

Correlation between Thyrotropin and Fasting Lipid Profile in Patients of Sub Clinical Hypothyroidism

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Abstract

A controversy exists regarding the association between subclinical hypothyroidism (SCH) and dyslipidemia. Moreover, studies on lipid ratios in SCH are rare, particularly in Asian Countries. The study also aims to find out whether any correlation exists between serum TSH levels and fasting lipid levels, which would indirectly affect morbidity and mortality.

Methods: The study was conducted at Physiology department, KEMU and Centre for Nuclear Studies KEMU & Mayo Hospital, Lahore which is a tertiary-care center. It was a cross-sectional study carried out over a period of 6 months. Control group consisted of 50 euthyroid persons taken from a population coming for whole-body health checkup. Case group consisted of 50 patients with SCH. Confounding variables were removed. Fasting blood samples were taken in a plain gel vacutainer tube with an aseptic blood collection technique. The samples were centrifuged within 1 h at 3000 rpm for 5 min. These were

processed to obtain serum for the estimation of serum lipid profile and Thyrotropin (TSH) hormone level.

Results: The study examined the link between Thyrotropin levels and fasting lipid profile in patients of SCH versus euthyroid normal controls in a cross sectional adult population over a period of six months. Patients with SCH had significantly lower HDL-C, as compared to Controls. The Lipid profiles were each categorized and mean Thyrotropin levels were higher in subjects in the dyslipidemic sub-class than subjects in normal sub-class. Thyrotropin was positively associated with serum Triglyceride and negatively associated with HDL-C in cases of SCH. Thyrotropin is also positively associated with Total Cholesterol (TC) along with VLDL-C and LDL-C. In the Euthyroid (Control Group) population, Thyrotropin was positively associated with TC.

Conclusion: To conclude, Serum Thyrotropin was correlated with dyslipidemia in SCH and euthyroid subjects. In simple words, when Thyrotropin (TSH) increases upto 10 mIU/L the signs and symptoms of Hypothyroidism are not manifested, but chemical changes start to take place in the body, and the lipid metabolism is starting to take its toll. In SCH patients, TC, Triglyceride, LDL-C, HDL-C, start to rise as compared to normal euthyroid control groups. Thus there is a positive correlation between lipids and Thyrotropin, less HDL, which exhibited negative correlation in SCH subjects.

Keywords: Dyslipidemia, lipid profile, subclinical hypothyroidism.

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Introduction

Subclinical hypothyroidism (SCH), is described as a condition which presents with elevated serum level of Thyrotropin (TSH) normal levels of free Thyroxine (T₃)

and free Tetriodothyronine (T_4), is a common disorder having a prevalence of about 7.5–8.5% in females and 2.8–4.4% in males, worldwide.^{1,2}

Numerous studies have shown that overt hypothyroidism is associated with abnormalities of lipid metabolism such as elevated lipids viz. VLDL(Very low density Lipoprotein) LDL (Low Density Lipoprotein) TC (Total Cholesterol) and Triglycerides (TG) thereby predisposing individuals to vascular diseases.³⁻⁵ However, the association of SCH with abnormalities in lipid parameters have been studied with conflicting results.^{4,6} Some studies have also shown a link between SCH and metabolic syndrome while others have been unable to prove this.^{7,8} Numerous studies have depicted that even little alterations in TH serum status within the reference range might influence the severity of atherosclerosis.⁹

Now a days, serum lipid ratios such as TC/high-density lipoprotein-cholesterol (TC/HDL-C), TG/HDL-C, and LDL-C/HDL-C have been shown to be better predictors of cardiovascular risk compared to conventional lipid profile.¹⁰ Small dense LDL, a subtype of LDL has been described as the main determinant of the atherogenicity of LDL-C.¹⁰ However, studies on the complex interrelationship between SCH and lipid have been extremely rare.

Although the effect of overt hypothyroidism on abnormalities in lipid parameters has already been established, the relationship between SCH and lipid metabolism needs further study. Furthermore, there is insufficient information regarding the effect of SCH on lipid profile. This is particularly true in our part of the world, especially in the female population where SCH is more prevalent. Therefore, this study was conducted to understand the association of SCH with abnormalities in the serum lipid profile in a sample of local population. The study also aims to find out whether any correlation exists between serum TSH levels and fasting lipid profile.

Patients & Methods

The study was conducted at Physiology department, KEMU and Centre for Nuclear Studies KEMU & Mayo Hospital, Lahore. This is a tertiary-care center. It was a cross-sectional study carried out over a period of 6 months. Control group consisted of 50 euthyroid persons taken from a population coming for whole-body health checkup. Case group consisted of 50 patients with sub clinical hypothyroidism. This group subjects were selected from patient population coming to Medicine and ENT OPD for the routine checkup. Confounding variables were removed. Fasting blood samples were taken in a plain gel vacutainer tube with an aseptic blood collection technique. The samples were centrifuged within 1 h at 3000 rpm for 5 min. These were processed to obtain serum for the estimation of serum lipid profile and thyroid hormone level.

After collection of data it was entered in SPSS 21, quantitative variables like age, gender were expressed as $\pm$ SD. Qualitative variables were expressed as frequency and percentages. PEARSON'S correlation test was used to correlate TSH with Lipid Profile.

Results

The level of TSH has not put a significant impact on Cholesterol. As is evident from the figure below. The rise in TSH which would depict a trend towards hypothyroidism and parallel decrease in free T_3 & T_4 would affect the Cholesterol concentration. But the cases we took the cutting point was 10mIU/L which has not affected the Cholesterol significantly. The controls also had the same sort of trend as in the SCH. It shows that, to have a significant effect on the levels of Cholesterol the TSH has to be higher than 10mIU/L, may be 50 or above, in a full blown hypothyroid, than it might affect the total serum fasting Cholesterol levels. In our study the correlation has been negative for TSH and cholesterol, but not significant.

Table 1: Descriptive Statistics of Cholesterol.

	Cases of Sub-Clinical Hypothyroid			Euthyroid (Controls)		
	Correlation	P-Value	Mean Cholesterol Level MG/DL	Correlation	P-Value	Mean Cholesterol Level MG/DL
TSH Vs. Cholesterol	0.093	0.519	190	0.214	0.135	189.12

The figure clearly elaborates, that with rise in TSH the Triglycerides tend to rise, whereas in normal healthy individuals the Triglycerides show a continuous pattern. In cases of SCH the TSH is taken between 4 and 10mIU/L which shows a marked trend in increase in triglyceride levels with rise in TSH levels.

The figure shows a clear trend in TSH raised and normal healthy individuals. The TSH raised subjects show the HDL is low. While the healthy subjects the HDL is raised with TSH within normal limits. HDL is a friendly and protective form of cholesterol and does not let cholesterol molecules to oxidize and help form atheromatous plaque. It enhances with physical activity and normal or raised Thyroid hormones. In SCH there is a trend of lowering of HDL which is a very unhealthy and dangerous sign. In controls the pattern was as expected, the rise or at the normal range which is individual's attitude towards life, eating habits and physical activity pattern. If we consider all the lipid groups in the human serum, High density lipoprotein HDL is found to be most human friendly, which does not let lipids to adhere to the capillary wall. In our study the HDL was shown not to be affected in cases of SCH.

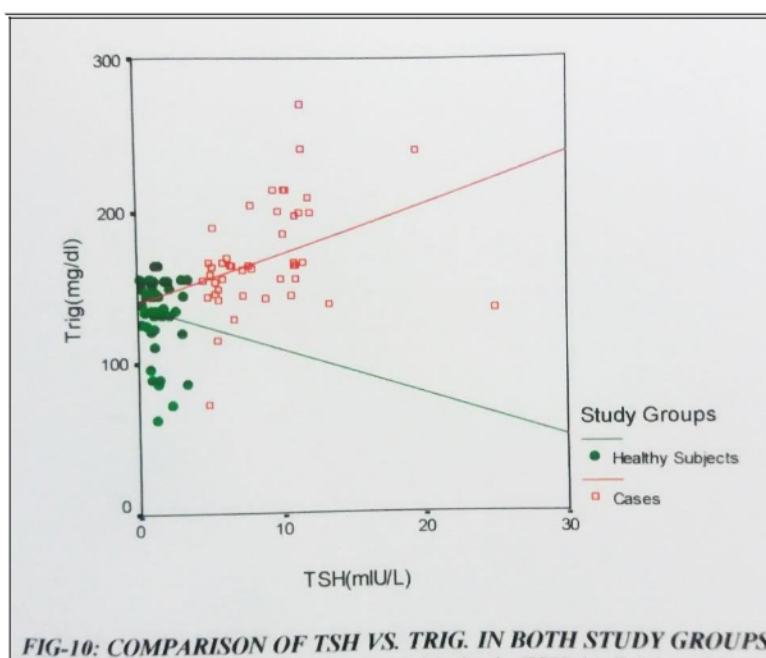
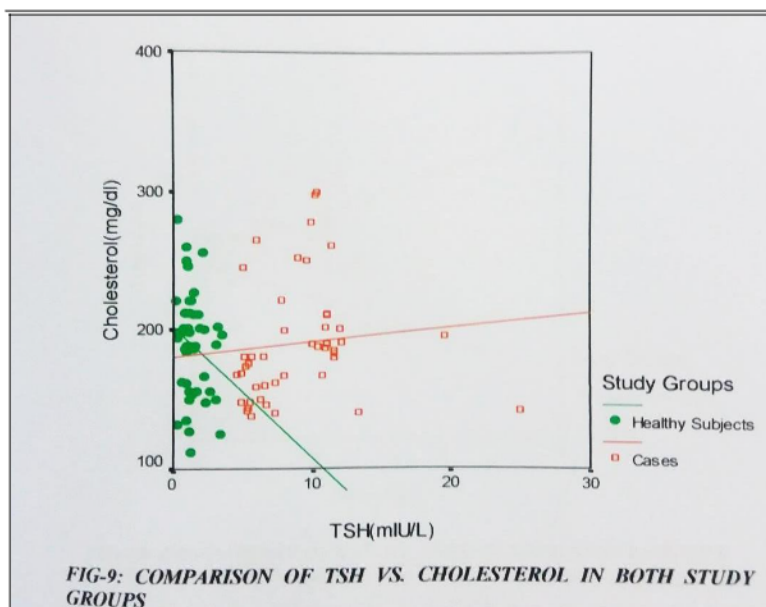


Table 2: Comparison of TSH VS Triglycerides in Both Study Groups.

	Cases of Sub-Clinical Hypothyroid			Euthyroid (Controls)		
	Correlation	P-Value	Mean TRG Levels MG/DL	Correlation	P-Value	Mean TRG Levels MG/DL
TSH Vs Triglyceride	0.368	0.009	168.28	0.098	0.97	133.62

Table 3: Comparison of TSH Vs HDL in Both Study Groups.

	Cases of Sub-Clinical Hypothyroid			Euthyroid (Controls)		
	Correlation	P-Value	Mean HDL-C Level MG/DL	Correlation	P-Value	Mean HDL-C Level MG/DL
TSH Vs HDL	-0.009	0.953	39.74	-0.082	0.569	43.48

LDL is affected the most. If you look at the figure the normal control cases with TSH within normal range the LDL is at a constant normal range level. While with increasing TSH the LDL levels increase. Increase in TSH and decline in free T₃ and free T₄ levels depicts a hypothyroid pattern.

TSH vs. Cholesterol (mg/dl) correlation for SCH is +0.093 and for euthyroid it is -0.214. There is a positive correlation between TSH and Cholesterol, i.e. if the TSH levels enhance the Cholesterol levels also enhance. Enhanced TSH levels mean hypothyroidism; T₃ & T₄ would be decreased. The metabolism of Cholesterol badly affected and the correlation is not positively depicted in control group and both the entities are statistically insignificant. TSH vs. Trig (mg/dl) correlation for SCH is 0.368 and for Euthyroid is 0.098. There is a positive correlation between TSH and Triglyceride, i.e. if the TSH levels enhance the Triglyceride levels also enhance. Enhanced TSH levels mean hypothyroidism; T₃ & T₄ would be decreased. The metabolism of Cholesterol badly affected and the correlation is also positively depicted in control group and both the entities are statistically insignificant. TSH vs. HDL (mg/dl) correlation of SCH is -0.009 and for euthyroid it is -0.082. There is a negative correlation between TSH and HDL, i.e. if the TSH levels enhance the HDL levels will decrease. Enhanced TSH levels mean hypothyroidism; T₃ & T₄ would be decreased. The metabolism of Cholesterol badly affected and the correlation negatively depicted in control group and both the entities are statistically insignificant.

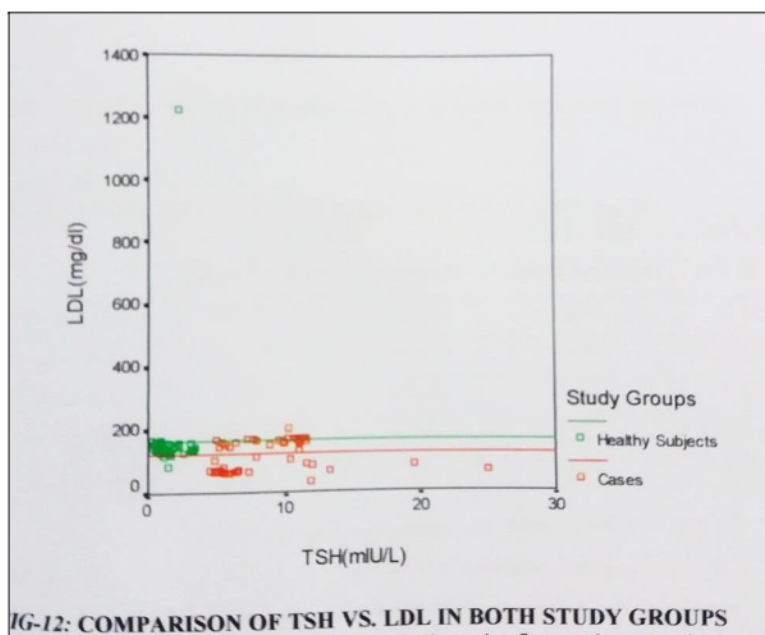
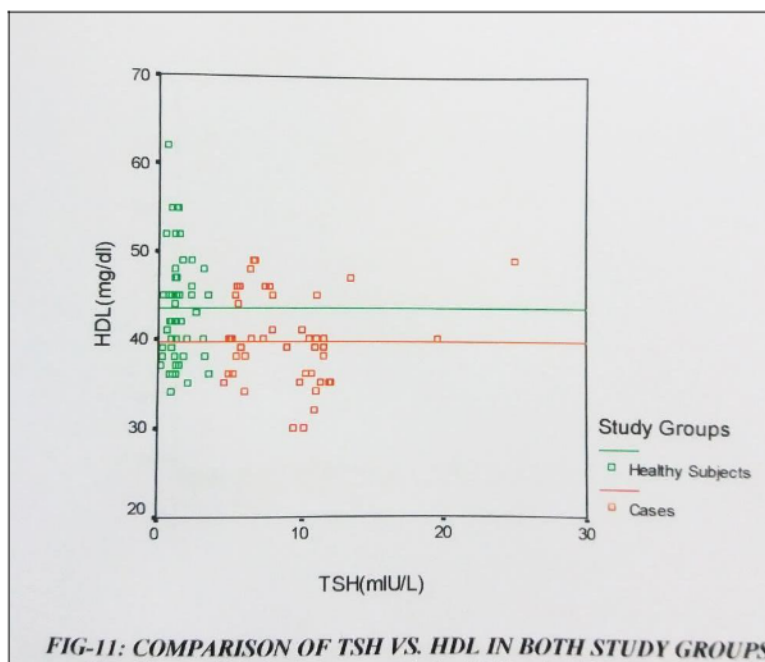


Table 4: Comparison of TSH Vs LDL in Both Study Groups.

	Cases of Sub-Clinical Hypothyroid			Euthyroid (Controls)		
	Correlation	P-Value	Mean LDL –C Levels mg/dl	Correlation	P-Value	Mean LDL –C Levels mg/dl
TSH Vs. LDL	0.008	0.958	182.82	0.148	0.306	161.24

Table 4: Correlation of Different Parameters Vs TSH (mg/dl).

	Cases		Healthy Subjects	
	Correlation	P-Value	Correlation	P-Value
TSH vs. Chol (mg/dl)	0.093	0.519	0.214	0.135
TSH vs. Trig (mg/dl)	0.368	0.009	0.098	0.497
TSH vs. HDL (mg/dl)	-0.009	0.953	-0.082	0.569
TSH vs. LDL(mg/dl)	0.008	0.958	0.148	0.306
TSH vs. VLDL (mg/dl)	0.143	0.323	0.016	0.913

TSH vs. LDL (mg/dl) correlation is +0.008 and +0.306 for SCH and controls. There is a positive correlation between TSH and LDL, i.e. if the TSH levels enhance the LDL levels also enhance. Enhanced TSH levels mean hypothyroidism; FreeT3 & FreeT4 would be decreased. The metabolism of Cholesterol badly affected and the correlation is not positively depicted in control group and both the entities are statistically insignificant. TSH vs. VLDL (mg/dl) correlation was positive 0.143 for SCH and .016 for euthyroid as controls. There is a positive correlation between TSH and VLDL, i.e. if the TSH levels enhance the VLDL levels also enhance. Enhanced TSH levels mean hypothyroidism; FreeT3 & FreeT4 would be decreased. The metabolism of Cholesterol badly affected and the correlation is not positively depicted in control group and both the entities are statistically insignificant.

Discussion

The link between dyslipidemia and SCH has been explored in a large number of studies of varying methodologies in different parts of the world.^{2,9,13,14,15} However, studies on the abnormalities in lipid ratios are better markers of cardiovascular risk than conventional lipid profile are rare. With this background, we conducted a cross sectional-control study, where we

studied patient who were asymptomatic for Hypothyroid, but their TSH levels were below 10 mU/L to investigate the status of their fasting lipid profile and compared them with 50 persons with normal TSH levels as controls. The study also aimed to find out if there was any correlation between TSH and fasting lipid profile.

In our study, the mean age of SCH patients 37.50 similar to other studies done in Tamil Nadu (India), Greece, and Turkey but higher than studies done in Kashmir (India), Italy, and Turkey.^{4,9,16,17,18} The differences can be explained by the different study populations used in the different studies which differed on ethnicity, gender preponderance, race, etc., However, if we compare our results with studies carried in EU the levels of TSH were notably higher.⁹ In our study, we also reported that the mean free T₃ and T₄ was significantly lower in SCH as compared to EU though in both groups the values were within normal reference ranges. This is in contrast to the other study done in Tamil Nadu where no significant difference was noted.⁹ The difference could be explained by our larger sample size of 50 individuals whereby the study in Tamil Nadu had a sample size of 30.⁹

Regarding lipid profile parameters, our study showed higher TC and LDL-C level and a meaningfully higher TG level in SCH as compared to EU. Several other studies conducted in India and Europe

have also reported similarly higher TG levels, but TC and LDL-C were also reported to be higher in SCH as in our study.^{2,5} Contrary to all what is being said, an amazing result was presented in National Health Examination Survey III, in which 215 subjects with diagnosed SCH and 8013 Euthyroid individuals were checked for fasting lipid profile. Strangely no difference was found in the lipid profile picture of SCH and Euthyroid individuals.¹⁹ In overt hypothyroidism, the molecular basis of this dyslipidemic pattern has been elucidated. In overt hypothyroidism, due to the reduced activity of LDL-C receptors, the catabolism of LDL-C, and intermediate density lipoprotein-cholesterol are affected, consequently increasing serum TC and LDL-C.^{20,21} Moreover, in overt hypothyroidism, the activity of the enzyme lipoprotein lipase is lowered, thereby inhibiting the removal of TG-rich lipoproteins leading to a high serum TG level.²² In our study, the mean HDL-C was lower in SCH than in European Union, but the difference was not statistically significant. This result is in contrast to the study done in Tamil Nadu where the HDL-C was significantly lower in SCH compared to European Union.⁹ In our study, the lower than desirable HDL-C levels in both SCH and EU can be explained by the lack of exercise and sedentary lifestyle among the study participants. In the our context, this poses a serious health risk and needs to be investigated further by large population-based studies as well as experimental studies to guide the people further. Several studies have also shown that thyroxine therapy has led to significant improvement in dyslipidemia in SCH patients, but we have not studied this aspect.²³ In contrast, in overt hypothyroidism, elevation of serum HDL-C levels may be seen due to increased concentration of HDL2 particles.²⁴

Considering our results about the lipid levels, our study showed a significantly higher LDL in SCH as in comparison with the studies undertaken in EU, no worth mentioning changes were seen in HDL in both the groups we studied. In a study, it was proved that 6-month treatment with levothyroxine led to normalization of TSH, and this improved the adverse lipid profile of elderly women with SCH. This effect was reflected in the lipid levels.²⁵ However controversies exist regarding the association of SH with cardiovascular risk, to the best of our knowledge, not much research work study has investigated the status of lipid ratios in SCH. Thus, to fill this knowledge lacuna, we decided to perform our study.

In our study, mean TSH levels were 8.69mIU/L in SCH and 1.39mIU/L in controls, with p value as

0.0000 which was significant. Total mean Cholesterol in SCH 190.00mg/dl whereas in controls it was 189.12, with p. value as 0.912 which was insignificant. Mean Triglyceride in SCH was 168.28 mg/dl and in controls it was 133.62 mg/dl, p-value as 0.0000 which was significant. There is a wide range of difference in TRG levels. Mean HDL levels were 39.74 mg/dl in SCH and 43.48 mg/dl in controls. P-value was 0.001 significant. Both values are within normal range but for SCH it is towards lower margins. The mean levels of LDL in SCH were 182.82 mg/dl and controls it was 161.24 mg/dl. The studies have shown SCH to be associated with highly atherogenic pattern B of LDL-C subfractions.²⁶ It has been reported that as a marker of lipoprotein particle size, the value of LDL and VLDL adds predictive value beyond that of the individual lipids, and/or TC/HDL-C ratio.²⁷ This could also indicate that SCH is associated with high LDL & VLDL and thereby a highly atherogenic lipid profile. In other metabolic disease states such as metabolic syndrome, hyperuricemia, and diabetes mellitus, AIP was found to be a good predictor of cardiovascular risk.^{10,28} In overt hypothyroidism also AIP levels have not been studied, but conflicting results were seen in studies investigating the impact of overt hypothyroidism on LDL-C subfractions, particularly LDL.⁵ Though a recent study conducted on newly diagnosed hypothyroid patients showed an association between hypothyroidism and elevated LDL, other studies could not conclusively prove such an association.^{29,30,31} All these results reiterate the need for studies on the association of fasting Lipid levels with SCH. In our study, we have attempted to bridge this gap and from our results, it could be speculated that though serum LDL-C was higher in SCH subjects and useful cholesterol HDL was comparatively low. We failed to find any correlation between Cholesterol and TSH levels in SCH subjects. Several studies have reported that dyslipidemic changes were not apparent when serum TSH levels were below 10 mIU/L but above this level, dyslipidemia was more overt. An Indian study reported that there was no association between lipid abnormalities and SCH when the value of serum TSH was < 10 mIU/L.³² On the other hand, patients with TSH concentrations >10 mIU/L had significantly greater levels of TC and LDL-C as well as lower HDL-C compared with controls.³² Based on these findings, it would not be wrong to speculate that since a majority of our patients had a TSH level <10 mIU/L Dyslipidemias could be correlated with TSH levels in SCH patients.

Thus, the positive association of dyslipidemia and

SCH indicates a need for regular screening of SCH patients for dyslipidemia to enable early diagnosis and treatment of the condition. Even in patients who have a normal conventional lipid profile, lipid ratios, the patients should be regularly assessed for fasting lipid profile for better assessment of cardiovascular risk in SCH patients. The finding of low HDL levels retells the need for counseling of patients regarding healthy dietary habits and regular exercise. High LDL levels in SCH population too underline the need for large-scale, community-based programs for health awareness and lifestyle modification. The physicians attending the Cardiac patients or the patients facing the consequences of Atherosclerosis, or dyslipidemias must consider getting the Thyroid profile checked in particular who show no explicit signs and symptoms of Hypothyroidism. It is long process which would take its course with chemical changes in the body, which would over the years, may cause drastic ill-health effects. These bad effects could be prevented if a correct diagnosis is made in time, and remedial measures suggested.

Conclusion

This study investigated the relationship between serum Thyrotropin (TSH) levels and dyslipidemia in sub-clinical hypothyroid and euthyroid subjects. We saw that patients of SCH had significantly low HDL as compared to Euthyroid controls. Lipid profile was each categorized and means Thyrotropin levels were higher in dyslipidemic sub-class than subjects in the normal sub-classes. Thyrotropin was positively associated with serum TRG and negatively associated serum HDL in cases of SCH. Thyrotropin was also positively associated with Total Cholesterol, along with VLDL, and LDL. The TC, TRG, VLDL, LDL start to rise as compared to normal. It is as per our hypothesis we made at the beginning of study. i.e. there is a positive correlation between lipids and Thyrotropin less HDL; it exhibited negative correlation with Thyrotropin in cases of SCH. It is thus recommended that physicians, cardiologists, neurologists, neuro-surgeons when confront with diseases where thickening of the blood vessel wall due to deposition of fat (Atherosclerosis) is the under lying pathology of the ailments, they must consider reviewing the Thyroid status of the individual. Timely finding out SCH could help the patient a lot of difficulty and disaster.

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