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Editor-in-Chief

We should mind our patients' cholesterol because it may affect their minds, not just their hearts

## The puzzling relationship between cholesterol and psychopathology

**Cholesterol generally is regarded as a cardiovascular risk factor when elevated. However, numerous studies suggest that cholesterol levels—both high and low—may be associated with various psychiatric brain disorders.<sup>1</sup> Thus, psychiatrists should mind their patients' cholesterol because it may affect their minds, not just their hearts.**

The relationship between cholesterol and mental illness is fascinating, complex, and perplexing. Whether elevated or reduced, cholesterol's effects can be deleterious or salutary, but the literature is riddled with conflicting reports. Physicians should measure their patients' serum cholesterol levels not only to assess cardiovascular risk, but because cholesterol can be associated with certain neuropsychiatric disorders or may predict the lack of response to psychopharmacotherapy.<sup>2</sup>

The fact that lowering total cholesterol levels in people with hypercholesterolemia reduces the risk of coronary heart disease is indisputable. Large-scale cardiology clinical trials have shown a significant reduction in mortality from heart disease or stroke with cholesterol-lowering drugs (statins). However, the same trials found an uptick in

“unnatural deaths,” mostly suicide or homicide.<sup>3</sup> Those findings triggered numerous intriguing reports of the association between cholesterol levels and psychopathology.

Consider the following:

- Low cholesterol levels have been associated with depression, antisocial personality disorder, borderline personality disorder, and dissociative disorder.<sup>4</sup>
- High cholesterol levels have been associated with schizophrenia, obsessive-compulsive disorder, panic disorder, generalized anxiety disorder, and post-traumatic stress disorder.<sup>4</sup>
- Some studies suggest that high cholesterol levels are associated with better mental health, mental processing speed, social skills, responsibility, self-control, and self-awareness.<sup>5</sup>
- In the Clinical Antipsychotic Trials of Intervention Effectiveness schizophrenia study, better cognitive scores were found in patients with higher fasting cholesterol and triglyceride levels (H.A.N., unpublished data, 2017).

The brain is only 2% of body weight, but it contains 25% of the body's cholesterol.<sup>6</sup> Cholesterol is important for brain function and neurotransmission because neuroactive steroids (NASs) are synthesized from cholesterol and they modulate brain processes and interact with  $\gamma$ -aminobutyric acid, *N*-methyl-D-aspartate, and serotonin

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receptors (all of which are implicated in psychiatric disorders) as well as neurotrophins such as nerve growth factor.<sup>7</sup> NASs are involved in mood regulation and cognition, and regulate synaptic plasticity, apoptosis, and neuroprotection.<sup>7</sup> For the brain to function normally, NASs must maintain normal levels, because low levels may lead to adverse consequences, such as depression, neuroinflammation, epilepsy, multiple sclerosis, and psychosis. On the other hand, high levels may lead to attention-deficit/hyperactivity disorder and stress. Thus, NASs—such as pregnane, androstane, and sulfated neurosteroids, all synthesized from cholesterol—are critical molecules with major neuropsychiatric activity.<sup>8</sup> This may provide clues to the mechanisms of action by which cholesterol levels influence psychiatric brain functions. Cholesterol has been described as a multipurpose molecule that is a critical component of neuronal cell membranes and a precursor for many signaling molecules.<sup>9</sup>

Interestingly, both extremes in cholesterol levels represent a high risk for premature mortality.<sup>10</sup> Hypercholesterolemia leads to early death from coronary artery disease. Studies that evaluated statins to lower cholesterol found increased mortality from suicide, accidents, and violence.<sup>11</sup> Even without statin treatment, among persons with naturally low cholesterol, there is a significant increase in mortality from non-medical causes.<sup>12</sup> However, some studies did not find an association between hypocholesterolemia and suicide.<sup>13,14</sup>

There also is some evidence that elevated cholesterol may play a role in dementia.<sup>15</sup> Reducing cholesterol with statins decreases beta-amyloid in mice, while the opposite occurs with elevated cholesterol.<sup>2</sup> Another possible mechanism by which high cholesterol worsens dementia is that

neurodegeneration in Alzheimer's disease (AD) breaks down neuronal cell membranes, which releases the neurotoxic metabolite of cholesterol (24-hydroxycholesterol), which leads to further neurodegeneration.<sup>16</sup> Statins may decrease the production of 24-hydroxycholesterol in AD patients and slow down neurodegeneration.<sup>16</sup>

A large study of 4,444 consecutive patients in Taiwan found that those with low total cholesterol (<160 mg/dL) had higher scores of anxiety, phobia, psychoticism, and aggressive hostility.<sup>17</sup> In the same study, women with low high-density lipoprotein cholesterol (<35 mg/dL) had significantly higher scores for depression, phobia, anxiety, interpersonal sensitivity, somatization, and aggressive hostility.<sup>17</sup>

Not surprisingly, low cholesterol has been proposed as a biomarker for mood dysregulation, depression, and suicidality,<sup>18</sup> as well as a predictor of the depression severity and increased suicide risk.<sup>19</sup> Clinical recovery in depression may be accompanied by a significant increase of total cholesterol<sup>20</sup> but, interestingly, a decrease in cholesterol levels after treatment of mania. High cholesterol was reported to predict poorer response to selective serotonin reuptake inhibitors, and total cholesterol levels >200 mg/dL were associated with lack of response to fluoxetine and nortriptyline.<sup>2</sup> Interestingly, clozapine, which elevates lipids, exerts a strong anti-suicide effect in schizophrenia and schizoaffective disorder, but that may not be the main reason for its efficacy in preventing suicide in patients with psychosis.

Cholesterol is an important lipid for brain function. At lower levels, it appears to be associated with depression, suicide, violence, anxiety, schizophrenia, and severe personality disorders (including antisocial personality disorder and borderline personality disorder). However, at high levels, it may improve cognition

From the Editor  
continued from page 5

in schizophrenia and ameliorate the pace of AD and neurodegeneration. Psychiatrists should monitor patients for hypercholesterolemia and hypocholesterolemia, both of which are common among psychiatric patients. High levels may be genetic or the result of weight gain, hypercortisolemia, diabetes, or immune or inflammatory processes. Similarly, low levels may be genetic or secondary to statin therapy.

The bottom line: As psychiatric physicians, we should protect both the hearts and brains of our patients.



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