Review Article

Serum cholesterol and depression: An update

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ABSTRACT

A large number of studies have been performed to establish a correlation between serum cholesterol and depression. Majority of the studies have suggested that depression and suicide are associated with low levels of serum total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides. However, few researchers have also denied the association between serum cholesterol and depression or suicide. We carried out an extensive literature search for the studies performed on serum cholesterol and depression, and found that a relationship definitely exists between the two.

Keywords: Cholesterol, depression, suicide

Access this article online

Quick Response Code:

Website: www.mjdrdypu.org

DOI: 10.4103/0975-2870.140361

Introduction

Cholesterol is an important component of biological membranes. It is said that the ratio of phospholipids and free cholesterol determines the fluidity of biological membranes. Brain membranes have a very high content of essential poly-unsaturated fatty acids, for which they depend on alimentation.[1] Cholesterol is also required for the correct functioning of neurotransmission in the central nervous system.[2] Several studies have suggested the relationship between lipid metabolism and serotonin function. Some studies have also suggested that the pharmacological treatment of depression results in a rise of the serum cholesterol levels.[3,4] A large number of studies have suggested a relationship between serum cholesterol levels and various psychiatric illnesses, including depression,[5-7] suicide,[8] bipolar disorder,[9] mood disorders associated with physical violence,[10] schizophrenic violent suicide attempters[11] and borderline personality disorder.[12,13] We performed an extensive literature search to determine whether there exists a relationship between serum cholesterol and depression.

Pathophysiological Mechanisms Explaining the Relationship Between Cholesterol and Depression

The exact pathophysiological mechanism linking cholesterol and depression is still debatable. Various hypotheses are proposed. Papakostas *et al.* suggest that low serum cholesterol levels are associated with decreased serotonergic function.[14] Few researchers have also suggested an inter-relationship between serum cholesterol, leptin,[7] dietary intake of fats,[15] interleukin-2[16] and genetics.[17] Recent observations indicate that interleukin-2 has an important role in lipid metabolism, depression and atherosclerosis.[16]

It is believed that low serum total cholesterol (TC) concentration also alters the metabolism of serotonin, leading to depression and poor control of aggressive impulses, resulting in an increased risk of suicides.[18] Some epidemiological and clinical studies showed that low serum cholesterol levels are associated with suicidal behavior, and microarray experiments have shown genes involved in these pathways.[17]

Few researchers have also reported a positive correlation between TC and level of cerebrospinal fluid (CSF) 5-HIAA (5-Hydroxyindolacetic acid) in suicide attempters.[19,20] Engelberg[21] hypothesized that decreased cholesterol levels not only decrease the serotonin precursors but also

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alter the viscosity and functions of serotonin receptors and transporters. These changes cumulatively cause an increase in suicide ideas. Maes *et al*. proposed that the gene encoding lecithin–cholesterol acetyl transferase (LCAT) is located on chromosome 16. Because LCAT is responsible for esterification of cholesterol, its defects lead to defective cholesterol esterification and decreased lipid microviscosity in neural membranes. These changes further result in reduced exposure of serotonin receptor on the membrane, resulting in hypofunction of such receptors and thereby increasing suicide ideation.[22]

Maes *et al*.[23] suggested that lower serum high-density lipoprotein cholesterol (HDL-C) levels are probably induced by the immune/inflammatory response in depression. They also suggested that there is an impairment of reverse cholesterol transport from the body tissues to the liver in cases of depression. It has also been found that both TC and alfa-tocopherol at baseline significantly prevent progression of depressive status in men.[7] Tearo *et al*. performed a study to test the hypotheses that serum cholesterol and serotonin receptor function are related. They concluded that there is a positive relationship between the two.[24]

It has also been hypothesized that a decreased consumption of poly-unsaturated fattyacids, especially omega-3 fattyacids, may be a risk factor for depression.[25,26]

Serum Cholesterol and Depression

Studies have shown that patients with major depression (MD) have low HDL-C concentrations and higher ratios of total cholesterol/high-density lipoprotein cholesterol (TC/HDL-C) and low-density lipoprotein cholesterol/high-density lipoprotein cholesterol (LDL-C/HDL-C).[7,23,27] It has also been suggested that low TC,[28] adiposity and high waist to hip ratio are associated with MD and suicidal behaviors.[29] Majority of the studies have suggested a relationship between cholesterol levels and depressed mood.[25,26,30-35]

General Population Studies

Studies conducted to prove the association between serum cholesterol, depression and suicidality are rarely performed on healthy populations. We report few such studies. Partonen *et al*. investigated 30,000 participants of the Finnish community and found that low serum cholesterol levels were associated with depressed mood and a heightened risk of hospitalization for depression.[36]

Zhang *et al*. conducted a study on the general healthy population of United States (US) to examine a relation between serum cholesterol and suicide. They found that serum cholesterol is unrelated with suicide ideation in both men and women. However, they found that low HDL is significantly associated with suicide attempts in women but not in men.[37]

Outpatient Samples

Rafter carried out a study on a normal population in a primary care setting and found that patients with low cholesterol scored significantly higher on the Hamilton Rating Scale for Depression.[38]

Gambi *et al*. analyzed the HDL and TC of 37 adult outpatient department (OPD) patients and concluded that lower levels of HDL are seen in patients with suicidal risk. However, TC levels did not show a significant correlation in the suicide risk group.[39]

Inpatient Samples

Chang *et al*. performed a study on Taiwanese adults and concluded that the HDL-C level has a reverse J-shaped association and triglyceride has a positive association with suicide.[29]

Shin used meta-analytic techniques to evaluate the associations among TC and HDL, respectively, and depression in empirical studies. They found that higher TC was associated with lower levels of depression. High HDL was related to higher levels of depression, especially in women.[40]

Ghaemi *et al*. studied 50 hospitalized patients in affective disorder using the DSM-IV criteria. They found that TC levels were lower in patients with current manic and depressive illness than in mixed episodes. However, manic patients had much lower cholesterol levels than depressive and mixed episode patients.[41]

De Berardis *et al*. studied 90 patients with bipolar disorder-1 and calculated their scores according to the Young Mania Rating Scale (YMRS), Bech–Rafaelsen Manic Rating Scale (BRMRS) and Hamilton Rating Scale for Depression (HAM-D). They found that TC is low in all clinical groups compared with controls. They also found that TC negatively correlates with BRMRS, YMRS and HAM-D.[42]

Troisi also confirmed the finding of low cholesterol in the patients of mood disorder.[43]

Maes *et al*. performed a study on 36 patients of major depression and found that lower serum HDL-C levels are a marker for major depression and suicidal behavior in depressed men.[23]

Cholesterol, Suicide and Parasuicide

Tripodianakis studied 111 patients admitted in a general hospital after suicide attempt. Out of these suicide attempters, 25 patients were diagnosed with depression according to the DSM-IIIR criteria and assessment of suicide intent with Beck's Suicidal Intent Scale (SIS). It was found that serum TC was significantly lower in both violent and non-violent attempters compared with the control group.[44]

Jokinen *et al*. studied 13 medication-free male suicide attempters and healthy volunteers. They found that serum HDL was low in the suicidal groups than in the controls. They suggested that HDL levels can be used to plan the subscale of suicide intent in non-violent suicide attempters. They also suggested that the levels of serum HDL correlate with the CSF levels of 5-HIAA.[45]

Kim *et al*. compared serum cholesterol in 149 suicidal depressive patients, 149 non-suicidal depressive patients and 251 normal controls. They found significant differences in serum cholesterol levels between suicide patients and non-suicide depressive patients and between violent suicide and non-violent suicide. They also calculated the discriminative cut-offs between suicidal and non-suicidal depressive patients to be 180 mg/dL with a sensitivity of 82% and 150 mg/dL with a specificity of 72%.[46]

Coryell *et al*. studied 74 in-patients with major depressive disorder and found that low TC is associated with suicide risk.[47]

Rabe *et al*. studied 102 patients with recurrent major depression (according to DSM-IV) and divided them into three subgroups: With and without suicidal ideation (S+, S-) and after suicidal attempts (AS). They found that TC 160 mg/dL or less and the level of LDL-C of 100 mg/dL or less was observed in persons with suicidal behavior only (S+ and AS). However, all the patients with acute depression showed low cholesterol levels.[48]

Alvarez *et al*. also confirmed the finding of low TC in suicide attempters.[49] Kunugi *et al*. also confirmed the finding of low TC in suicide attempters.[50]

Gallerani *et al*. compared the cholesterol levels in the people who were admitted to the hospital for parasuicide, and they found low cholesterol concentrations after parasuicide.[51]

Atmaca *et al*. also concluded that suicide attempters have lower levels of cholesterol.[8]

Cholesterol and Depression in Special Populations

Vevera *et al*. performed a retrospective case-control study comparing serum TC in violent and non-violent suicide women attempters. They found that lower cholesterol levels are seen in patients with violent suicide attempters than in non-violent attempters and control groups.[52]

Cadeddu *et al*. performed a study on elderly depressive patients over 65 years and concluded that the group with lower cholesterol (cut-off ≤ 160 mg/dL) had a prevalence of depression three-times greater than subjects with higher cholesterol.[53]

Shibata *et al*. studied elderly depressive patients assessed by the Geriatic Depression Score (GDS), and found that LDL, VLDL and TC, at a baseline level, significantly prevents the progression of depression.[7] The correlation between low cholesterol and depression in the elderly patients has also been established in Greek patients[54] in a sample of Finnish males[55] and US patients over 70 years of age.[56] Studies have also indicated a relationship between low cholesterol levels and post-partum depressed mood.[57,58] Pjrek *et al*.[59] demonstrated low cholesterol levels in patients with seasonal affective disorder.

Studies with Negative Findings

Deisenhammer *et al*. measured serum cholesterol in 92 in-patients after major depressive episodes after 1 week and 4 weeks of antidepressant treatment. They found that after antidepressant treatment, neither a significant change in serum cholesterol levels nor a correlation between cholesterol levels and clinical improvement was found. Further, there were no significant differences in lipid levels between patients with and without a history of attempted suicide.[60]

Almeida-Montes *et al*. performed a study on the depressive patients who had recently attempted suicide and found that there is no difference in the levels of TC, HDL and LDL among the patients who were depressive and attempted suicide and those who were depressive and did not attempt suicide.[61]

Tsai *et al*. performed a study on acute in-patients with bipolar-1 disorder and found that there was no significant difference in the fasting levels of serum cholesterol between suicide completers and living controls.[62]

Pompili performed a study on 26 patients of mood disorders (bipolar disorder and major depressive disorder) and found that suicide attempters had non-significantly higher serum levels of TC and lower serum levels of triglycerides. The use of biologic indicators such as levels of serum cholesterol and triglycerides in the prediction of suicide risk in mood disorders was not fully supported from this small sample.[63]

Few other studies have also suggested negative findings between serum cholesterol and depression.[64-69] Similar results have also been described in post-partum females.[70,71] Few researchers have also proposed no correlation between serum cholesterol and suicide attempts[72-75] or parasuicidal behavior.[76]

Few investigators have also reported high levels of TC, LDL and triglycerides in depressive patients.[77,78]

Cholesterol-lowering Drugs, Psychotropic Drugs and Depression

Several studies suggested that cholesterol-lowering drugs are associated with suicides.[16,79] Boston *et al*. in a course of primary prevention of cardiovascular diseases concluded that cholesterol-lowering agents increase the risk of suicides.[80]

It is also seen that various antidepressants and mood stabilizers, doxepin, imipramine, paroxetine and even following treatment with electroconvulsive therapy results in an increase in serum cholesterol levels.[81-85] However, few studies have also suggested that antidepressant drugs do not cause a rise in the cholesterol levels.[86,87]

However, Muldoon *et al*. concluded in a meta-analysis that deaths from suicides, accident and violence were not significantly increased among participants randomized to a cholesterol-lowering intervention.[88] Other studies have also denied the association between cholesterol-lowering drugs and suicide.[89,90]

Other metabolic markers associated with depression

A study performed on 35 patients enrolled in the United States marine basic combat training has proven that high HDL, fructosamine, free fatty acids, dehydroepiandrosterone-sulfate and substance P are associated with depressed moods ($P < 0.05$). However, increased LDL, triglycerides, fructosamine and adreno-corticotropic hormone (ACTH) were associated with improvement in mood ($P < 0.05$). It was also found in the same study that glucose, cortisol and C-reactive protein have no associations with mood.[91]

Conclusions

Several studies have been performed to establish a relationship between cholesterol levels and depression. Majority of the studies have concluded that low cholesterol levels are associated with depression and suicide,[92,93] whereas few studies have denied any relationship between the two. We tried to review the literature about this interesting topic and conclude that a relationship definitely exists between the low cholesterol levels and depression.

Abbreviations

TC: Total cholesterol
HDL-C: High-density lipoprotein cholesterol
MD: Major depression
LDL-C: Low-density lipoprotein cholesterol
DSM-IV: Diagnostic and Static Manual of Mental Disorders, 4th Edition
LCAT: Lecithin–cholesterol acetyl transferase
5-HIAA: 5-Hydroxyindolacetic acid

Acknowledgments

The authors acknowledge Randy A. Sansone, Domenico De Berardis, Stefano Marini, Monica Piersanti, Marilde Cavuto, Giampaolo Perna, Alessandro Valchera, Monica Mazza, Michele Fornaro, Felice Iasevoli, Giovanni Martinotti and Massimo Di Giannantonio for their guidance. We also acknowledge Engineer Ayush for his technical help.

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How to cite this article: Budania SK, Rathi M, Singh S, Yadav S, Mittra P. Serum cholesterol and depression: An update. Med J DY Patil Univ 2014;7:543-9.

Source of Support: Nil. **Conflict of Interest:** None declared.