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Cholesterol, mood, and vascular health: Untangling the relationship

Does low cholesterol predispose to depression and suicide, or vice versa?

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A growing body of literature examining the putative links among cholesterol, mood disorders, and suicide has produced inconsistent findings and unclear clinical implications that may leave psychiatrists unsure of how to interpret the data. Understanding cholesterol's role in mood disorders may be relevant to the 2 primary causes of excess deaths in patients with mood disorders: suicide and vascular disease.[1]

Plausible links

In the early 1990s several studies suggested a link between low cholesterol (<160 mg/dL) and unnatural deaths, including suicide.[2-4] Follow-up studies confirmed associations between low cholesterol and suicide attempts, especially violent ones.[5] These associations are compelling given the neurobiologic effects of cholesterol, such as a net reduction of serotonergic function (***Box 1, page 18***). Low cholesterol may predispose an individual to aggression, impulsivity, and violence (***Table 1, page 19***).[6] Many studies have found that patients with mood disorders have lower cholesterol levels;[7] however, other research suggests they are at increased risk of hyperlipidemia, typically hypertriglyceridemia rather than hypercholesterolemia.[8]

Depression. Several studies have shown an association between low cholesterol and depressive symptoms, although this finding has not been replicated in Asian subjects.[9,10] Patients with manic or mixed syndromes

Cholesterol and depression

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Current evidence does not support considering low serum cholesterol a risk factor for suicide

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Box 1

Neurobiologic implications of low cholesterol

The neurobiologic effects of low cholesterol—particularly those related to serotonergic hypofunction—are thought to be mediate impulsive, aggressive, and violent behaviors that may predispose an individual to suicide.[a,b] The CNS contains one-fourth of the body's free cholesterol,[c] which is synthesized primarily in situ.

Cholesterol improves membrane stability, reduces permeability, and may influence serotonergic function. Cholesterol depletion may impair function of 5-HT1A and 5-HT7 receptors[d,e] and serotonin transporter activity.[f] Reduced cholesterol after treatment with simvastatin—an HMG-CoA reductase inhibitor that readily crosses the blood-brain barrier—resulted in acute (1-month) increases in serotonin transporter activity followed by subacute (>2 months) decreases.[g] Lower cholesterol levels may further decrease expression of serotonin receptors and cause a net reduction in serotonergic activity.

In addition, cholesterol is necessary for synapse formation and myelin production. Cholesterol depletion may have more diffuse effects on neurotransmission, such as gamma-aminobutyric acid receptors,[h] *N*-methyl-D-aspartate receptors,[i] opioid signaling,[j] and excitatory amino acids transport.[k]

Impulsivity associated with low serotonergic function and low total cholesterol has been suggested as a potential pathway for suicide.[l] Low cholesterol is associated with self-report measures of impulsivity;[m] however, increased impulsivity associated with lipid-lowering therapy may be temporary,[n] which is similar to the time-limited changes in serotonin transporter activity.[g] Human and animal data have suggested that low cholesterol may be linked to violent behaviors, including suicide.[o]

Source: For reference citations, see this article at CurrentPsychiatry.com

have been found to have lower serum cholesterol,[11] and individuals with major depression and bipolar disorder have lower cholesterol levels in the brain compared with healthy controls.[12] Some studies have observed higher total cholesterol levels after patients receive pharmacotherapy for major depressive symptoms.[13] These findings have led to speculation that low serum cholesterol in patients with mood disorders is partially a state-dependent effect of depressive illness.

Suicide. Cohort, case-control, and cross-sectional studies have linked low cholesterol to an increased risk of suicide.[2,5] Individuals who attempt suicide by violent means have lower cholesterol compared with those who use less violent methods.[5,14] A meta-analysis found statistically significant correlations between low cholesterol and future or past suicidal behavior; however, low cholesterol explained <0.01% of suicidal behavior.[15] Studies comparing cholesterol levels of individuals following violent vs nonviolent suicide attempts have demonstrated stronger associations.[15]

Assessing suicide risk. Current evidence does not support considering low serum cholesterol a risk factor for suicide. One study used cholesterol as a clinical predictor of suicide,[16] but this model has not been prospectively validated. As a whole, the evidence does not suggest that cholesterol levels explain a substantial portion of suicidal behaviors.

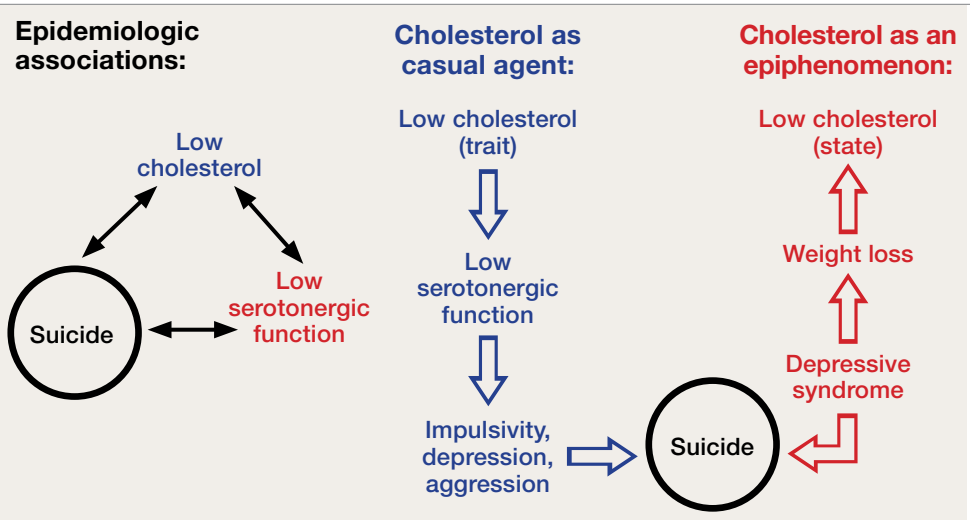
Effects of lipid-lowering agents

If there is a causal relationship between low cholesterol and mood disorders, then it stands to reason that using cholesterol-lowering drugs would increase the risk of depression and suicide. However, the data do not support that conclusion.

Many case reports have documented adverse psychiatric reactions to statins, including depression, suicidality, emotional lability, agitation, irritability, anxiety, panic, and euphoria.[17] In an early analysis of primary prevention trials, patients receiving cholesterol-lowering treatment—mainly non-statins—were estimated to have twice the risk of death by suicide or violence compared with controls.[3] However, a more recent meta-analysis of larger clinical trials of lipid-lowering agents including statins and observational studies did not reveal an association between lipid-lowering medications and suicide.[15,18]

Figure

Cholesterol, depression, and suicide: How are they linked?



Low cholesterol may be considered a trait marker, predisposing patients to lower serotonergic function and placing them at greater risk for impulsivity, depression, aggression, and suicide. Other models suggest that lower cholesterol is a state-dependent consequence of depression, and not part of a causal chain toward suicide

In a large case-control study, statin users had a lower risk of depression (adjusted odds ratio [OR] 0.4, 95% confidence interval [CI], 0.2 to 0.9) than patients taking non-statin lipid-lowering drugs (adjusted OR 1.0, 95% CI, 0.5 to 2.1).[19] However, statins reduced cholesterol more (30% to 50%) than non-statin drugs (10% to 20%). A clinical trial of >1,000 patients with stable coronary artery disease treated with pravastatin—an HMG-CoA reductase inhibitor with low lipophilicity that is less likely than other statins to cross the blood-brain barrier—revealed no changes in self-reported anger, impulsiveness, anxiety, or depression.[20]

This study did not exclude patients with psychiatric illness—who are at greatest risk of suicide—but other trials of lipid-lowering drugs did.[21] As a result, the effects of lipid-lowering medications on psychiatric patients are unclear. A clinical trial is underway to assess the effects of pravastatin (low lipophilicity), simvastatin (high lipophilicity), or placebo on mood, sleep, and aggression.[21]

Low cholesterol: State or trait?

Much of the research linking low cholesterol, mood disorders, and suicidality could be confounded by depressed mood leading to reduced serum cholesterol. There has been considerable debate about whether low cholesterol predisposes patients to suicide or if depression independently leads to poor nutrition and therefore low cholesterol and increased suicide risk.[6,22]

Some researchers have suggested that depression lowers cholesterol and increases risk of suicide,[23] but study designs have limited the ability to discern the directionality of the relationship. Attempts to control for depression-related malnu-

Table 1

Psychiatric features associated with low cholesterol*

Symptoms
Anxiety, depressed mood, emotional lability, euphoria, impulsivity, irritability, suicidal ideation, aggression
Syndromes
Anorexia nervosa, bipolar disorder, borderline personality disorder, major depressive disorder, seasonal affective disorder
Behaviors
Suicide and suicide attempts, violence

*Small studies have suggested possible relationships with dissociative and panic disorders

Clinical Point

Research linking low cholesterol and suicidality could be confounded by depressed mood leading to reduced serum cholesterol

Table 2

National Cholesterol Education Program recommended LDL levels

Risk category*	LDL goal	When to consider medications
CHD or CHD equivalent	<100 mg/dL	≥130 mg/dL
≥2 major risk factors	<130 mg/dL	≥130 to 160 mg/dL (based on 10-year risk)
0 or 1 risk factor	<160 mg/dL	≥190 mg/dL

CHD: coronary heart disease; HDL: high-density lipoprotein; LDL: low-density lipoprotein

*Risk category is based on the presence of CHD or equivalent and major risk factors for CHD. CHD equivalents include symptomatic carotid artery disease, peripheral artery disease, and abdominal aortic aneurysm. Major risk factors include smoking, hypertension, low HDL, family history, and age. LDL levels to consider medications for those with ≥2 major risk factors vary by 10-year CHD risk

Source: National Cholesterol Education Program, Adult Treatment Panel III (ATP III) Quick Desk Reference. www.nhlbi.nih.gov/guidelines/cholesterol/atglance.htm

Clinical Point

Multiple randomized controlled trials have not shown increased depression and suicide with use of lipid-lowering agents in healthy populations

Box 2

Recommendations for treating hyperlipidemia

National Cholesterol Education Program guidelines state that when a patient's low-density lipoprotein cholesterol (LDL-C) exceeds targets (***Table 2***), first recommend lifestyle changes such as a diet low in saturated fat (<7% of calories) and cholesterol (<200 mg/d), weight management, and exercise. Increases in soluble fiber (10 to 25 g/d) and plant stanols/sterols also may be considered. If LDL-C levels are still too high, pharmacologic therapy such as an HMG-CoA reductase inhibitor is suggested.

Treatment of elevated triglycerides (≥150 mg/dL) includes reaching the target LDL-C, intensifying a weight management program, and increasing exercise. Address quitting smoking and limiting alcohol when indicated. If triglyceride levels are ≥200 mg/dL after the LDL-C target is reached, set a secondary goal of reaching a target non-high-density lipoprotein cholesterol (HDL-C) (non-HDL-C; total cholesterol minus HDL-C) 30 mg/dL greater than the LDL goal. This can be achieved by adding an LDL-lowering drug such as a statin, nicotinic acid, or ezetimibe. When triglycerides are ≥500 mg/dL, more aggressive intervention, such as with a fibrate, omega-3 fatty acids, very low-fat diets, and exercise, is required to prevent pancreatitis.

Source: National Heart Lung and Blood Institute. National Cholesterol Education Program. www.nhlbi.nih.gov/guidelines/cholesterol/index.htm

trition and weight loss—which lowers total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)[24]—suggest the association may be independent of these variables.[25-27] These findings suggest that cholesterol may be considered a trait marker and is not entirely state-dependent. However, multiple, large, long-term randomized controlled trials have not shown increased depression and suicide with use of lipid-lowering agents in healthy populations.[20]

The ***Figure (page 19)*** illustrates known epidemiologic associations of low cholesterol, low serotoninergic function, and suicide and contrasts conceptual models of cholesterol as a state and a trait marker. A case can be made for cholesterol as both a state and a trait marker, and these models could overlap, with depression-induced decreases in cholesterol further mediating changes in serotonergic function and related behavioral sequelae.

Improving cardiac health

Limited epidemiologic studies suggest that patients with mood disorders may have lower levels of total cholesterol and LDL-C, but higher rates of hypertriglyceridemia compared with the general population.[8] Unfortunately, psychiatric patients—who may be at increased risk of developing cardiovascular disease—may be less likely to be screened and appropriately treated for lipid abnormalities.[28] To address this disparity, consider assuming an active role in assessing and managing hyperlipidemia in your patients with

mood disorders. Be aware of your patients' lipid profile and ensure that they follow monitoring recommendations.

The National Cholesterol Education Program recommends screening all adults age >20 for hyperlipidemia every 5 years using measures of total cholesterol, LDL-C, HDL-C, and triglycerides. If LDL-C or triglycerides exceed target values (***Table 2***), appropriate management includes recommending lifestyle changes and pharmacotherapy (***Box 2***).

Patients should receive a fasting lipid profile before and 12 weeks after starting any antipsychotic and semiannually thereafter.[29] Consider closely monitoring lipids when patients gain weight with psychotropics. Refer patients with hyperlipidemia to a primary care physician, but in the absence of such a provider, mental health clinicians who are familiar with treatment guidelines can manage these patients.[30]

Closely monitor individuals with mood disorders for changes in behavior or mental status after starting a lipid-lowering agent. Consider discontinuing the drug if a patient develops an adverse reaction. If symptoms return after medication rechallenge, consider other management strategies such as an alternate lipid-lowering agent or re-emphasizing behavioral measures.

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Consider assuming an active role in assessing and managing hyperlipidemia in your patients with mood disorders

Cholesterol and depression

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Closely monitor individuals with mood disorders for changes in behavior or mental status after starting a lipid-lowering agent

Related Resources

- Fiedorowicz JG, Coryell WH. Cholesterol and suicide attempts: a prospective study of depressed inpatients. Psychiatry Res. 2007;152(1):11-20.
- National Cholesterol Education Program, Adult Treatment Panel III (ATP III) Quick Desk Reference. www.nhlbi.nih.gov/guidelines/cholesterol/atglance.htm.
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Drug Brand Names

Ezetimibe • Zetia
Pravastatin • Pravachol
Simvastatin • Zocor

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Bottom Line

Low cholesterol has been associated with suicide, but not strongly or consistently enough to warrant routine use in suicide risk assessment. Lipid-lowering therapies do not appear to increase overall suicide risk. Patients with mood disorders are at higher risk of developing cardiovascular disease and should not be deprived of potentially life saving, lipid-lowering treatment, although close monitoring for adverse effects is warranted.

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Box 1

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