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Total serum cholesterol level in patients with major depressive disorder: Simple yet undermined

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Human brain cholesterol acts as structural components of cellular membrane, synapse and dendrite formation. Researchers have found a possible association between low serum cholesterol levels and mood disorders though the literature from India in this regard is limited. To estimate serum levels of total cholesterol in patients with major depressive disorder. 75 patients of MDD were compared with equal number of age and sex matched controls. 5 ml of fasting sample of blood was obtained in a plain vacutainer to analyse total cholesterol level by Cholesterol oxidase-peroxidase method. Statistical analysis: The obtained results were tabulated and analyzed by multiple logistic regression analysis, independent *t*-test, Chi-square test and area under the curve. The mean level of cholesterol in cases (158.85±61.22 mg/dL) which was significantly lower compared to the controls (182.71±40.98 mg/dL) with P <0.01. The symptoms of MDD negatively correlated with lower serum cholesterol level with odds ratio of 0.99. There was statistically significant lower level of cholesterol in the MDD group below 140 mg/dL compared to the control group with P <0.001. As the measurement of total serum cholesterol is simple and cost effective, it can be used as an important biochemical marker for MDD.

Keywords: Anti-depressants, Major depressive disorder (MDD), Neuro-inflammation, Serotonin, Serum cholesterol level, Synapse

Brain functions like analysis, processing, co-ordination and execution of electrical signals involves extremely complex processes and is dependent on an extensive neuronal network covered by myelin sheath rich in lipids[1]. Neuronal lipids contains equimolar proportions of sphingolipids, glycerol-phospholipids and cholesterol[2]. Brain has about 20% of the body's total cholesterol and forms important structural components of neuronal membrane, dendrites, neuronal synapse[3], and is essential for the differentiation of dendrites, axonal elongation and long term potentiation[4]. It is not only important structurally to the brain and peripheral tissue, where it helps to build and maintain the cell membrane, but is also important to maintain various cellular functions, decide membrane dynamics, permeability, modulate fluidity and transport across cell membrane. The interaction of the cholesterol moiety with various protein components in the cell membrane can alter its physical properties[5]. Recent evidence suggests the role of cholesterol in the function and organization of neuronal Serotonin 1A receptor (5HT1A), which belong to G-protein coupled receptor (GPCRs) family. 5HT1A receptors are present indigenously in the hippocampal region of the brain which directs cognition, emotion and memory. It is hypothesized that the level of cholesterol modulates the neurotransmitter release in the brain and thus lower cholesterol level can lead to behavioral dysfunction, depression, suicide and memory loss[6]. Peripheral cholesterol is an important precursor molecule for the synthesis of Vitamin D, steroid hormones, bile salts which emulsifies fat and help in intestinal absorption.[6]

The rate of cholesterol synthesis in humans is highest during the peak of brain myelination process along with rapid increase in cholesterol flux. Thus, the process of myelination can get delayed when the cholesterol synthesis is deficient[7]. After the myelination of the brain is complete, the synthesis of cholesterol continues at a low level mainly relying on

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the external source[8]. Few neurons in adults depend on oligodendrocytes and astrocytes for the supply of cholesterol. Astrocytes express apoE *in vivo* which is taken up by neurons through receptor-mediated endocytosis of lipoproteins which is later cleaved to free cholesterol in the lysosomes which is later transported to the membrane[9].

The half-life of cholesterol in adult brain is about 6 months and 5 years, compared to plasma cholesterol which is only a few days[10]. Many studies have tried to establish a relationship between serum cholesterol levels and various psychiatric illnesses like depression, suicide, bipolar affective disorder associated with physical violence, violent suicidal attempts with schizophrenia and borderline personality disorder[11].

The etiology of depression is not completely understood. Research has implicated a possible role of monoamine neurotransmitter dysfunction in the causation of depressive symptoms[12]. The fact that only a portion of such patients respond to the same antidepressants highlights the possibility of many other mechanisms, neuronal pathways and brain regions that could be implicated in the illness[13]. More recent reports suggest a possible association between low serum cholesterol levels and mood disorders though its pathophysiology is not clear. It is hypothesized to be due to altered lipid metabolism and changes in serotonin functioning. A study by Sansone RA *et al*., highlighted that there are inconsistencies in the data. They highlighted that only some individuals with low serum cholesterol levels exhibit depressive symptoms, suicidal ideations or attempts and suspected if the association is causal or secondary to the depressive psychopathology[14]. Few other investigators have hypothesized the possible roles of serotonin transporters[15], decreased serotonin receptors[16], inter-relationships with leptin[17], decreased serotonin turnover[18], interleukin-2[19] and genetics[20] which may lead to MDD. A study by Sullivan NR *et al.*[21], suggested that supplementation of omega-3 fatty acids would be beneficial when added to standard treatment of unipolar depression. Though there is growing evidence correlating lower serum cholesterol level in MDD, the findings are inconclusive and there is limited data in this regard from India as explained by Budania SK *et al.* in his review article mentioning thatmajority of the studies have suggested that depression and suicide are associated with low levels of serum total cholesterol[22]. Thus, our study is a small step to correlate the serum cholesterol level of patients diagnosed with MDD and comparison with healthy controls.

Materials and Methods

A total of 75 cases and 75 controls aged between 18-60 years who consented for the study based on inclusion and exclusion criteria were included in our study. Institutional Ethics Committee permission was sought from USM-KLE, International Medical Program. Patients attending the out-patient unit (OPD) at Dr Anand Pandurangi's, Shree Psychiatric Centre in Dharwad city, catering to the patients of North Karnataka, diagnosed to have MDD without psychotic features (both first and multiple episodes) based on DSM lV-TR criteria based on clinical examination and confirmed by Mini International Neuropsychiatric Interview (MINI), who were not on treatment were recruited. Control subjects were apparently healthy persons without any symptoms or signs of MDD based on a clinical examination at inclusion. The diagnosis and the decision regarding the management of the patient was taken by the treating psychiatrist in which the authors had no say. The socio-demographic details of the participants were noted using a semi-structured proforma. A brief history of symptoms and physical examination findings were noted. 5 mL of fasting sample of blood was obtained from ante-cubital vein was collected in a plain vacuitainer and was transported to the laboratory for analysis by afternoon. In this duration serum would have separated and taken out in labeled eppendorf. Those who visited the clinic in the afternoon and volunteered to be part of the study in the afternoon were called next morning to give the sample. The procedure of data collection and sample collection were done according to ethical standards. The serum was used to analyze total cholesterol level by Cholesterol oxidase-peroxidase method. Data obtained was tabulated and analyzed statistically by Chi-square test, *t*-test and multiple logistic regression analysis.

Exclusion criteria- Severe medical conditions which require admission, known case of metabolic syndrome, substance use disorder, hypothyroidism, Parkinson's disease, dementia, malignancy, on treatment for hyperlipidemia, on steroids or antipsychotics drugs.

Results

A total of 75 cases and 75 controls were included in our study. The mean age among the cases was 40.41±11.53 years which was higher than the controls with 33.49±7.88 which were statistically different with "*P* value" <0.001. There were 35(46.6%) male and 40(53.3%) female participants in the case group

and 32 (42.6%) male and 43 (57.3%) female participants in control group. Majority 33(44.0%) in case group and 34 (45.3%) in control group were homemakers while 16 (21.3%) in case group and 12 (16%) in control group were farmers. 44 (58.7%) were from rural background and 31 (41.3%) from urban background in case group while 29 (38.6%) from rural background and 46 (61.3%) from urban background in control group which was statistically different with "*P* value" =0.014. 62 (82.6%) belonged to lower middle and 13 (17.3%) were from upper middle SES in case group while 66 (88%) were from lower middle and 9 (12%) were from upper middle SES in control group. 63 (84%) were married and 12 (16%) unmarried in case group while 64 (85.3%) were married and 11 (14.7%) unmarried in control group. 13 (17.33%) were illiterate and 44 (58.6%) studied up to high school and 18 (24%) were educated up to degree in case group while 3 (4%) were illiterate 7 (9.3%) were educated up to primary school and 65 (86.7%) up to degree which was statistically different with "*P* value" <0.001. 37 (49.3%) cases had history of MDD. In the case group 56 (74.7%) were from joint family while 64 (85.3%) in control group were from nuclear family, which was statistically significant with "*P* value" <0.001. Majority 69 (92.0%) of the participants among cases did not have family history of depression.

Nuclear family status had significant association with serum cholesterol level in the control group with majority of the participants having cholesterol between 140-200 mg/dL with "*P* value" =0.033. Other variables did not have any statistically significant comparison with serum cholesterol level.

The mean level of cholesterol in the case group was 158.85±61.22 which was significantly lower compared to the control group which was 182.71±40.98 with "*P* value" <0.01.

43 (57.3%) cases and 8(10.6%) controls had Serum Cholesterol (*S. Cholesterol*) level below 140 mg/dL while 15 (20.0%) cases and 49 (65.3%) controls had *S. Cholesterol* between 140-200 mg/dL while 17 (22.6%) cases and 18 (24.0%) controls had *S. Cholesterol* above 200 mg/dL. There was statistically significant lower level of cholesterol in the case group compared to the control group with the possibility of MDD more likely to be present with serum cholesterol level below 140 mg/dL with "*P* value"<0.001.

Multiple regression analysis with a negative z-score (−1.29) suggests that the observed values are lesser than the mean value. Odds ratio value of 0.99 suggests that the symptoms of MDD is inversely correlated with *S. Cholesterol* level.

AUC (area under curve) is 0.31 (below 0.50) indicates that lower values of serum total cholesterol predict MDD.

Discussion

Demographic characteristics of patients and controls groups are presented in Table 1 and its correlation with serum cholesterol level has been presented in (Table 2). The mean level of cholesterol in the case group was 158.85±61.22 mg/dL which was significantly lower compared to the control group which was 182.71±40.98 mg/dL with "*P* value"<0.01 (Table 3). The level of cholesterol was further divided into 3 groups *i.e* <140 mg/dL, 140-200 mg/dL and >200 mg/dL (Table 4). There was statistically significant lower level of cholesterol in the case group below 140 mg/dL compared to the control group with "*P* value" <0.001. Multiple regression analysis with a negative z-score (−1.29) suggests that the observed values of *S. Cholesterol* in the cases are lesser than the mean value. Odds ratio value of 0.99 suggests that the symptoms of MDD are inversely correlated with *S. Cholesterol* level. The findings of our study corroborate with the finding of a study by Borgherini G *et al.*[23], which suggested that low total cholesterol was associated with MDD and suicidal behaviors. In another case control study by Marcela SM *et al.*[24], in North Mexican population comparing MDD with and without suicidal attempt and healthy controls; defined *S. Cholesterol* below 150 mg/dL as hypocholesterolemia. In this study the mean *S. Cholesterol* level was 167.9± 45.1 mg/dL in cases which was significantly lower compared to controls with 172.5 ± 25.3 mg/dL and concluded that lower levels of cholesterol are associated with mood disorders like MDD and suicidal behavior. In our study we observed that MDD had significant association with cholesterol level of <140 mg/dL which is like the observation of the above-mentioned study (Tables 5 & 6 and Fig. 1). However, another study by Ergun UGO *et al.*[16], who evaluated the level of cholesterol on 189 subjects with MDD over 65 years and concluded that there was no association between depression and low serum cholesterol levels after adjustment for confounding factors.

In a meta-analysis by Wei YG *et al.*[25], which included 11 case-control studies with 690 subjects with

Table1 — Demographic characteristics of case and control groups

Variable	Case- 75(%)	Control 75 (%)	Chi-square	"*P* value"
Mean age	40.41±11.53	33.49±7.8	18.488	<0.001*
Male	35(46.6)	32(42.6)	0.243	0.622
Female	40(53.3)	43(57.3)		
Occupation				
Business	1(1.3)	2(2.6)	3.186	0.527
Student	3(4.0)	4(5.3)		
Farmer	16(21.3)	12(16.0)		
Homemaker	33(44.0)	34(45.3)		
Skilled	18(24.0)	22(29.3)		
Unskilled	2(2.6)	1(1.3)		
Unemployed	2(2.6)	0(0.0)		
Domicile				
Rural	44(58.6)	29(38.6)	6.004	0.014*
Urban	31(41.3)	46(61.3)		
Socio-economic status(SES)				
Lower Middle	62(82.6)	66(88.0)	0.852	0.356
Upper Middle	13(17.3)	9(12.0)		
Marital status				
Married	63(84.00)	64(85.33)	0.051	0.821
Unmarried	12(16.00)	11(14.67)		
Qualification				
Illiterate	13(17.33)	3(4.00)	57.832	<0.001*
Primary	22(29.33)	7(9.33)		
High School	20(26.67)	0(0.00)		
Degree	18(24.00)	65(86.67)		
Postgraduate	2(2.67)	0(0.00)		
Type of family				
Joint	56(74.67)	11(14.67)	54.621	<0.001*
Nuclear	19(25.33)	64(85.33)		

Table 2 — Association between Demographic Variables and Serum Cholesterol. The level of cholesterol was divided into ≤140, 140 – 200 and >200 mg/dL.

Demographic Variables	Cases (N=75) Serum Cholesterol			"*P* value"	Controls (N=75) Serum Cholesterol			"*P* value"
	≤140	140 – 200	>200		≤140	140 – 200	>200	
≤25 Years	4	2	3	0.838	2	8	0	0.298
26 to 50 Years	29	11	11		6	37	17	
≥51 Years	10	2	3		0	4	1	
Male	18	8	9	0.626	4	19	9	0.646
Female	25	7	8		4	30	9	
Employed	21	9	10	0.785	7	25	9	0.210
Unemployed	22	6	7		1	24	9	
Rural	26	8	10	0.790	0	21	8	0.764
Urban	17	7	7		8	28	10	
Lower	1	0	0	0.683	0	0	0	0.263
Lower Middle	33	12	16		8	41	17	
Upper	2	0	0		0	0	0	
Upper Middle	7	3	1		0	8	1	
Married	38	11	14	0.482	6	45	13	0.148
Separated	1	0	0		0	1	0	
Unmarried	4	4	3		2	3	5	
Literate	34	14	14	0.064	8	46	18	0.652
Illiterate	9	1	3		0	3	0	
Joint	33	11	12	0.877	0	11	0	0.033*
Nuclear	10	4	5		8	38	18	

Table 3 — Comparison of *S. Cholesterol* levels in cases and controls by independent *t*-test

Variable	Groups	Mean	*t*-value	"*P* value"
Serum Cholesterol	Case	158.85±61.22	−2.8039	<0.01*
	Control	182.71±40.98		

Table 4 — Comparison of case and control groups with levels of serum cholesterol

Levels of serum	Case (%)	Control (%)	Chi-square	*P* value
<140 mg/dL	43(57.33)	8(10.67)	42.111	<0.001*
140-200 mg/dL	15(20)	49(65.33)		
>200 mg/dL	17(22.67)	18(24)		

Table 5 — Multiple logistic regression analysis

Variables	Odds Ratio(OR)	Std. Err.	z-value	95%CI for OR		"*P* value"
				Lower	Lower	
S. Cholesterol	0.99	0.01	−1.29	0.98	1.00	0.1980

Table 6 — Area under the Curve

Variable	Area	Std. Error	*P* value	Asymptotic 95% Confidence Interval	
				Lower Bound	Lower Bound
S. Cholesterol	0.3150	0.0460	<0.001	0.2240	0.4060

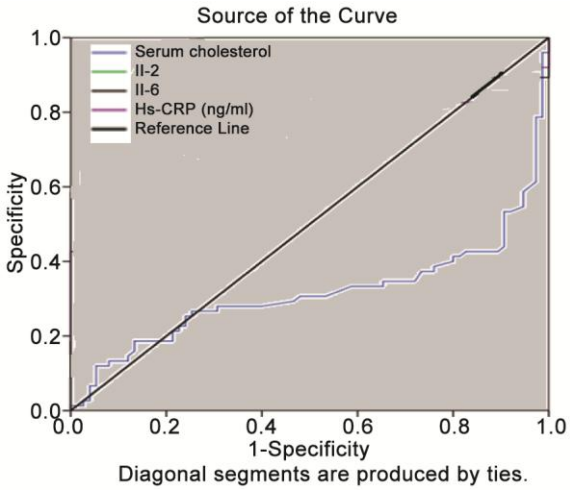

Fig. 1 — Area under curve by Sensitivity *v/s* 1-specificity

first-episode MDD and 614 healthy controls concluded that there was no significant difference was found in LDL cholesterol and total cholesterol levels between the two groups.

A study by Gabriel A *et al.*[26], observed that participants with MDD had higher total cholesterol levels after pharmacotherapy. There is conflicting literature about whether low cholesterol increases the risk of suicide or depression which predisposed by poor nutrition leading to low cholesterol level and then suicide. Fawcett J *et al.*[18] opined that that low cholesterol in MDD may be a may be a trait marker and not necessarily state dependent. However, our observation was cross sectional and will not be able to comment on this.

The mean age of participants in the case group was 40.41±11.53 years which was significantly higher compared to control group with mean age of 33.49±7.88 years with <0.001. In the above-mentioned study by Marcela SM *et al.*[24], the mean age of cases was 37.3 ± 10.0 and 36.8 ± 6.6 among the controls which were comparable with the age of the participants in our study. However, there was no significant difference between the groups. The higher mean age among the participants in our study may be because we have included both, first and multiple episodes both, in our study.

There was significant difference in the domicile of the participants with majority 44 (58.6%) cases from rural background compared to 29 (38.6%) in the controls with "*P* value" =0.014. Moreover 33 (44.0%) were homemakers in the case group. The site from where the sample was collected caters to a large number rural population. In our study majority of the cases were from rural background where they are involved in farming and other physical labour along with household work which might have contributed for lower *S. Cholesterol*. The level of serum cholesterol is known to decrease with malnutrition and disability which might have had a bearing on the high number of MDD patients from the rural areas and joint families in our study.

The participants in the control group were more educated compared to cases with 13 (17.3%) being illiterate and 44 (58.6%) having studied up to high school in case group while 3(4.0%) being illiterate and 65 (86.6%) having studied up to degree which was statistically significant with "*P* value"<0.001. In the case group 56 (74.6%) were from joint family while 64 (85.3%) in control group were from nuclear family which was significant with "*P* value" <0.001.

These observations in our study could be because majority of the cases were from rural background where even today the focus is more towards work and earning livelihood rather than education, though there has been a marked change in the recent times and also joint family system is still prevalent in these areas while majority of controls were from urban background where it is absent.

We also tried to analyze the association of various socio-demographic variables with the different categories of cholesterol. Nuclear family status had significant association with serum cholesterol level in the control group with majority of the participants having cholesterol between 140-200 mg/dL with "*P* value"=0.033 (Table 4). Other variables did not have any statistically significant comparison with *S. Cholesterol* level.

There are some strengths to our study. The findings of our study will help clinicians to select appropriate antidepressants to the patients with MDD as the data in Indian population is limited. Few patients with MDD also require use of atypical antipsychotics as augmenting agent or when associated with psychotic symptoms along with antidepressants which are likely to have an impact on *S. Cholesterol* level in which case the knowledge about the serum cholesterol becomes very essential. *S. Cholesterol* level can be used as a biochemical marker in patients with MDD. Our findings, if replicated in studies with larger sample could possibly guide policy makers and researchers focus on preventive aspects of mental illnesses like MDD. However, as the observations in our study was cross sectional, we will not be able to justify whether the lower cholesterol level is a state or a trait marker or if it improves with treatment. We have included only patients with MDD. If this association can be applied to minor forms of depression, patients with psychotic symptoms and population below 18 years of age need to be assessed further. We have not included Bipolar depression and if the same findings can be generalized to this subset of depression cannot be commented upon. Half of the cases had history of MDD and thus the effect of past history on the current findings cannot be commented upon.

Conclusion

The patients with MDD have lower serum cholesterol levels compared to general population. As measurement of cholesterol is simple and cost effective can be used as an important biochemical marker for MDD. Whether it is causal or observed as a result of MDD and if dietary modification to improve *S. Cholesterol* level can help prevent or improve depressive symptoms, needs to be evaluated further.

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Conflict of interest

All authors declare no conflict of interest.

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