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Original Article

The correlation between statin usage and incidence of depression in a tertiary care hospital

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ABSTRACT

Background: Investigators found that low serum cholesterol levels are an inconsistent possible biological marker for the manifestation of depression and/or suicidal ideation in some individuals. The results of many studies showed that the effect of long-term cholesterol depletion in the brain might trigger depression. **Objectives:** To find out the correlation between long term use of STATINS and depression and to study the effect of STATINS on lipid profile. **Material and methods:** The study is a hospital based prospective study conducted in patients using STATIN medication. Hamilton depression rating scale is used to assess the correlation between the drug usage and incidence of depression at baseline and at the end of 3 and 6 months. Lipid profile is also measured at baseline and again at the end of 3 and 6 months of treatment period. **Results:** All statistical analysis done by using SPSS version 21 and MS Excel 2007. One way Anova performed to know the mean difference among various continuous variables. All the values for total cholesterol, triglycerides, HDL, LDL, VLDL and HAM-D are considered highly significant, the p-value being .000. **Interpretation and conclusions:** As there is reduction of lipid levels at the end of 6 months and there is corresponding increase in depression score, it was concluded that there is correlation between Statin usage and incidence of depression.

KEY WORDS: Lipid profile, serotonin, Hamilton depression rating scale and neurotransmitter.

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INTRODUCTION

Research finding going back to the early 90s show that total serum cholesterol is low in more depressed patients than in non-depressed individuals and that clinical improvement following antidepressant therapy is often associated with a significant increase in total serum cholesterol levels. A review of 6 randomised trials dating from the 1980s through the early 1990s found that while lowering abnormally high cholesterol levels (below 150mg/ dL) decreased the number of deaths from coronary heart disease, cholesterol lowering was actually associated with increased mortality due to suicide or violence. [1] Several studies have found that low serum lipid levels are associated with persistently low platelet serotonin levels in depressed suicidal patients. [2,3]
It has been hypothesized that low cholesterol levels indirectly lead to reduced brain serotonin because of the requirement of adequate cholesterol in nerve cell membranes to maintain the functional integrity of the serotonin receptors.[4]

The cholesterol-serotonin hypothesis was initially proposed to explain the link between low cholesterol levels and depression. This hypothesis states that reduction of serum total cholesterol may decrease brain cell membrane cholesterol and thereby lowering micro viscosity of cell membrane and subsequently decreasing the exposure of protein serotonin receptor on the membrane surface resulting in poorer uptake of serotonin from blood and less serotonin into brain cells leading to depression.[5] Low serum cholesterol in depression could be a consequence of depression because of their poor health and decreased food intake. And also treating depression has been shown to increase serum cholesterol concentration. [6] Papakostas et al.[7] have proposed that both elevated and low cholesterol levels may be associated with seretonergic dysfunction. Historically Hippocrates first described depression as a condition associated with "aversion to food, sleeplessness, despondency, irritability and restlessness." [8]

The World Health Organisation (WHO) has ranked depression as fourth in a list of most urgent problems worldwide. [9] Pazarlis and colleagues postulated that lipophilic Statins may cause deleterious effects on mental health through an immunomodulatory mechanism.[10] The more lipophilic statins readily penetrate the blood brain barrier where they inhibit HMG CoA reductase, suppress several cytokines (including interferon - gamma, and interleukins IL-2 and IL-12) which results in lowering of tryptophan availability in the brain and decreased serotonin synthesis.

Medications and effects on cholesterol: The literature on the psychiatric effects of cholesterol lowering medications is controversial. For eg Boston et al indicate that there is substantial evidence that lowering cholesterol levels with medications is associated with an increase in various psychiatric disorders (depression and violent deaths)- findings that emerged in cardiovascular primary prevention studies.[11] However, other investigators indicate that no such relationship is evident in their empirical studies.[12,13]

MATERIALS AND METHODS

The patients were enrolled for the study after approval from Institutional Ethics Committee after obtaining written consent.A total of 50 patients who attend the medical out-patient department of GSL general hospital satisfying the inclusion criteria are selected for the study. HAM-D or Hamilton Depression Rating scale is employed for measuring the severity of depression.

DEPRESSION diagnosed according to the diagnostic criteria of ICD-10 and all the cases first assessed by Psychiatrist to exclude depressive disorder and at the end of the study, severity assessed according to Hamilton Depression Rating Scale (HAM-D). It is abbreviated as HAM-D, is a multiple item questionnaire used to provide an indication of depression, and as a guide to evaluate recovery. Max Hamilton originally provided this scale in 1960 and later revised in 1967, 69 and 1980. A score of 0-7 considered as normal. Scores of 20 or higher indicate moderate, severe or very severe depression.

According to the treatment guidelines as per ACC/AHA guidelines, recommend high dose Statins (Atorvastatin 40-80 mg or Rosuvastatin 20-40 mg) for those with clinical evidence of ASCVD, LDL 190 mg/dL or a 10yr ASCVD risk greater than 7.5%. This study includes patients who are diagnosed with Diabetes Melletus, CVD, CVA and/or associated with dyslipidemias who are prescribed Statin medication for the first time. The patients who fulfil the inclusion criteria were given 40 mg of Atorvastatin per day for a period of 6 months.Baseline values of lipids and HAM-D were taken at the beginning and at 3 months and 6 months of the study.

Statistical Analysis: Statistical analysis performed by using SPSS software trial version 21 and MS Excel 2007. Descriptive data presented as Mean $\pm$ standard deviation and percentages. Correlation was used to assess the relation between various continuous variables

Anova 1-way has been performed to assess mean differences among various continuous variables.
For all statistical analysis p value <0.05 was considered as statistically significant.

OBSERVATION AND RESULTS

When compared with the baseline values, all the values of total cholesterol, triglycerides, HDL, LDL and VLDL are reduced both at 3 months' time and also after 6 months interval. The values are highly significant within the groups and also between the groups. The statistical value has been considered highly significant, the value being .000.
There is some reduction of lipid levels after treatment with the Statins for 3 months' time. But the reduction of lipids is more marked when the Statin is used for 6 months. When the values between the groups are compared, it appears that the lipids are markedly reduced after treatment with the Statin after 6 months than after 3 months.

With regard to the Hamilton depression rating scale, it was observed that the scores on the rating scales are being increased after 6 months treatment, but there is no considerable increase in the score after treatment with Statins for 3 months showing that long standing use of Statins can cause proportionate decrease of lipids along with causing depression. The score on the Hamilton depression rating scale is also highly significant after treatment with Statins after 6 months, the value being .000.

DISCUSSION

50 patients with hyperlipidemia were selected for the study. The study includes patients in the age group 30-65 years of both the sexes, who are diagnosed with diabetes mellitus, cardiovascular disease, cerebrovascular accident associated with dyslipidemias who are prescribed Statin medication for the first time.

Statins are the lipid lowering or hypolipidaemic drugs. They are called as HMG CoA Reductase inhibitors. These drugs act on the HMG CoA Reductase, which is the rate limiting enzyme in the biosynthesis of cholesterol. Atorvastatin and its congeners are structurally similar to HMG CoA and are therefore competitive inhibitors of the enzyme HMG-CoA Reductase. This drug has got good potency and efficacy and a longer duration of action. It effectively lowers LDL-CH and to some extent triglycerides. It is a popular hypolipidemic and is a commonly used drug. In this particular study, we have assessed the correlation between Statin usage and incidence of depression in a tertiary care hospital, GSL General hospital, Rajamahendravaram (A.P.)

There are many studies showing the effects of psychotropic medications on serum cholesterol. In samples of depressed patients, several studies indicate that effective mood-disorder treatment results in an increase in serum cholesterol levels. These findings have been reported with various antidepressants and mood stabilizers[14], Doxepin [15] ,Imipramine [16] , Paroxetine [17] and even following treatment with electroconvulsive therapy (ECT). [18]

There are also studies indicating that antidepressant treatment does not effect cholesterol levels. For eg.in a six week study with Trazodone [19] and a six month study of Bupropioon- both showed negative findings. [20]
In the study published in Journal of Biochemistry in June 2010, Shrivastava and colleagues examined the effect of chronic cholesterol depletion induced by the cholesterol lowering drug Mevastatin on the function of human serotonin 1A receptors expressed in hamster ovary cells. They reported a significant reduction in the level of serotonin binding and G-protein coupling to serotonin 1A receptors resulting from chronic cholesterol depletion following treatment with Mevastatin which is one of the more lipophilic statins.

The above findings show that low nerve cell membrane cholesterol directly results in a decrease in the number of serotonin receptors, resulting in an overall reduction of serotonergic transmission in the brain. Significantly the researchers also showed that the effects of chronic cholesterol depletion on serotonin binding resulting from Statin use is completely reversible when the drug is stopped.

Research suggests that there may be a connection between low cholesterol and poor mood. For example, research looking at mothers after giving birth demonstrates that low postpartum levels of total cholesterol have been associated with symptoms of depression[21] Other studies show that adults with lower cholesterol on medications will have significantly increased relapse rates of depression. [22]

A number of studies in various types of populations have found an association between low cholesterol levels and depressive symptoms and mood disorders.

In a study conducted on general population in a Finnish community sample of nearly 30,000 participants, investigators found that low serum cholesterol levels were associated with depressed mood and heightened risk of hospitalisation for depression. [23]

In the outpatient samples in an Irish study of primary care patients, Rafter found that participants with low serum cholesterol levels scored significantly higher on depression assessments. [24] With regard to depression in patient samples, in an Italian study, Borgherini and colleagues found that lower serum cholesterol levels correlated with higher scores on the depression assessment scale that was used in this study. [25]

While a good number of studies indicate an association between low serum cholesterol levels and depressive symptoms and diagnoses, not all studies have found support for such a relationship. For eg in a sample of Japanese males, investigators found that higher serum cholesterol levels were associated with depression. [26] Associated with the previous findings among large retrospective sample of patients suffering from affective psychosis Fritze and colleagues found no association between low serum cholesterol and depressive symptoms.[27]

It was observed that low serum cholesterol concentrations have been reported to be associated not only with a decline in death from coronary heart disease but also with an increase in deaths due to suicide.[28] Various studies have shown a significant correlation between lower serum cholesteol concentration and suicides due to depression.[29,30]

CONCLUSION

Based on the present study, and the research findings of the many previous studies, it can be concluded that low serum cholesterol levels indirectly lead to the depletion of serotonin which further results in the causation of depression. Hence while treating dyslipidemias, it should be kept in mind that low lipid levels may cause depression in the patient. Hence repeated lipid profile checking to be done and if there is any drastic reduction in the lipid levels the Statins to be stopped, However, this finding has to be supported by further studies.

TABLE 1: AGE AND SEX DISTRIBUTION OF PATIENTS

Age	Male	Female
31 - 40 yrs	4	6
41 - 50 yrs	10	8
51 - 65 yrs	11	11

ANOVA

Table-2		**Descriptives**								
		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Min	Max	p-Value
						Lower Bound	Upper Bound			
TCh	1	50	226.68	36.658	5.184	216.26	237.1	176	298	0.000
	2	50	197.5	27.979	3.957	189.55	205.45	158	256	
	3	50	158.16	26.819	3.793	150.54	165.78	15	190	
	Total	150	194.11	41.586	3.396	187.4	200.82	15	298	
TG	1	50	150.06	28.18	3.985	142.05	158.07	94	192	0.000
	2	50	125.78	23.904	3.381	118.99	132.57	76	174	
	3	50	105.48	17.132	2.423	100.61	110.35	71	140	
	Total	150	127.11	29.664	2.422	122.32	131.89	71	192	
HDL	1	50	49.18	4.094	0.579	48.02	50.34	38	59	0.000
	2	50	51.46	3.412	0.483	50.49	52.43	42	59	
	3	50	52.9	3.738	0.529	51.84	53.96	43	62	
	Total	150	51.18	4.037	0.33	50.53	51.83	38	62	
LDL	1	50	134.88	12.621	1.785	131.29	138.47	120	198	0.000
	2	50	118.46	8.814	1.246	115.96	120.96	89	148	
	3	50	94.88	9.619	1.36	92.15	97.61	78	116	
	Total	150	116.07	19.485	1.591	112.93	119.22	78	198	
VLDL	1	50	38.84	8.911	1.26	36.31	41.37	25	58	0.000
	2	50	34.46	8.442	1.194	32.06	36.86	24	54	
	3	50	31.14	8.502	1.202	28.72	33.56	20	56	
	Total	150	34.81	9.129	0.745	33.34	36.29	20	58	
HAM- D	1	50	6.4	0.756	0.107	6.19	6.61	4	8	0.000
	2	50	10.54	1.432	0.202	10.13	10.95	7	13	
	3	50	18.82	2.569	0.363	18.09	19.55	8	21	
	Total	150	11.92	5.466	0.446	11.04	12.8	4	21	

1 - Shows baseline values at the start of the study
2 - Shows the results at the end of 3 months
3 - Shows the resutls at the end of 6 months

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