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SERUM LIPIDS : NEW BIOLOGICAL MARKERS IN DEPRESSION ?

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ABSTRACT

Several studies suggest that a low cholesterol concentration is associated with depression. The authors sought to determine whether an association exists between serum lipid concentrations and depression. 28 drug-naive patients of major depression diagnosed according to DSM-III-R criteria were included in the study and severity of depression was measured on Hamilton Rating Scale for Depression. Suicidal intent was assessed on Suicidal Intent Questionnaire. 28 normal healthy controls were selected and matched for age, sex and body-mass index with the depressives. Serum lipid estimations were done in each subject after 12 hours overnight fasting.. The main finding of the study is that total serum cholesterol, serum triglycerides and serum LDL cholesterol are decreased while serum HDL cholesterol is increased in depression and these changes were more marked in depressed subjects with definite suicidal intent. On regression analysis, total serum cholesterol was the most important predictive variable of the severity of depression.

Key words : Depression, total serum cholesterol, serum triglycerides, serum LDL cholesterol, serum HDL cholesterol.

The impetus for studying serum cholesterol concentrations in depression came from studies reporting that clinical trials designed to lower serum cholesterol in coronary heart disease patients were offset by a significant rise in suicide (Muldoon et al., 1990; Engelberg 1992; Lindberg er al., 1992). A metaanalysis of six primary prevention trials of cholesterol low regime in men (pooled N=24, 847) revealed that the intervention group, as compared to control subjects, experienced a reduction in the incidence of coronary heart disease but not in total mortality (Muldoon et al., 1990). This discrepancy appeared in part to be due to an increase in non-illness related mortality (i.e. suicide, violence and accident) in the cholesterol lowering group.

Several studies have examined the relationship between cholesterol level and psychopathology. Among male homicidal offenders, those who had attempted suicide had lower cholesterol level than those who had not (Virkkunen, 1983). Male homicidal offenders who are habitually violent under the influence of alcohol (Virkkunen, 1979), and boys with both attention deficit disorder and aggressive conduct disorder (Virkkunen & Tentinnen, 1984) were found to have lower cholesterol levels than comparison subjects.

Depression is a risk factor for suicides and fatal accidents (Murphy et al., 1989) and there are biologically plausible mechanisms

linking low cholesterol with depression. Morgan et al. (1993) reported that among men aged 70 years and older, depression was three times more common in subjects with lowered cholesterol concentration and a significant inverse relationship between cholesterol levels and severity of depression was obtained by them. Maes et al. (1994) reported a significantly lower esterified cholesterol ratio in depressed subjects.

The effect of low cholesterol on mood is supported by studies of increased aggressive behaviour in non-human primates when serum cholesterol is decreased by low-fat diet (Kaplan et al., 1991).

Because membrane cholesterol is in equilibrium with serum cholesterol, low serum cholesterol could contribute to low levels of serotonin, which in turn are associated with poor suppression of harmful behavioural impulses (Engelberg, 1992). There is an inverse association between serum cholesterol concentrations and platelet serotonin uptake velocity (Guicheney et al., 1988). Low cholesterol could increase serotonin reuptake velocity in the brain (Meltzer, 1989), and thereby contribute to depression.

Bond (1993) stressed upon determining the full lipid profile to elucidate any potential relationship between cholesterol and depression. Unfortunately, none of the studies done so far have attempted to look at the lippoprotein fractions which comprise total serum cholesterol. A link between cholesterol and depression is intriguing because of the possibility of developing biological markers that would improve assessment of depression. Therefore, we sought to determine whether an association exists between triglycerides, serum HDL cholesterol and serum LDL cholesterol and depression and if so, whether serum lipids can be potential biological markers for depression.

MATERIAL AND METHOD

All consecutive drug-naive patients of depression of both sexes between 17-60 years of age who attended the adult psychiatry OPD of K.G.'s Medical College, Lucknow, and fulfilled the criteria for major depression, single episode (296.2) or recurrent depression (296.3) according to DSM-III-R (APA, 1987) were screened. Exclusion criteria were pregnancy, lactation, use of oral contraceptives, cigarette smoking, alcohol/drug abuse or dependence and presence of medical illness, especially, hypertension, coronary artery disease, diabetes mellitus, hypothyroidism, nephrotic syndrome, liver disorder and familial hyperlipidaemia.

Control group comprised of normal healthy volunteers matched one to one for sex and group matched for age (in groups of ten years) with depressives. Controls were screened on Cornell Medical Index (CMI) (Broadman et al., 1949) and those who gave thirty or more 'yes' responses on entire CMI and/or ten or more 'yes' responses on M-R section were excluded. Controls with present, past or family history of depression were also excluded from the study. Other exclusion criteria were same as for the depressive group.

A total of 76 drug-naive patients of depression were screened and 32 were selected who fulfilled the selection criteria. 4 patients did not report for repeat serum lipid estimation and they were dropped from the study. Finally 28 patients completed the study. 28 age and sex matched normal controls were selected who fulfilled the selection criteria. Informed consent was obtained from all the subjects.

Specially designed semistructured proforma was used to record the socio-demographic data, present history, past history, history of suicide attempt, family history, medical history, dietary history, physical examination, anthropometric measurements, mental status examination, diagnosis and classification. Height and weight of the subjects were measured and body-mass index was calculated using the formula (Pope & Hudson, 1989) : weight (in kg.) /height^2 (in m.). Severity of depression was rated on 17 item

Hamiltion Rating Scale for Depression (HRSD) (Hamilton, 1960). Suicidal intent was assessed using Suicidal Intent Questionnaire (SIQ) (Gupta et al., 1983).

Depressives were divided into three groups on the basis of SIQ score : Suicidal intent noncommunicators (SIQ Score 0-1), partial communicators (SIQ Score 2-4) and definite communicators (more than 4) (Gupta et al., 1983).

Routine blood investigations, blood sugar, blood urea, serum creatinine, serum bilirubin and electrocardiogram were done in all subjects and those with abnormal tests were excluded from the study.

Subjects were kept fasting overnight for 12 hours and in the morning 5 ml. venous blood was taken from the cubital vein using disposable syringe. Blood was collected in a non-ox tube. The blood sample was centrifuged and serum analysed for serum lipid estimation in the lipid laboratory of Central Drug Research Institute, Lucknow.

All the subjects of depressive group were advised tablet lorazepam 2 mg. at night time and no other medication was given for seven days. Controls were not given any medication. All the subjects were instructed not to change their usual dietary habits during this one week period. Repeat blood sample was taken after 12 hours overnight fasting and serum lipids estimation was done again to get two serum lipid profiles at one week interval in each subject. Mean of the two estimations was taken for the analysis of the results (Nityanand et al., 1989).

Total serum cholesterol, serum triglycerides and serum HDL cholesterol level (in milligrams per decilitre) were determined using Merckotest kit by enzymatic method (Allain et al., 1958) and serum LDL cholesterol was determined by Friedewald's equation (Friedwald et al., 1972).

Student 't' test was used to find out the level of significance of difference between serum lipid profiles of depressives and controls. Correlation matrix and stepwise regression analysis was done on MStat statistical software.

RESULTS

The study sample comprised of 28 patients of major depression and equal number of age and sex matched controls. Mean age of depressives and controls was 38.64±10.74 and 39.25±10.88 years respectively and there was no significant difference between the two. No subject was below 20 years of age. There were 15 males and 13 females in each group. Maximum number of subjects were educated upto class V and majority had Rs. 1000-2000 family income per month. Height, weight and body mass index also did not differ significantly and the two groups were found to be matched on these variables too.

Table 1 shows the comparison of serum lipid profiles of depressives and controls. Mean total serum cholesterol in depressives and controls was 166.39±27.81 mg/dl and 181.40±30.90 mg/dl respectively. Though total serum cholesterol was lower in depressives as compared to controls, but it was not statistically significant. Serum triglyceride concentration was 140.32±24.63 mg/dl in depressives and 157.32±27.47 mg/dl in controls and the difference was significant (p<.05). Serum HDL cholesterol was 45.57±4.08 mg/dl in

TABLE 1
MEAN (S.D.) OF SERUM LIPID PROFILES OF DEPRESSIVES AND CONTROLS

	Depressives (N=28)	Control (N=28)	Significance
Total serum cholesterol (mg/dl)	166.39±27.81	181.40±30.90	t=1.87; d.f.=54; NS
Serum triglycerides (mg/dl)	140.32±24.63	157.32±27.47	t=2.44; d.f.=54; p<.05
Serum HDL cholesterol (mg/dl)	45.57±4.08	40.21±5.32	t=4.23; d.f.=54; p<.001
Serum LDL cholesterol (mg/dl)	93.18±25.17	109.71±28.76	t=2.29; d.f.=54; p<.05

TABLE 2
STEPWISE REGRESSION ANALYSIS OF HAMILTION RATING SCALE FOR DEPRESSION SCORE

I	HRSD =	Age	[-0 0158] +24.8979
II	HRSD =	Age	[.5866] + TC [-.2516] + 43 3325
III	HRSD =	Age	[4702] + TC [0.2788] + TG [.0814] + 40.9793
IV	HRSD =	Age	[3456] + TC [-0.3036] + TG [.1884) +HDL [.2802] + 22.1673
V	HRSD =	Age	[.3516] +TC [-1.1286] + TG [.3483] +HDL [1.0714] + LDL [.8171] + Constant

HRSD = Hamilton Rating Scale for Depression Score
TC = Total serum cholesterol, TG= Serum triglycerides,
HDL=Serum HDL cholesterol, LDL=Serum LDL cholesterol

TABLE 3
SERUM LIPID PROFILES OF SUICIDAL INTENT NONCOMMUNICATORS (NC), PARTIAL COMMUNICATORS (PC) AND DEFINITE COMMUNICATORS (DC)

	NC	PC	DC	NC vs PC	NC vs DC	PC vs DC
Total serum cholesterol (mg/dl)	174.46±30.21	172.33±21.45	140.00±13.56	t=0.18	t=2.64*	t=3.26**
Serum triglycerides (mg/dl)	146.23±26.18	145.11±19.10	120.33±23.60	t=0.11	t=2.16*	t=2.24*
Serum HDL choleserol (mg/dl)	44.54±3.33	45.00±3.84	48.67±5.32	t=0.28	t=1.03	t=1.56
Serum LDL cholesterol (mg/dl)	101.06±27.45	99.68±18.64	67.27±12.43	t=0.13	t=2.86*	t=3.72**

d.f. for NC vs PC=20, NC vs DC=17, PC vs DC=13
*p < .05 **p < .01

depressives and 40.21±5.32 mg/dl in controls and the difference was highly significant (p<.001). Serum LDL cholesterol was 93.18±25.17 mg/dl in depressives and 109.71±28.76 mg/dl in controls, and the difference was significant (p<.05). Total serum cholesterol was lower in all age-groups of depressives but it was statistically significant in age-groups 30-39 years (p<.01), 40-49 years (p<.01) and 50-59 years (p<.01). Serum triglyceride level was significantly lower in depressives in all age-groups: 20-29 years (p<.05), 30-39 years (p<.01, 40-49) years (p<.01) and 50-59 years (p<.001). Serum HDL cholesterol was significantly higher in depressives in all age-groups : 20-29 years (p<.05), 30-39 years (p<.05), 40-49 years (p<.05) and 50-59 years (p<.001). Serum LDL cholesterol was significantly lower in depressives in all age-groups : 20-29 years (p<.05), 30-39 years (p<.01), 40-49 years (p<.01) and 50-59 years (p<.01).

Table 2 shows the stepwise regression analysis to determine the variables predicting severity of depression (HRSD score). The values in bracket represent the regression coefficient. Age was not a predictive variable alone (step I). Combination of age and total serum cholesterol influenced the severity of depression (step II). In combination of age, total serum cholesterol and serum triglycerides, total serum cholesterol was the most predictive variable (step III). In combination of age, total serum cholesterol serum triglycerides and serum HDL cholesterol, total serum cholesterol was again the most predictive variable (step IV). Finally, in combination of age, total serum cholesterol serum triglycerides, serum HDL cholesterol and serum LDL cholesterol, total serum cholesterol was the most important predictive variable followed by serum HDL cholesterol and serum LDL cholesterol (step V).

Table 3 shows the comparison of serum lipid profiles of suicidal intent-communicators, partial communicators and definite communicators. Total serum cholesterol, serum triglycerides and serum LDL cholesterol were significantly lower in definite communicators only. Table 4 shows the correlation matrix of different variables. Significant positive

TABLE 4
CORRELATION MATRIX OF DIFFERENT VARIABLES OF DEPRESSIVES

	Age	HRSD	SIQ	TC	TG	HDL	LDL
Age	1.00000						
HRSD	-0 .04153	1.00000					
SIQ	- 0 .24207	0.48313*	1.00000				
TC	0.94264	- 0. 22586	- 0.37345*	1.00000			
TG	0.97626	-0.09474	- 0. 29444	0.96177	1.00000		
HDL	- 0.51345	0.19384	0.27608	-0.51346	- 0. 58415	1.00000	
LDL	0.92554	-0.22538	-0 . 3938	0.99145	- 0. 95325	- 0. 60816	1.00000

*=p<.05

HRSD = Hamilton Rating Scale for Depression Score
SIQ = Sucidal Intent Questionnaire Score
TC = Total serum cholesterol
TG= Serum triglycerides
HDL=Serum HDL cholesterol
LDL=Serum LDL cholesterol

correlation (p<.05) was present between suicidal intent (SIQ score) and the severity of depression (HRSD score). Significant negative correlation (p<.05) was present between suicidal intent (SIQ score) and total serum cholesterol and serum LDL cholesterol.

DISCUSSION

The main finding of present study is that total serum cholesterol, serum triglycerides and serum LDL cholesterol are decreased while serum HDL cholesterol is increased in depression. All the studies done so far have determined only total serum cholesterol in depression. In the present study step wise regression analysis suggests that total serum cholesterol was the most important predictive variable of severity of depression followed by serum HDL cholesterol and serum LDL cholesterol.

Studies suggest that reduction of cholesterol concentration and low cholesterol levels may be associated with completed suicide (Muldoon et al., 1990). Gulier et al. (1995) have reported that male psychiatric patients with low cholesterol levels were twice as likely to have made a medically serious suicide attempt than men with cholesterol levels above the 25th percentile. None of the subjects in the present study had history of suicide attempt. The present study measured suicidal intent on suicidal intent questionnaire. Depressed subjects with definite suicidal intent had significantly lower total serum cholesterol, serum triglycerides and serum LDL cholesterol as compared to noncommunicators and partial communicators. Significant negative correlation was found between SIQ score and total serum cholesterol & serum LDL cholesterol.

Low cholesterol levels have also been linked with other forms of aggression (Virkkunen, 1979, 1983, 1984). Depression, suicide and impulsive aggression have been reported to be associated with lower than normal CNS serotonergic activity (Mann et al., 1989; Coccaro, 1989). Several authors have hypothesized mechanisms whereby cholesterol lowering could result in diminished central serotonergic transmission (Barrados et al., 1992; Engelberg, 1992).

A number of biological markers have been studied in depressed patients and include CSF-5 HIAA, urinary MHPG, dexamethasone suppression text, corticotropin releasing hormone, platelet MAO activity and sleep EEG (Kaplan et al., 1994). The issue of specificity remains a problem for the clinical utility of the

tests. Differences in laboratory assay techniques and accuracy may also account for the variability in the reports.

Though there are no reports on assessment of apolipoproteins in depressed patients, there is evidence that serum levels of apolipoproteins A-1 and B as well as the ratio of Apo A-1 to Apo B are better indicators of CHD (Vaswani et al., 1997). However the present study would have been stronger if apolipoproteins could have been studied.

There are inherent limitations in studying serum lipids because of multiple factors affecting them. We used strict selection criteria to exclude conditions affecting lipid homeostasis. Depression induced anorexia could conceivably result in low cholesterol. So the depressives and controls were matched for age, sex and body-mass index to overcome this effect (Bajwa et al., 1992). It is difficult to determine causality in a cross sectional study. Prospective studies with serial serum lipid estimations should be done on larger number of subjects. Future research may establish serum lipids as new biological markers for depression and suicide risk.

REFERENCES

Allain, C.C., Poon, L.S., Chan, C.S.G., Richmond, W. & Fu, P.C. (1974) Enzymatic determination of total serum cholesterol. *Clinical Chemistry*, 20, 470-475.

American Psychiatric Association (1987) Diagnostic and statistical manual of mental disorders, Edn. 3, (Revised) Washington DC : American Psyhciatric Association.

Bajwa, W.K., Asnis, G.M., Sanderson, W.C., Irfan, A. & Van Praag, H.M. (1992) High cholesterol levels in patients with panic disorder. *American Journal of Psyhciatry*, 149, 376-378.

Barrados, M.A., Mikhailidis, D.P. & Winder, A.F. (1992) Low serum cholesterol and suicide (letter). *Lancet*, 339,1168

Bond, A.J. (1993) Fowkes et al's serum cholesterol, triglycerides and aggression in general population. *British Journal of Psychiatry*, 163, 666-668.

Broadman, K., Erdmann A.J., Large, T. & Wolft, H.G. (1949) The cornell medical index : an adjunct to medical interview. *Journal of American Medical Association*, 140, 530.

Coccaro, E.F. (1989) Central serotonin and impulsive aggression. *British Journal of Psychiatry*, 155 (suppl 8), 52-62.

Engelberg, H. (1992) Low serum choesterol and suicide. *Lancet*, 339, 727-729.

Friedewald, W.T., Levy, R.I. & Fredrickson, D.S. (1972) Calculation of LDL cholesterol. *Clinical Chemistry*, 18, 499.

Guicheney, P., Devynck, M.A., Cloix, J.F., Pernollet, M.G., Grichois, M.L. & Meyer, P. (1988) Platelet 5-HT content and uptake in essential hypertension : role of endogenous digitialis like factors and plasma cholesterol. *Journal of Hypertension*, 6, 873-879.

Gulier, J.A., Marzuk, P.M., Leon, A.C., Weiner, C. & Tardiff, K. (1995) Low serum cholesterol and attempted suicide. *American Journal of Psychiatry*, 152, 419-423.

Gupta, S.C., Trivedi, J.K. & Anand, R. (1983) Development of suicidal intent -questionnaire. *Indian Journal of Psychiatry*, 25 (1), 57-62.

Hamilton, M. (1960) Rating scale for depression. *Journal of Neurology Neurosurgery and Psychiatry*, 23, 56.

Kaplan, H.I., Sadock, B.J. & Grebb, J.A. (1994) Mood disorder. In : Synopsis of Psychiatry, Edn.6, pp.516-555, Baltimore : Williams & Wilkins.

Kaplan, J.R., Manuck, S.B. & Shivley, C. (1991) The effects of fat and cholesterol on social behaviour in monkeys. *Psychosomatic Medicine*, 53, 634-642.

Lindberg, G., Rastam, L., Gullberg, B. & Ekluand, A. (1992) Low serum cholesterol concentration and short term mortality from injuries in men and women. *British Medical Journal*, 305, 277-279.

Maes, M., Delanghe, J., Meltzer, H.Y., Scharpe, S., D'Hodt, P. & Cosyns, P. (1994) Lower degree of esterification of serum cholesterol in depression : relevance for depression and suicide research. *Acta Psychiatrica Scandinivica*, 90,

252-258.

Mann, J.J., Marzuk, P.M., Arango, V., Mcbride, P.A., Leon, A.C. & Tierney, H. (1989) Neurochemical studies of violent and non-violent suicide. *Psychopharmacology Bulletin*, 25, 407-413.

Morgan, R.E., Palinkas, L.A., Barrett-Conner, E.L. & Wingard, D.L. (1993) Plasma cholesterol and depressive symptoms in older men. *Lancet*, 341, 75-79.

Muldoon, M.F., Manuck, S.B. & Mathews, K.M. (1993) Lowering cholesterol concentration and mortality : a quantitative review of primary prevention trials. *British Medical Journal*, 34, 1-43.

Murphy, J.M., Munson, R.R., Olivier, D.C., Sobol, A.M., Pratt, L.A. & Leigton, A.H. (1989) Mortality risk and psychiatric disorders : results of a general physician survey. *Psychiatry Epidemiology*, 24, 134-142.

Nityanand, S., Srivastava, J.S. & Asthana, O.P. (1989) Clinical trials with gugulipid : a new hypolipidaemic agent. *Journal of Association of Physicians of Inida*, 37 (5), 323-338.

Pope, H.G. Jr. & Hudson, J.I. (1989) Eating disorders. In : *Comprehensive Textbook of Psychiatry*, Vol.5, (Eds.) Kaplan, H.I & Sadock, B.J., pp 1854, Baltimore : Williams & Wilkins

Vaswani, M., Hemraj, P., Desai, N.G. & Tripathi, B.M. (1997) Lipid profile in alcohol dependence. *Indian Journal of Psychiatry*, 39 (1), 24-28.

Virkkunen, M. & Tentinnen, H. (1984) Serum cholesterol in aggresive conduct disorder : A preliminary study. *Biological Psychiatry*, 19, 435-439.

Virkkunen, M. (1979) Serum cholestrol in anti-social personality. *Neuropsychobiology*, 5, 27-30.

Virkkunen, M. (1983) Serum cholesterol levels in homicidal offenders : a low cholesterol level is connected with habitual violent tendency under the influence of alcohol. *Neuropsychobiology*, 10, 65-69.

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