Serum Cholesterol Levels in Patients with Generalized Anxiety Disorder (GAD) and with GAD and Comorbid Major Depression

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Objective: To investigate risk for cardiovascular disease in patients with GAD, as well as the effects of comorbid major depression (MD).

Method: Predrug-trial serum cholesterol and triglyceride levels were assessed in 38 patients with pure GAD and compared with those of 21 patients with mixed GAD and comorbid (MD).

Results: Significantly higher cholesterol and triglyceride levels were found in the GAD group.

Conclusion: Increased noradrenergic activity may be responsible for elevations in lipid levels in patients with pure GAD.

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Key Words: generalized anxiety disorder, major depression, cholesterol

Elevated serum cholesterol levels have consistently been identified as a major risk factor for coronary heart disease (1–3). Several studies have documented increases in cholesterol levels as a result of prolonged occupational stress (4), natural disasters (5), and experimentally induced acute mental stress (6,7). Moreover, mental stress has been reported to induce silent myocardial ischemia in patients with coronary artery disease (8); in one study of cardiac transplant candidates, a significant proportion of patients with idiopathic cardiomyopathy also met DSM-III-R (9) diagnostic criteria for panic disorder (10), thus raising the question of an association between the 2 disorders. Also, 2 retrospective studies by Coryell and others (11,12) reported a twofold increase over expected mortality from cardiovascular disease in male patients with anxiety disorders and specifically with panic disorder.

Interestingly, in spite of this evidence linking anxiety and panic to cardiovascular disease, relatively few studies have examined the relationship of cholesterol and serum lipids to psychiatric disorders. Hayward and others (13) measured plasma lipids in 102 subjects with panic disorder and agoraphobia and found that in women, but not men, a significantly higher number of subjects had cholesterol values that exceeded the 75th percentile of national reference values for their age and sex. Significantly higher cholesterol levels were found in the sample of panic disorder patients compared with both those with major depression and normal control subjects. Furthermore, Bajwa and others (14) found that histories of anxiety disorders (GAD, simple phobia, panic disorder) in patients with major depression were also associated with higher cholesterol levels. Such findings suggest a relationship, therefore, between heightened noradrenergic activity and elevations in serum cholesterol levels in patients with panic disorder, thus placing them at increased risk for cardiovascular disease.

As yet, no studies have documented the presence of increased serum cholesterol levels in GAD patients. GAD is typically characterized by symptoms of chronic apprehension accompanied by a pervasive state of high negative affect and persistent sympathetic overarousal (15). Given that elevated levels of cholesterol have been reported in panic disorder, it seems reasonable to hypothesize that cholesterol levels would also be elevated in GAD. If documented, such increases may signal that GAD patients, particularly when untreated, are at increased risk for cardiovascular disease. The aim of the present study was to measure serum cholesterol levels in a sample of GAD patients and compare them with levels in a group of GAD patients with comorbid MD.
Method

Subjects

Patients included in this study were recruited primarily through media advertisements for participation in 2 separate drug trials, one for “pure” GAD and the other for mixed GAD with MD. All patients were required to meet DSM-III-R diagnostic criteria for GAD. In the first study, individuals with a concurrent diagnosis of MD were excluded. In the second study, all patients met diagnostic criteria for concurrent MD. Patients with comorbid simple phobia or social phobia were allowed in either protocol. Patients meeting diagnostic criteria for other major Axis I disorders, including alcoholism or other substance abuse, drug-induced psychosis, obsessive–compulsive disorder, paranoia, mania, cyclothymia, schizophrenia, and dementia were excluded from both protocols. Additional exclusion criteria for patients in either protocol included a history of epilepsy or significant head trauma, pregnancy or lactation, and any clinically uncontrolled renal, hepatic, cardiac, pulmonary, thyroid, or collagen disorders. All of the potential subjects were initially screened by a psychiatrist who also confirmed the diagnoses by the Structured Clinical Interview for DSM-III-R, Upjohn version (16). The “pure” GAD sample consisted of 38 patients (16 men and 22 women), whereas the mixed GAD/MD sample included 21 patients (5 men and 16 women). Characteristics of patients in both groups are presented in Table 1.

All patients in both the “pure” GAD and mixed GAD/MD groups were administered an electrocardiogram and blood tests (complete blood count [CBC], liver profile and blood chemistries) as part of the initial, routine screening protocol; those patients whose test results indicated possible organic etiology for their symptoms were excluded from the study. Patients were not instructed to change their usual dietary habits or to fast prior to having their blood test since recent reports have indicated that mean plasma cholesterol concentration is not necessarily significantly altered following a fat-rich meal (13,17). Plasma cholesterol and triglycerides were measured by means of enzymatic procedures using a Boehringer Mannheim/Hitachi 717 Analyzer, which has met the accuracy and precision standards of the Centers for Disease Control since 1982. All patients in both groups were also administered the Hamilton Anxiety Rating Scale (18).

Statistical Analyses

Dependent variables included anxiety ratings, age, gender, height, weight, cholesterol level, triglyceride level, and body mass index (BMI). BMI is a ratio representing each patient’s weight (in pounds) divided by height (in inches). Data underwent analyses of variance (ANOVA) using Statistical Analysis Software (SAS) to evaluate differences associated with diagnostic group.

Cholesterol and triglyceride levels were dichotomized as high (>199 mg/dL) and low (< 200 mg/dL); chi-square statistics evaluated the relative frequency of patients within the 2 diagnostic groups who fell into the low and high categories for the 2 measures.

Results

As shown in Table I, the mean cholesterol and triglyceride levels of the “pure” GAD patients were significantly higher than the respective means of the mixed GAD/MD patients (cholesterol: \( F[1,58] = 4.25, P < 0.05 \); triglycerides: \( F[1,58] = 9.20, P < 0.01 \)). No significant differences in age, height, weight, BMI, or anxiety scores were found between the 2 groups. In addition, there were no significant differences in the relative frequency with which male and female patients from the 2 diagnostic groups were categorized as having either high cholesterol or high triglycerides.

Discussion

The findings from the present study indicate that patients with pure GAD have significantly more elevated serum cholesterol and triglyceride levels compared with patients with mixed GAD/MD. This observation appears consistent with reports by Bajwa and others (14) and Reifman and Windle (19), who found that patients with panic disorder had higher cholesterol levels than did patients with mixed GAD/MD or MD only.

A mechanism that may account for the findings in the present study involves the sympathetic nervous system. Sympathetic activation commonly seen in patients with GAD most likely precipitates increased noradrenergic activity (20), which causes a release of epinephrine and corticosteroids into the blood. As a result of altered adrenergic function, these hormones, in conjunction with norepinephrine, may theoretically increase the activity of lipoprotein lipase, resulting in an increase of free fatty acids in the serum, which in turn may be converted by the liver into cholesterol (21). Thus we hypothesize that patients with GAD may have increases in serum cholesterol and triglycerides due to catecholamine-

<table>
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<tr>
<th>Table I</th>
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<td>Characteristics of Patients with GAD and Mixed GAD/MD in a Study of Cholesterol Levels</td>
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<td>Variables</td>
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<td>Cholesterol level (mg/dL)</td>
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<td>Triglyceride level (mg/dL)</td>
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<sup>a</sup> \( P < 0.05 \).
<sup>b</sup> \( P < 0.01 \).
induced changes in lipoprotein lipase activity similar to those observed in patients with panic disorder (22).

One intriguing finding suggested by this study, as well as the prior report by Bajwa and others (14), is the possible “protective” effect of coexistent depression in patients with anxiety in regard to cholesterol and triglyceride levels. The explanation for this effect is unknown, but it may be due to lower levels of circulating catecholamines in anxious individuals with coexisting depression. Several recent studies have reported an association between depression and lowered levels of cholesterol (23–25), although the levels of comorbid anxiety were not examined; to our knowledge, there have not been any reports on the effect of comorbid anxiety in depressed patients (or vice versa) upon levels of circulating catecholamines. Thus the current hypothesis remains speculative. An alternative explanation for the lower cholesterol found in the mixed GAD/MD group may be the links between cholesterol, serotonin, and emotional behaviour. In a review of studies on cholesterol and depression, Wardle (3) suggested a relationship between the specific effects of lowered cholesterol on neurotransmitters such as serotonin, which is known to modulate emotional behaviour.

Since neither fasting levels nor high-density lipoprotein (HDL) or low-density lipoprotein (LDL) cholesterol levels were measured in the present study, specific inferences as to cardiovascular risk potential in patients with GAD need to be made with caution. Nonetheless, when these findings are considered in the context of previously cited reports by Coryell (11,12), which presented evidence of elevated cardiovascular mortality rates among patients with anxiety disorders, mild to moderate elevations in cholesterol levels in patients with GAD should serve as a signal for closer monitoring and screening of cardiovascular risk factors in this population. Furthermore, additional research into the effectiveness of cognitive–behavioural treatments, such as relaxation-based therapies (26) for lowering serum cholesterol levels in patients with GAD, would appear to be indicated.

### Clinical Implications

- Individuals with “pure” GAD had significantly higher levels of serum cholesterol than those with concomitant MD.
- Paradoxically, MD may serve a “protective” function in GAD patients by altering cholesterol and triglyceride metabolism.

### Limitations

- The implications of these findings in regard to the risk of cardiovascular illness cannot be assessed because of the lack of necessary laboratory values.
- A comparison group of normal controls without psychiatric illness was not included.
- The potential effects of dietary differences among the 2 groups were not controlled.

### References

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Résumé

Objectif : Examinier les risques de maladie cardiovasculaire chez les personnes souffrant d’un trouble d’anxiété généralisée (TAG).

Méthode : On a mesuré la concentration de cholestérol et de triglycérides dans le sang de 38 personnes qui présentaient les symptômes exacts du TAG avant l’essai de médicaments et on a comparé les résultats à la concentration relevée chez 21 patients présentant les symptômes du TAG et d’une grave dépression.

Résultat : Le taux de cholestérol et de triglycérides des personnes atteintes du TAG est significativement plus élevé.

Conclusion : Il se pourrait qu’une plus forte activité noradrénergique soit à l’origine de l’élévation de la lipidémie chez les personnes souffrant uniquement du TAG.