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Lipid-Lowering Medication Use and Aggression Scores in Women: A Report from the NHLBI-Sponsored WISE Study

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Abstract

Aim—The aim of this study was to examine the association between the use of lipid-lowering medication and aggressive responding, hostility, cynicism, and depression scores in women undergoing coronary angiography.

Methods—The cohort included 498 women from the National Heart, Lung and Blood Institute (NHLBI)-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. WISE is a four-center study of women with chest pain who underwent quantitative coronary angiography for suspected myocardial ischemia. The psychosocial indices included the Cook Medley Hostility questionnaire, measuring aggression, hostility, and cynicism, and the Beck Depression Inventory (BDI).

Results—Compared to those not on lipid-lowering medication, women receiving lipid-lowering pharmacotherapy were older (62 vs. 55 years, $p < 0.001$) and had more hypertension, dyslipidemia, diabetes, and coronary artery disease (CAD, defined as ≥50% stenoses in at least one epicardial artery) (all $p < 0.003$). Women on lipid-lowering medication had higher aggressive responding scores than those not on medication, 3.0 ± 1.8 vs. 2.7 ± 1.7, respectively (age-adjusted $p < 0.003$). This association persisted after adjustment for coronary risk factors, education, and extent of angiographic disease (CAD) ($p < 0.005$), and after exclusion of women using psychotropic medications ($p < 0.001$). Hostility, cynicism, and depression scores did not differ by medication use.

Conclusions—In women, lipid-lowering medication may predispose to aggression without affecting hostility or mood, but this hypothesis requires evaluation in placebo-controlled clinical trials.

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INTRODUCTION

A CROSS MANY OBSERVATIONAL STUDIES, low serum cholesterol has been associated with violence and suicidality and with heightened rates of nonillness mortality (death from suicide or trauma).[1-9] This literature raises some concern because there is a worldwide emphasis on reducing serum cholesterol levels as a means of preventing cardiovascular disease (CVD). A 1990 meta-analysis of clinical trials of cholesterol reduction in men free of vascular disease at enrollment (Le., trials of primary prevention) found that cholesterol-lowering treatments increased nonillness mortality by about 70%.10 Subsequently, however, statin-class medications have become the predominant physician-prescribed modality for treating hypercholesterolemia, and such drugs have not been associated with any increase in nonillness mortality in several large trials.11

It should be noted that the large majority of participants in even these more recent clinical trails have been men, and, moreover, the eligibility requirements have tended to exclude individuals with psychiatric disorders, such that few deaths from suicide or trauma occur. Also, there is accumulating evidence that cholesterol-lowering drugs may adversely affect the brain, cognitive performance, and mood.[12-16] Although such findings are not universal,[17] questions persist about the possible effects of serum cholesterol reduction on suicide and violence,[18, 19] and information concerning this issue in women is particularly scarce.

Among several psychological mechanisms through which low or lowered cholesterol might be associated with suicide and violence, depression, hostility, and aggression are considered in the current study. A history of aggression predicts future aggressive acts and antisocial behavior, as well as suicide risk in both youth and older adults.[20,21] Here, we examine the relationship between cholesterol-lowering interventions (predominantly statin drugs) and self-reported aggressive responding, hostile affect, cynicism, and depression in a cohort of women undergoing evaluation for suspected myocardial ischemia.

MATERIALS AND METHODS

The Women's Ischemia Syndrome Evaluation (WISE) study is a National Heart, Lung and Blood Institute (NHLBI)-sponsored four-center study that aims to improve diagnostic testing in the evaluation of ischemic heart disease in women. A total of 954 women aged ≥ 18 years were enrolled between 1996 and 2000. Each center obtained institutional review board approval and participant consent before the initiation of testing. All women had clinically indicated angiograms for chest pain or suspected myocardial ischemia or both. Baseline evaluation included a physical examination, phlebotomy for a fasting blood sample, and the collection of demographic and psychosocial data, all of which were obtained at a single visit. Use of cholesterol-lowering medication was self-reported on the baseline fonn. Major exclusion criteria for the WISE were comorbidity that could compromise 1-year follow-up, pregnancy, contraindications to provocative diagnostic testing, cardiomyopathy, New York Heart Association class IV congestive heart failure (CHF), recent myocardial infarction (MI), significant structural heart disease, and a language barrier to questionnaire testing. Full details of the protocol and design of the WISE study have been published.[22]

Lipoprotein analyses

Lipoprotein detenninations were performed at a core laboratory at Cedar-Sinai Medical Center, Los Angeles, California, enrolled in the Centers for Disease Control and Prevention (CDC) lipid standardization program. Total plasma cholesterol (TC), triglycerides, and high-density lipoprotein cholesterol (HDL-C) were determined by enzymatic assay, and low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald fonnula as previously

published.[23] The coefficients of variation (CV) for TC, HDL-C, and triglycerides were 1.80%, 1.23%, and 3.93%, respectively.

Quantitative coronary angiographic analyses

Coronary angiograms were analyzed by an experienced core laboratory at Rhode Island Hospital, Providence, Rhode Island. Measurements included quantitative assessment as to the presence, severity, and complexity of epicardial coronary stenosis, using previously published methods.[24] Coronary artery disease (CAD) was defined as ≥50% stenosis in one or more epicardial arteries.

Psychological measures

Cook Medley scores used in the WISE study consisted of 27 items from the larger 50-item version of the Cook Medley hostility inventory (Ho) that measures aggressive responding, cynicism, and hostile affect. There are 9 items that assess aggressive responding (range 0–9), 5 items that measure hostile affect (range 0–5), and 13 items that assess cynicism (range 0–13). The internal reliability (Cronbach's alpha) of the sum of the 27 items of the Ho used in this sample was alpha = 0.83. The Ho scale is often described as a measure of cynical attitudes and the cognitive component of hostility. Total Ho scores are prospectively associated with coronary heart disease (CHD) and events and all-cause mortality.[25,26] Although there have been failures to replicate the prospective association between Ho scores and health outcomes,[27-29] a meta-analysis[30] concluded that the Ho scale is most predictive of all-cause mortality and, to a lesser extent, CHD (after controlling for other CHD risk factors) relative to other measures of hostility. The test/retest reliability of the Ho was 0.84 over 4 years in a sample of 1653 men.[25] Sample items from the cynicism scale include: No one cares what happens to you. It is safer to trust no one. Most people make friends because friends are likely to be useful to them. The aggressive responding scale includes: When someone does me wrong, I feel I should pay him back if I can just for the principle of the thing. I have at times had to be rough with people who were rude or annoying. I do not blame a person for taking advantage of someone who lays him-self open to it. The hostile affect subscale includes: People often disappoint me. Some of my family have habits that bother and annoy me very much. I do not try to cover up my poor opinion or pity of a person so that he won't know how I feel.

The Beck Depression Inventory (BDI) is a 21-item instrument designed to measure the symptoms of depression in both adolescents and adults. The BDI measures severity of cognitive and somatic symptoms of depression and includes items that describe manifestations of depression in relation to general life satisfaction, relations with others, appetite, sleep, and libido. The questions ask about symptoms within the last 2 weeks. The items are rated on a 4-point scale, with a range from 0 to 3 in terms of severity; total scores range from 0 to 63. Higher scores are indicative of more symptoms of depression.[31]

Statistical methods

Data are presented as means and standard deviations (SD) or standard errors (SE) for continuous variables and frequencies for categorical variables. The general characteristics of women using and not using cholesterol-lowering drugs were compared with two sample *t* tests and Wilcoxon tests for continuous measures and chi-square tests for discrete measures. Comparisons of psychosocial scores were conducted using a general linear model with adjustments for age. Stepwise linear regression analysis was used to further model any associations between use of cholesterol-lowering drugs and psychosocial measures. Predictor variables included use of lipid-lowering medication (yes/no), age (continuous), education (high school/less), race (white/other), CAD (yes/no), and risk factors [history of hypertension and history of diabetes (yes/no)]. Criterion for entry into the model was $p = 0.15$. Probability values

<0.05 were considered statistically significant. Analyses were performed using SAS software 8.2 (SAS Institute, Cary, NC).

RESULTS

Of the 498 women with complete demographic, psychosocial, and angiographic data, 173 (35%) indicated that they were taking lipid-lowering medication at the baseline visit. Of those on lipid-lowering medication, 145 (84%) indicated that they were on statins, 21 (12%) were on other (nonspecified) cholesterol-lowering drugs, and 7 women (4%) reported that they were on both statins and other nonspecified drugs.

Table 1 presents the demographic and clinical characteristics of this population by use of lipid-lowering medication. Compared with those not on such treatment, women on cholesterol-lowering medication were older, had a greater prevalence of coronary risk factors, such as a history of hypertension, dyslipidemia, and diabetes, and angiographic evidence of CAD (all $p < 0.01$). In addition, women reporting treatment with a cholesterol-lowering drug had lower serum total and LDL-C levels. The two groups of women were similar in race, education, body mass index (BMI), smoking, and use of psychotropic medications.

Psychosocial data are presented in Table 2. Women on lipid-lowering medication had significantly higher Cook Medley aggressive responding scores than those not on cholesterol-lowering pharmacotherapy (age-adjusted $p = 0.002$). There were no differences in Cook Medley hostile affect and cynicism scores or BDI scores.

Next, we evaluated whether reported use of lipid-lowering medication independently contributed to Cook Medley aggressive responding scores. Use of lipid-lowering medication continued to predict aggression scores (Table 3) after adjustment for education, race, menopausal status, coronary risk factors (history of hypertension and diabetes), and CAD ($p = 0.006$). Several models were also developed with low TC (lowest quartile vs. others) in the model along with the variables of interest. Low TC never entered the model as a significant independent predictor of scores. With both low TC and use of lipid-lowering medication in the model, use of these medications was still a significant independent predictor of Cook Medley aggressive responding ($p < 0.05$).

Subgroup analyses, examining women with LDL-C levels <100 ($n = 230$), had similar outcomes. Aggressive responding but not hostile affect, cynicism, or depression scores were higher for women on lipid-lowering medications in comparison to those not on these medications (age-adjusted $p < 0.005$). When we limited our analyses to women not on anxiolytics or antidepressants, aggression scores were 3.1 for those on cholesterol-lowering medications vs. 2.7 for those not (age-adjusted $p < 0.001$). Similar results were found for the subgroup of women on hormone replacement therapy (HRT) ($n = 208$, age-adjusted $p < 0.002$) and in analyses restricted to women with CAD ($n = 167$, $P < 0.004$). Finally, when we examined women on statins ($n = 152$), we found the same results: women on statins had higher aggressive responding scores than women not on lipid-lowering medication (age-adjusted $p = 0.03$), and use of statins was an independent predictor of aggressive responding scores in the regression analyses.

DISCUSSION

In our population of 498 women with complete demographic, psychosocial, and angiographic data, 35% indicated that they were taking cholesterol-lowering medication, mainly statins. Women on this kind of pharmacotherapy were older and had more CAD and coronary risk factors than women not on these drugs. They also had lower TC, LDL-C, and triglyceride levels. Although the two groups of women were similar in depression, hostility, and cynicism,

Cook Medley aggressive responding scores were 11% higher for women on the cholesterol-lowering medications in comparison to those not. Multivariable modeling demonstrated that use of lipid-lowering medications was a significant independent predictor of aggressive responding scores in this population after adjustment for age, CAD, and risk factors. Analyses restricted to women with CAD, to women with relatively low cholesterol levels, and to women not receiving any psychotropic medications reproduced the latter finding.

In prior observational studies, depression and depressive symptoms have not been consistently associated with low serum cholesterol,[32,33] and most randomized, clinical trials of men and women have not found treatment effects on mood.[16,17,34] In the current analysis of women with chest pain, we found no difference in depressive symptoms between those receiving and not receiving a cholesterol-lowering treatment. Reports of adverse mood effects of cholesterol reduction generally derive from relatively small studies.[15,35,36]

With respect to aggression and violent behavior, a variety of observational studies have found, compared with that of controls, lower mean TC concentrations in violent criminals, violent psychiatric patients, individuals with antisocial personality disorder, and the victims of death from suicides, accidents, and violence.[1-5,37-39] As noted earlier, in placebo-controlled clinical trails, deaths from suicides, accidents, and violence may be increased by diet modifications and older cholesterol-lowering medications, but such does not appear to occur with statin drugs.[10,11] Based on a prior report based on WISE study participants and evidence from other investigators, neither low nor lowered cholesterol is consistently associated with hostility or anger.[17,40,41] On the other hand, it is not known if cholesterol-lowering treatments *per se* affect aggressive behavior or cause the feeling of aggression toward others. In experiments using nonhuman primates, animals assigned to cholesterol-lowering diets acted more aggressively and exhibited less affiliative behavior than those on a high-fat diet.[42] The current study suggests that statin drugs may increase aggression.

The current analysis did not find a relationship between serum lipid levels and psychological variables, but the lipid data in this sample are confounded by use of cholesterol-lowering drugs in many of the women. Note, for example, that women on these medications had lower average cholesterol concentrations than other women but likely had much higher levels before treatment. Unfortunately, lipid data prior to beginning cholesterol-lowering drugs are not available. The study's cross-sectional design also precludes causal inference about the nature of the relationship between cholesterol-lowering drugs and aggressive responding. In this regard, aggressive women may be more assertive in medical encounters, which may lead physicians to prescribe more medical treatments. Finally, the results were based on observations made in a population of women referred for coronary angiography and, therefore, may not be generalizable to other individuals.

Cholesterol-lowering drugs might affect the brain and behavior through several mechanisms. In animals, manipulation of dietary fat can affect neuronal membrane lipid composition and fluidity[43] and possibly also central serotonergic function.[44,45] Statins may affect behavior via their effects on brain cholesterol metabolism[46-49] and inhibition of coenzyme Q synthesis and protein prenylation.[50-52] Finally, statin therapy appears to alter serum concentrations of long-chain polyunsaturated fatty acids,[53] which serve important roles in the brain and the regulation of behavior.[54,55]

In summary, cholesterol-lowering medications are being prescribed to increasingly large numbers of patients worldwide, and this report finds that such treatment in women is associated with increased self-reported aggression but not hostility or depression. These results are observational in nature and, therefore, could be spurious because of residual confounding.

Nonetheless, further evaluation of the putative behavioral effects of cholesterol-lowering in placebo-controlled clinical trials is warranted.

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Table 1

Clinical and Demographic Characteristics by Lipid-Lowering Medication Use

Clinical and demographic characteristic	No lipid-lowering medication (n = 325)	Lipid-lowering medication (n = 173)	p value
Age years	55 ± 11[a]	62 ± 11	0.0001
Race, % black	16	19	0.39
Education, % high school or more	44	40	0.38
Total cholesterol, mg/dL	200 ± 43	184 ± 40	0.0001
HDL-C, mg/dL	55 ± 13	53 ± 12	0.15
LDL-C, mg/dL	117 ± 38	99 ± 35	0.0001
Triglycerides, mg/dL	152 ± 128	168 ± 114	0.05
Body mass index	29 ± 6	30 ± 7	0.72
Waist/hip ratio	0.83 ± 0.09	0.85 ± 0.10	0.18
History of hypertension, %	53	67	0.002
History of dyslipidemia, %	34	94	0.001
History of diabetes, %	15	38	0.001
Current smoking, %	18	19	0.78
Postmenopausal, %	66	85	0.001
Current HRT, %	55	43	0.03
Use of anxiolytics, %	20	44	0.30
Use of antidepressants, %	18	19	0.80
Significant disease defined as ≥ 50% stenosis in one or more epicardial arteries, %	22	53	0.001

[a]Mean ± standard deviation unless noted otherwise.

Table 2

Psychosocial Scores by Use of Lipid-Lowering Medication

Psychosocial score	No lipid-lowering medication (n = 325)	Lipid-lowering medication (n = 173)	p value (age-adjusted)
CM[a] aggressive responding	2.7 ± 0.1[b]	3.0 ± 0.1	0.002
Age-adjusted	2.6	3.1	
CM hostile affect	2.0 ± 0.1	1.7 ± 0.1	0.12
Age-adjusted	2.0	1.8	
CM cynicism	5.0 ± 0.2	4.8 ± 0.3	0.97
Age-adjusted	4.9	4.9	
Beck Depression Inventory	10.8 ± 0.5	9.7 ± 0.5	0.94
Age-adjusted	10.5	10.4	

[a] CM, Cook Medley.

[b] Mean ± standard error.

Table 3

Significant Indepfndent Predictors of Aggressive Responding Scores[a]

Variable	Parameter estimate	Standard error	p value
Use of lipid-lowering medication	0.45	0.16	0.006
Age (continuous)	−0.03	0.009	0.0002
Education (high school/less)	−0.40	0.009	0.0001
Intercept	4.45	0.45	–

[a]Race, menopausal status, and history of hypertension, diabetes, and CAD were entered into the model but were not significant independent predictors. Women taking lipid-lowering medication had higher Cook Medley aggressive responding scores than those not on these medications.