



## ROLE OF CHOLESTEROL & CHOLESTEROL LOWERING DRUGS IN DEPRESSION: A REVIEW

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### ABSTRACT

A possible association between cholesterol, cholesterol-lowering drug therapy and depression remains an issue of debate. Cholesterol-lowering drugs in general help to control elevated levels of different forms of lipids in patients with hyper-lipidemia. The present review demonstrated that recent research describes the idea that cholesterol can play an important role in governing depression. In this review, several topics such as lipid parameters and central nervous system disorders, lipid parameters and depression, lipid parameters and suicidal attempts, antidepressant effects of cholesterol lowering drugs, cholesterol lowering effects of antidepressants have been discussed. Deepening the studies in this field could be a promising avenue for future research, with implications for treating people with hypercholesterolemia along with depression.

**KEYWORDS:** Anti-hyperlipidemic drugs, Cholesterol, Depression, Hypercholesterolemia

### INTRODUCTION

Depression is a multi-factorial disease being caused by biological, psychological, and social factors. It is the leading cause of ill health and disability worldwide. Despite current and newer drugs being used in depression there is either relapses occur frequently or the treatment does not seem to be very effective. There is a need to develop newer treatment options that are more effective with few adverse effects. In light of this, significant interests have evolved on correlation between cholesterol levels and mood regulations. Cholesterol is an important component of biological membranes. It has been reported that the ratio of phospholipids and free cholesterol determines the fluidity of biological membranes. Cholesterol is also required for the correct functioning of neurotransmission in the central nervous system<sup>1</sup>. Several studies have suggested the relationship between lipid metabolism and serotonin function. A large number of studies have suggested a relationship between serum cholesterol levels and various psychiatric illnesses including depression and suicide<sup>2</sup>. In this review, an extensive literature search has been done to establish the significant role of cholesterol and cholesterol altering drugs in depression.

### LIPID PARAMETERS AND CENTRAL NERVOUS SYSTEM (CNS) DISORDERS

#### Role and Regulation of Cholesterol in Central Nervous System Disorders

The pivotal effects of brain cholesterol on different cellular processes in the CNS have become apparent in the last decades. Human and animal studies are complicated by different expression of genes involved during development as well as by cell specific differences. Another challenge is the role of the blood brain barrier, which also changes during development and can be regulated under certain pathological conditions. The sterol flux between central nervous system cells is only poorly understood<sup>1</sup>. However, whole CNS cholesterol production can be very elegantly studied by analyzing the concentrations of 24-S-

hydroxycholesterol, the exclusive metabolite of CNS cholesterol. The analysis of lipoproteins present in cerebrospinal fluid revealed some data on brain cholesterol metabolism. A great number of studies have addressed the rather complicated molecular processing and the effects of cholesterol both in the whole organism as well as in single cells on this processing<sup>1</sup>.

### LIPID PARAMETERS AND DEPRESSION

#### Low Serum Cholesterol Levels and Depression

Total cholesterol (TC) has been identified as a risk factor for older adult mortality but is commonly attributed to the fact that low TC levels indicate malnutrition, chronic infections, and subclinical or hidden diseases<sup>3-5</sup>. It has been found that the TC levels were significantly low in patients suffering from depression as compared to healthy individuals. This may be due to changes in the cholesterol content of the synaptosomal membrane and a decrease in the number of serotonin receptors due to a decrease in cholesterol concentration. Since membrane cholesterol freely exchanges with the cholesterol in the surrounding medium, a lowered cholesterol concentration may contribute to a decrease in brain serotonin, with poorer suppression of aggressive behavior<sup>6-7</sup>. Low lipid levels can be the cause of decreased activity of serotonin receptors and serotonin transporter by decreasing the lipid microviscosity of the membrane of the neural cell<sup>8-9</sup>. Recent studies have been found that, men who have relatively low levels of cholesterol are four to seven times more likely to report symptoms of severe depression than men with high cholesterol levels<sup>10</sup>. This indicates that as the TC and LDL value decreases the severity of depression increases. In study group, other lipid parameters like TG and VLDL also showed significant negative co-relation with BDI scores, respectively. HDL does not show any significant co-relation with BDI score in study group. Very few of researchers have been able to assess the co-relation between low lipid levels and depression. It has been found that there is a strong negative correlation between lipid levels, particularly TC and LDL with depression.

### High Serum Cholesterol Levels and Depression

When reports of many studies claimed that low levels of cholesterol may be associated with depression. There are many reports that high levels of cholesterol may be associated with depression. It has been found a significant positive correlation of cholesterol levels with depression score system. This result contrasts with earlier findings of an inverse association between depression scores and total cholesterol<sup>11</sup>. Nevertheless, the studies demonstrates that high cholesterol concentrations are also associated with a higher susceptibility for depressive mood and the data thus adds to the existing controversy about an increased risk of suicide and violence in individuals with lower cholesterol or under cholesterol-lowering treatment<sup>12</sup>. The data also fit to the observation that cholesterol lowering may not only increase the risk of psychiatric illness<sup>13</sup> but also was found to improve depression. Depressive mood may be related to disturbed metabolism of serotonin<sup>14</sup>. Thus, individuals with depressive mood may increase their intake of dietary fat and of carbohydrates<sup>15</sup> and consequently, cholesterol concentrations would increase. It has been concluded that not only lower, but also higher cholesterol concentrations are associated with signs of depressive mood. Older age might contribute to the development of depressive symptoms, which is associated with increased cholesterol levels probably resulting from an increased dietary food intake.

### Low Serum Cholesterol Levels and Depression

It has been reported that plasma serotonin concentrations are lower in untreated men with persistently low serum cholesterol concentrations than in a reference group. This supports the hypothesis that serotonin metabolism may be implicated in the observed association between low cholesterol concentrations, behavioral changes, and violent death. The serotonin variables which determined are indirect measures of central nervous system serotonin activity, believed to be involved in the increased risk of violent death. Although plasma and platelet serotonin indices are an accepted model for serotonergic brain neurons, this has limitations that may partly explain the lack of an association of low cholesterol concentrations with platelet serotonin concentrations or serotonin binding as measured in the study. It has been reported in animal study that low cholesterol may lead to lower central nervous system serotonin activity<sup>16</sup>.

### Hypercholesterolemia and Depression in Elderly Patients

There has been reported that increased body mass and depressive symptomatology are associated with hypercholesterolemia, among elderly individuals. A few percentages of patients with hypercholesterolemia participants were under special diet or pharmaceutical treatment. Furthermore, in elderly with high blood cholesterol levels the prevalence of hypertension, obesity and diabetes was significantly higher than in participants with no hypercholesterolemia. Participants with hypercholesterolemia presented significantly higher values of diastolic blood pressure than the group of the elderly with normal cholesterol levels. Also, the group with hypercholesterolemia seems to have higher levels of serum triglycerides than the group with normal levels of blood cholesterol. Considering the growing population of elderly patients in industrialized nations the investigation of associations between cardiovascular risk factors and lifestyle, social as well as psychological factors among elderly patients surely is of interest. Taking into account the increased depression rates observed in the elderly, co-existence of this psychological disorder with high blood lipids levels may promote the development of cardiovascular disease<sup>17</sup>.

### Altered Lipid Levels and Depression in Animal Studies

Coronary heart disease (CHD) and depressive mood disorders are highly comorbid. It has been reported that depression may be associated with coronary artery atherosclerosis. Recent studies indicated that patients with major depression also exhibit systemic and central nervous system inflammation as shown by increases in inflammatory cytokines including tumor necrosis factor (TNF)-alpha, interleukin (IL)-1 and IL-6 as well as the acute phase protein, C-reactive protein (CRP) in peripheral blood and cerebrospinal fluid<sup>17-18</sup>. Depression has been suggested to be an independent risk factor for cardiovascular disease. The current study reveals that a large proportion of cynomolgus monkeys who were fed a high fat western diet exhibit depressive behavior that is associated with profiles of circulating lipids and lipid signaling molecules that are linked to obesity and cardiovascular disease<sup>19</sup>.

Specifically, alterations in three major lipid classes were associated with behavioral depression. First, depression was positively correlated with total plasma cholesterol and negatively correlated with HDL-C. The relationship between depression and circulating cholesterol concentrations has been of particular interest in several studies over the past few years. Low temporal cortex has been associated with depression in some human studies but not others<sup>20</sup>. The literature is also mixed in regard to the relationship between depression and HDL-C. More recently, dietary intakes of seed oils, which are rich in linoleic acid, have been associated with depressive symptoms in an elderly population. Lipid metabolism has an enormous impact on CHD risk, thus lipid perturbations in depression are likely one of the mechanisms that contribute to increase CHD among depressed patients<sup>19</sup>. It has been reported that lipid dysregulation characteristics that are typically associated with obesity, diabetes and the metabolic syndrome are also associated with behavioral depression in a nonhuman primate model in which depressed monkeys develop more coronary artery atherosclerosis.

### LIPID PARAMETERS AND SUICIDAL ATTEMPTS

#### Neurobiological Mechanism of the Relationships between Cholesterol and Suicidality

A hypothesis linking cholesterol and the serotonergic system had been presented by engelberg<sup>21</sup>. It has been hypothesized that a reduced serum cholesterol level may be accompanied by changes in viscosity and function of serotonin receptors and transporters as well as by decreased serotonin precursors that may cause an increase in suicide ideation. The serotonergic system is strongly recognized as being linked to suicidality and impulsive and aggressive behavior as lower concentrations of 5-hydroxyindolacetic acid in the cerebrospinal fluid in suicides and suicide attempters were found in several studies<sup>22</sup>. It was found a significant positive correlation between serum total cholesterol and level of CSF and in suicide attempters that remained significant after correction for age, gender, BMI, and comorbid substance abuse, even if earlier studies did not find an association<sup>23-24</sup>.

#### Study to Evaluate Correlation of Serum Cholesterol and Serotonin Levels in Suicidal Deaths

Suicidal behavior is emerging as a major public health problem, but the neurobiology of suicide is still unclear. Suicidal tendency has been related to decrease central serotonergic function and reduced cholesterol levels. It has been reported that the serotonergic system may be associated to serum cholesterol in suicidal deaths. It has been reported that concentrations of serum cholesterol and serotonin may be useful in predicting the suicide

risk<sup>25</sup>.

### **Relation of Serum Cholesterol and Severity of Depression and Suicide Attempts**

It was found that a significant difference in serum 5-HT and tryptophan level between subjects with recent suicide attempt and those who had never attempted suicide, even in those who were receiving antidepressant medication. It's also been observed that there is a significant correlation between the number of previous suicide attempts and serum 5-HT levels. It has been reported that the relation between serum and cerebrospinal fluid 5-HT levels is more positively conducted<sup>26</sup>.

Despite the controversial results about relationships between cholesterol levels and depressed mood, the majority of the literature on the same subject seems to show a consistent relationship between cholesterol and suicide<sup>27-28</sup>. The possible relationships between cholesterol levels and suicidality were initially suggested when an excess mortality for violence was observed following the use of cholesterol-lowering drugs<sup>29</sup>. Despite some lines of evidence of a link between higher cholesterol levels and increased suicidality<sup>30</sup>, mainly, as well as for major depression, a relationship was found between lower serum cholesterol levels and suicidality<sup>31</sup>. It has been investigated that there is an association between TC and suicidality in a sample of men and women with major depression and found a significant association between lower cholesterol levels and increased suicidality<sup>32</sup>. Moreover, it has been demonstrated that, in acutely depressed patients, low TC and LDL-cholesterol were significantly associated with higher suicide risk. It is found that the risk of suicide attempts increased in men and in women in the lowest cholesterol quartile compared to subjects in the highest quartile. Thus, serum cholesterol level may be a strong risk factor for suicidal behavior in patients with depressive symptoms<sup>33</sup>. It has been suggested that low levels of cholesterol may be associated with increased tendency for impulsive behavior and aggression and contribute to a more violent pattern of suicidal behavior. Further observations about relationships between impulsivity and violent behavior seem to bring other indirect evidence to the connection between lower cholesterol levels and violent suicide attempts<sup>34</sup>. Moreover, it has been reported that lower HDL-C levels were associated with an increased prevalence of suicide attempts in women. The finding of a lower HDL-C level in suicide attempters was also confirmed in other studies<sup>35</sup>.

### **Studies That Did Not Find an Association between Cholesterol and Suicidality**

However, especially during the last years, involvement of serum cholesterol in pathogenesis of suicide was doubted on the basis of some studies<sup>26,36</sup>. For instance, results of a retrospective study did not find significant differences in the serum cholesterol levels between patients who had and had not made a suicide attempt after controlling for age or body mass index<sup>37</sup>. In a prospective study, regardless of a significant reduction in depression and suicidality scores, analyses of serum lipid concentrations after 1 and 4 weeks of antidepressant treatment showed no significant differences in lipid levels between patients with and without a history of attempted suicide, even if in patients who used a violent suicide method, there was a trend for lower TC levels compared to those with nonviolent attempt<sup>38</sup>. Further evidence on the lack-of association hypothesis was also provided who evaluated serum lipid profiles during a 2-year period and found that even if serum lipid profile changes in patients with major depression during acute phase were observed, there were no significant differences of any kind in serum lipid profiles between major depressive patients with or without suicide attempts. There has been

evaluation of suicide attempters and found that low cholesterol levels were not associated with increased suicide risk but with a decreased risk in men<sup>39</sup>. However, the debate on relationships between cholesterol and suicide is open and longitudinal studies on a larger sample of patients are needed to further clarify this important issue, even if the time to get any conclusive data using longitudinal designs in items such as suicide.

### **ANTIDEPRESSANT EFFECT OF CHOLESTEROL LOWERING DRUGS**

#### **Long Term Statin Use and Psychological Well-Being**

It has been reported that long-term statin therapy consistently improves psychological well-being. A progressive, cumulative reduction in the levels of depression was observed over a prolonged period of statin use. The possible impact on psychometric scores was independent of the serum cholesterol level at baseline and of the degree of reduction in cholesterol level during follow up. This effect appears to be independent of the impact of statin use on serum cholesterol level<sup>40</sup>.

#### **Lovastatin Potentiates the Antidepressant Efficacy of Fluoxetine in Rats**

It has been reported that dietary supplementation with lovastatin increases the antidepressant efficacy of Fluoxetine in laboratory animals. It has been observed that this combination produced antidepressant-like effects to a greater extent than Fluoxetine alone, as evidenced by reduced immobility and increased swimming in rats. Effects on the swimming measures, rather than climbing, in the forced swim test suggest that the antidepressant like effects of lovastatin augmentation may be attributed to the alteration of serotonergic function<sup>41</sup>. All major classes of antidepressant treatments including NRIs, SSRIs, monoamine oxidase inhibitors and electroconvulsive shock therapy effectively reduce indicators of immobility in the FST. It is important to emphasize that statins can occasionally cause adverse effects, particularly with long-term exposure. Alteration in cholesterol and phospholipids of brain cell membranes may influence membrane fluidity, consequently affecting various catecholamine neurotransmitter systems, including 5-HT and noradrenaline<sup>42</sup>. Preclinical studies have demonstrated that low cholesterol levels may lead to decreased 5-HT function in the brain through reduced numbers and/or function of postsynaptic 5-HT receptors<sup>43</sup>.

#### **Acute Antidepressant Effects of Simvastatin and Its Mechanisms in Animals**

It has been reported that all doses of simvastatin, amitriptyline alone, sertraline alone, and the combined use of simvastatin with amitriptyline and sertraline decreased immobility time, while increasing the struggling time, except for sertraline alone, indicating an acute antidepressant effect. However, the antidepressant effect observed with sertraline alone was lower than the other groups, while combined use of sertraline and simvastatin had an antidepressant. However, it was also found that statins suppressed secretion of Th1 type cytokines IFN, IL-2, and IL-12 while enhanced production of Th2 type cytokines IL 4, IL 5, and IL 10<sup>44</sup>. Additionally, it was also reported that there is a relationship between low serum tryptophan levels due to immune activation and poor life quality in patients with colorectal cancer. It may be proposed that statins reduce the risk of depression. According to the results of the study, it is considered that simvastatin may be preferred due to its antidepressant features in hypercholesterolemia patients with depression eliminating the need for an antidepressant drug.

### Association between Serum Cholesterol and Brain Serotonin in Simvastatin Treated Animals

Long term administration of simvastatin caused a significant reduction in serum cholesterol level. Lowered serum cholesterol and incidence of anxiety related behavior has been previously reported. It has been reported that in healthy young adult women, low lipid and lipoprotein concentrations are inversely associated with trait measures of anxiety. It has been proposed that cholesterol can modulate the function of G protein coupled receptor either through a direct interaction with G protein coupled receptors which could induce a conformational change in the receptor or through an indirect way by altering the membrane physical properties in which the receptor is embedded, or through a combination of both<sup>45</sup>. It has been suggested reported an increased level of anxiety in HT<sub>1A</sub> receptor knockout mice in elevated plus maze model. A significant reduction in brain serotonin was obtained in the study. The brain's biogenic amines, especially the neurotransmitter serotonin, are considered to play a fundamental role in anxiety-related behaviors<sup>46</sup>.

### CHOLESTEROL LOWERING EFFECT OF ANTIDEPRESSANT DRUGS

#### Fluoxetine Induced Decrease in Serum Lipid Profile

Initially, there was no information on the effects of Fluoxetine on serum total cholesterol and triglyceride in patients with hyperlipidemia. However, it has been reported that serum TG was reduced in obese patients with diabetes mellitus after receiving Fluoxetine. It should be noted that body weight was also reduced in these patients. Hypercholesterolemia is considered to be a risk factor for coronary heart disease<sup>47</sup>. It was reported that Fluoxetine may be a useful antidepressant for hyperlipidemic women with postpartum depression.

### CONCLUSION

The current review tried to establish the role of cholesterol in the pathophysiology and treatment of depression. However, it can be concluded that an enormous amount of work remains to completely understand the relationships between cholesterol and human behavior.

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