinical assessment tool developed to detect depressive symptoms (33). The BDI has high reliability, is associated with other indices of depression and with clinical evaluations, and is responsive to changes in depressive symptoms over time (35,36).

Symptom Checklist-90-Revised (SCL-90): The SCL-90 measures psychological distress and contains nine subscales, including depression and hostility (32,37,38). The depression and hostility subscales have high internal consistency and test–retest reliability (32) and are correlated with indices of similar conditions (39). The depression scale is sensitive to changes in depressive symptoms over time (32,38).

Lipoprotein Analysis: Fasting blood samples were delivered on ice within 3 hours to the Northwest Lipid Research Laboratory and analyzed promptly. Results included total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides (31).

Statistical Analysis

The 319 participants with complete data at baseline and 24 months were compared to excluded participants on baseline measures of psychological distress; age; total caloric intake; percent of calories as fat; and total, LDL, and HDL cholesterol to assess the potential for selection bias.

Group means and standard deviations were computed for each administration of the BDI and SCL-90. Scores on the SCL-90 depression and hostility scales were converted to *T*-scores for analysis using nonpatient norms (32). Because it was anticipated that scores on measures of depression and hostility might be skewed, natural log transformations of BDI and SCL-90 scores were computed. All analyses were computed using both untransformed and log transformed values; where no differences in results were observed, untransformed values are reported.

Changes in symptoms of depression and hostility over the course of follow-up, irrespective of lipid lowering, were examined. Paired *t*-tests compared BDI and SCL-90 scores from baseline to 24 months.

Three separate simultaneous multiple linear regression analyses examined the adjusted relationship between change in LDL-C (defined as pretreatment LDL-C minus 24-month LDL-C) and each of three outcome measures: BDI, SCL-90 depression, and SCL-90 hostility scores. Each analysis adjusted for age, diet assignment, lipid disorder phenotype (either hypercholesterolemia or combined hyperlipidemia), baseline LDL-C, baseline caloric and fat intake from 4-day food records, and the appropriate baseline BDI or SCL-90 score (i.e. the baseline score on the measure of psychopathology that matched the outcome measure for a given analysis).

RESULTS

Those participants who completed the study and provided complete data and those who either dropped out or provided incomplete data were similar in baseline SCL-90 depression and hostility scores, LDL-C and HDL-C, age, and percent calories from fat (Table 1). Participants excluded from the analyses had slightly higher baseline plasma total cholesterol, slightly but not statistically significantly higher BDI scores, and lower reported baseline caloric intake. For both groups, SCL-90 depression and hostility *T* scores were comparable to normative scores and were within the normal range (32), and BDI scores were well within the nondepressed range (33,35). Among the 319 participants included in the current analyses, total cholesterol was lowered 5.3% (6.47 versus 6.13 mmol/L, $p < 0.001$) and LDL-cholesterol was lowered 6.7% (4.52 versus 4.22 mmol/L, $p < 0.001$) after 24 months.

TABLE 1
Comparison of Participants Included and Excluded from Analyses

	Included (n = 319) Mean ± SD	Excluded (n = 189) Mean ± SD
BDI[a]	3.3 ± 3.5	4.4 ± 4.1
SCL-90 depression[b]	49.5 ± 9.2	49.9 ± 10.3
SCL-90 hostility[b]	48.9 ± 8.2	49.3 ± 9.2
Total cholesterol (mmol/L)	6.46 ± 0.78	6.62 ± 0.85*
LDL-cholesterol (mmol/L)	4.52 ± 0.67	4.60 ± 0.80
Age (years)	46.7 ± 9.8	46.6 ± 10.2
Daily energy intake (Kcal)	2341 ± 597	2228 ± 551*
Kcals from fat (%)	35.4 ± 6.4	36.1 ± 6.7

Notes: SD = standard deviation; BDI = Beck Depression Inventory; SCL-90 = Symptom Checklist 90—Revised; mmol/L = millimoles per liter; LDL-C = low-density lipoprotein cholesterol; Kcal = kilocalories.
[a] Range, 0–63.
[b] *T*-scores based on nonpatient norms.
* $p < 0.05$.

TABLE 2
Mean Scores on Indices of Depression and Hostility at Baseline and 3 and 24 Months Post-Intervention

	Baseline Mean ± SD	24 months Mean ± SD
BDI[a]	3.8 ± 3.5	3.3 ± 3.5*
SCL-90[b] depression	49.5 ± 9.2	49.1 ± 9.3
SCL-90[b] hostility	48.9 ± 8.2	48.5 ± 8.5

Notes: SD = standard deviation; BDI = Beck Depression Inventory; SCL-90 = Symptom Checklist 90—Revised.
[a] Range, 0–63; observed range, 0–20.
[b] T-scores based on nonpatient norms.
* $p < 0.05$ for paired *t*-test.

Indices of depression and hostility at baseline and 24 months are shown in Table 2. BDI scores were significantly lower at 24 months compared to baseline. SCL-90 depression and hostility *T* scores showed no significant change between baseline and 24 months.

Results from multiple linear regression analyses revealed baseline BDI and SCL-90 scores to be the only substantial predictors of 24-month BDI and SCL-90 scores; higher baseline scores were associated with higher scores at 24 months (data not shown). Age; diet assignment; lipid disorder phenotype; and baseline calories, dietary fat, and baseline and 24-month LDL-C were not significantly associated with 24 month psychopathology. (In separate analyses, changes in calories from fat from baseline to 24 months were not associated with changes in depression or hostility scores.) Results did not differ using log transformed variables.

After adjustment for covariates, LDL-C changes were not independently associated with 24-month BDI ($B = 0.002$, $t = 0.20$, $p = 0.84$) or SCL-90 hostility ($B = 0.021$, $t = 1.01$, $p = 0.29$) scores. The adjusted association between LDL-C change and

24-month SCL-90 depression T scores was small but approached conventional levels of statistical significance ($B = 0.034$, $t = 1.76$, $p = .08$). For example, an LDL-C drop of 0.3 mmol/L—the mean change in the current study—would be associated with a 0.42-point increase in SCL-90 depression scores. Among those in the upper 10% of LDL-C reduction with a mean reduction of 1.1 mmol/L, a change in SCL-90 depression scores of 1.47 points would be expected. (No significant differences were observed between this group and other participants on changes in BDI or SCL-90 scores.)

DISCUSSION

As a group, participants in the Dietary Alternatives Study showed little evidence of increased psychological distress resulting from participation in the dietary cholesterol lowering trial. Scores on the SCL-90 depression and hostility scales at 24 months showed virtually no change from baseline. BDI scores improved slightly but significantly from baseline to 24 months. At all administrations, mean SCL-90 and BDI scores were well within "normal" ranges. These results suggest that, despite effective LDL-C lowering (30), the cholesterol lowering diets in the DAS were not associated with generally increased levels of psychological distress. There were no significant associations between LDL-C lowering and indices of psychological well-being in multivariate analyses. The adjusted association between 24-month SCL-90 depression scores and change in LDL-C levels approached conventional levels of statistical significance, but changes in LDL cholesterol greater than that observed in our dietary interventions would be required for important changes in depressive symptoms to be detected, even if a causal relationship between lipid lowering and depressive symptoms existed. Nevertheless, further investigation is warranted to determine whether specific subpopulations can be identified which are at risk of developing depressive symptoms as a result of lipid lowering.

Our results are consistent with two cohort studies and recent clinical trials and quantitative reviews. The Family Heart Study (20) reported positive associations between reduction in dietary fat intake and reductions in psychopathology among a cohort of individuals at low risk for heart disease. Significant decreases in hostility were reported among participants in the Coronary Artery Risk Development in Young Adults study with initially high cholesterol levels and who exhibited substantial nonmedicated decreases in cholesterol over 5 years (40). Overall, changes in hostility were unrelated to changes in cholesterol. While it is possible that these findings result from bias inherent in observational studies, it is also possible that successful dietary fat reduction and cholesterol lowering are associated with increased self-efficacy and sense of well-being (41).

Two large clinical trials of reductase inhibitors (statins) recently reported reductions in both CHD and total mortality, without evidence of increased non-CHD deaths (42,43). A reanalysis of early clinical trials by Cummings and Psaty (23) also found limited evidence of increased injury mortality among treated individuals. Furthermore, a comprehensive review by Gould and colleagues (44) reported a 30% increase in non-CHD deaths in fibric acid trials only and no association between non-CHD deaths and other interventions or between non-CHD deaths and degree of lipid lowering after accounting for treatment modality. These studies suggest that if lipid lowering is associated with psychopathology and injury, it may be confined to specific classes of medications and not with lipid-lowering per se, although the issue has not definitively been settled (29).

Our results reinforce the need to distinguish between cross-sectional studies associating low lipids and psychopathology and prospective studies examining lipid lowering and development of psychopathology (22). Cross-sectional studies of lipid levels and psychological symptoms have provided mixed results on this question and have not addressed the important issue of whether cholesterol lowering is associated with increased psychological symptoms.

Our study has potential limitations. First, the sample eligible for analysis was limited to the 76% of participants completing the 2-year follow-up with complete data. While generally similar to subjects available for analysis, noncompleting subjects had slightly higher total cholesterol levels and nonsignificantly higher BDI scores. In addition, individuals with psychiatric conditions or predisposition—and who may be more susceptible to any adverse psychological effects of lipid lowering—may have been less likely to be represented in an employed population or to volunteer for the study and, once randomized, less likely to complete the study or the questionnaires, or less likely to adhere to the dietary regimen. Mean BDI scores were similar for those who completed the study compared to those who did not, however, and groups did not differ on SCL-90 measures of depression and hostility. Our findings therefore do not rule out adverse effects among a subset of susceptible persons and do not address other populations, such as women and the elderly, although we have no reason to believe that findings would differ.

Our investigation focused on the possibility that changes in depression and hostility symptoms might mediate the potential relationship between cholesterol lowering and injury. It is possible that other mediating influences not investigated may also play a role in any association between lipid lowering and injury. In addition, it is possible that our measures of symptomatology, particularly for hostility, were not sensitive enough to detect changes over time.

Although recent clinical trials have reported substantially greater lipid lowering than our dietary intervention without increased injury mortality, our study does not address lipid lowering of the magnitude seen in drug trials. It is possible that our findings reflect the influence of a limited range of lipid lowering.

In summary, the current study suggests that lipid lowering by dietary means was not associated with general increases in psychological symptoms as measured by standard clinical inventories. Scores on measures of depression and hostility did not worsen over the course of an extended follow-up and cholesterol lowering was not significantly associated with increases in psychological symptoms. These findings are consistent with current dietary recommendations (45) aimed at reducing population cholesterol levels inexpensively and safely.

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