Original Article

Effect of Subclinical Hypothyroidism on Fasting Serum Low Density Lipoprotein-C and High Density Lipoprotein-C

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Abstract

Numerous effects on metabolism of Lipids, its absorption, amalgamation, and control is under the influence of Thyroid Hormone. The scientists at international are exploring the possibility of establishing a link between subclinical hypothyroidism and lipids. We conducted this research to test the hypothesis that TSH, and levels of LDL-C and HDL-C are significantly associated in subjects with SCH.

Methods: This cross sectional study was conducted at Physiology Department, KEMU in collaboration with Centre for Nuclear Medicine (CENUM), Mayo Hospital & KEMU, Lahore. Simple Random sampling technique was employed to collect the sample. A total of 100 cases were selected (50 with SCH and 50 with Thyroid Profile within normal range as control) Levels of TSH, LDL-C and HDL-C were measured in fasting serum samples.

Results: TSH levels in subclinical hypothyroidism SCH were 8.69 mlU/L and Euthyroid showed to be 1.39 mlU/L. Mean HDL levels were 39.74 mg/dL in Subclinical Hypothyroidism subjects and 43.48mg/dL in euthyroid. The LDL-C pattern was in SCH 182.82 mg/dL and Euthyroids 161.24 mg/dL.

Conclusion: The Subclinical hypothyroidism has statistically significant effect in lowering HDL-C and increasing LDL-C levels.

Key words: Subclinical hypothyroidism, TSH, HDL-C, LDL-C.

Introduction

The endocrinologists have recently focused their attention on the possibilities of an underactive thyroid gland undetectable by lack of its symptoms.[1] Thyroid stimulating hormone (TSH) level > 4.5 mlU/L in the absence of symptoms and presence of normal levels of thyroid hormones has become an important biochemical tool, not only in identifying SCH, but its evolution to clinical hypothyroidism in the medium term since approximately 4% of our patients develop it over time.[2]

Numerous effects on metabolism of Lipids, its absorption, amalgamation, and control are under the influence of Thyroid Hormone. Current studies reveal that if the levels of Thyroid Hormone are explicitly low, the levels of Cholesterol, LDL-C and Triglyceride rise.[3]

Thyroid disorders particularly hypothyroidism tends to effect the blood pressure of the individual (diastolic) and if it is added up with raised levels of lipids i.e. Triglyceride, & Cholesterol it would help formation of atheromatous plaques in the arteries and case of cardiovascular system they can be dangerous and life threatening. Hypothyroidism raises the levels of the lipids, which are a major contributing factor to heart disease. Dyslipidemia is a cause of many drastic

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All Authors have contributed in Study Design, Data Collection, Data Analysis, Data Interpretation, Manuscript Writing and Approval.

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diseases, viz. cardiovascular diseases, renal diseases and diseases of the eye, which were related to micro-vascular systems.[4]

It is predicted that 1 – 11% of all the patients reported to have high lipid and cholesterol levels are having SCH. Hypothyroidism causes the levels of TSH to rise, even before the signs and symptoms of hypothyroidism are visible to the physician. This state of the individual where T_3 & T_4 are at minimal boundary and TSH slightly raised with no signs and symptoms of Hypothyroidism is labeled as SCH. When the disease process continues un-abated the signs and symptoms do appear free T_3 & T_4 fall grossly, TSH is raised this is now called as Overt Hypothyroidism.

In a study in which he explained that serum HDL-C levels were low in patients of SCH as compared to controls or euthyroid subjects.[5]In another study done on young children and adults the only lipid to be effected by low thyroid levels was LDL, with TSH levels around > 10mIU/L vis a vis controls.[6]In another study from another angle, the deficiency in SCH and Overt Hypothyroid patients was corrected by administering them oral Thyroxin till euthyroid stage was reached and observed no change in Lipid profile before and after treatment.[7]

In a study carried out inpatients labeled as SCH showed elevated levels of total Serum Cholesterol and no change in serum LDL-C or HDL-C status.[8] It was stated in a study which was conducted with a team that the lipids VLDL, LDL were elevated and Cholesterol was also raised, HDL remained below normal or normal in patients of SCH.[9] It was also exhibited that there were effects on the lipid profile in SCH and Overt Hypothyroid states and it could be correlated with TSH levels.[10]

To summarize, scientists at international fora are exploring the possibility of establishing a link between SCH and lipids, which might contribute in atheroma formation and cause life threatening diseases like acute myocardial infarctions and strokes. No significant study has been undertaken to our knowledge to-date on these parameters in Pakistan so far, let us look into this aspect and if these trends are proved, then by correcting the thyroid levels at initial stages could modify and alter the course of disease, and decrease morbidity and mortality significantly. This study was conducted to find out the association of subclinical hypothyroidism to fasting serum LDL-C and HDL-C values.

Methods

This cross sectional study was conducted at Physiology Department, KEMU in collaboration with Centre for Nuclear Medicine (CENUM), Mayo Hospital & KEMU, Lahore. Simple Random sampling technique was employed to collect the sample.

Informed consent was taken from the subject on the consent form for collection of blood samples. A total of 100 cases were selected after taking history and general physical examination, from the patients who visited CENUM, for evaluation of their thyroid hormone status. Those with no signs and symptoms for thyroid disease were selected and their free T_3, free T_4 and TSH levels were checked. 50 individuals with free T_3, free T_4 within normal range but raised TSH level were included in the study. Another sample of 50 subjects with normal thyroid profile was taken as controls.

After selection of cases, they were asked to come to the outpatient department laboratory of Mayo Hospital again with 14 hours fasting. 5 ml venous blood, from the ante cubital vein in a disposable syringe was taken. After centrifugation, the serum was stored in a refrigerator and their lipid profile was evaluated for total cholesterol, triglycerides and HDL-C. All assays were carried out in duplicate.

Subject of both sexes were included:

Age 18 – 65 years, No history of heart disease or hypothyroidism.

Subjects having history of diabetes mellitus, hypertension, vascular disease or ischemic cardiac ailment:

Subjects having symptoms of hypothyroidism, Subject on iatrogenic thyroxin.

Determination of free thyroid hormones (FT_4 and FT_3) was carried out by using Radio-immuno assay (RIA) and TSH was estimated by immune-radiometric assay (IRMA) at RIA laboratories, CENUM, Mayo hospital Lahore by using commercial kits of Immunotech Inc. (Beckman Coulter, Czech Republic and France).

It was done by automatic chemistry analyzer installed in the pathology laboratory of Mayo hospital Lahore. The tests were being done by the kits of the crescent diagnostics on the enzymatic, liquid, colourimetric test (CHOD/PAP method).

By enzymatic method.

By phosphotungstic method (precipitation method).

Measurement of LDL is done by Friedwald equation.[11]

LDL-C (mg/dl) = Total cholesterol – HDL-C – Triglyceride/5.

Result are being presented as means (± SD), median or otherwise specified. Data was analyzed by using Statistical Package for Social Sciences (SPSS) version 17.0 (SPSS Inc. 2010, Mapinfo Corp. New York, USA). Group mean of thyroid related hormones was compared by student's "t" test. Chi-square test was used to compare frequencies among different groups. Correlations were carried out using regression analysis. All statistical tests are being considered statistically significant whenever P value is <0.05.

Results

Normal free T_3 was taken in a range of 2.5 to 5.8 pmol/L, Free T_4 in a range of 11.5 to 23.0 pmol/L and TSH was taken in a range of 0.20 to 4.00 mlU/L.

In the study, 50 cases of subclinical hypothyroid were taken, in which the TSH mean level has come out to be 8.69 with standard deviation (SD) of 3.83 and standard error of mean (SEM) is .54, which is reasonably high as compared to the upper normal limit for TSH which is 4. For control group, the mean value is 1.39 with SD of 0.82 and SEM is 0.11. The p-value is 0.0000 which shows that the statistical values are significant, as shown in chart 1 and fig.1 below.

Chart 1: *Descriptive Statistics of TSH (mIU/L).*

	Study Groups	
	Cases of SCH	**Control Group**
N	50	50
Mean	8.69	1.39
Std. Deviation	3.83	0.82
Std. Error Mean	0.54	0.11

p-value = 0.0000 (significant)

Normal range for HDL-C is 45 – 65 mg/dl. The levels we found in our study are towards lower side in cases of subclinical hypothyroidism, with mean as 39.74, SD as 4.85 and SEM as 0.69. The controls gave a better picture showing mean as 43.48 and SD as 6.14 and SEM as 0.87 as shown in fig.2 and chart 2 below.

The normal range of LDL-C is taken as 0 -150 mg/dl. In this study the mean value was 182.82 and 161.24 for SCH and healthy controls respectively. The SD was 201.87 and 154.07 and SEM was 6.34 & 21.87 for SCH and healthy controls respectively. The p-value was 0.0002 which declares the values as significant as shown in chart 3 and fig.3 below.

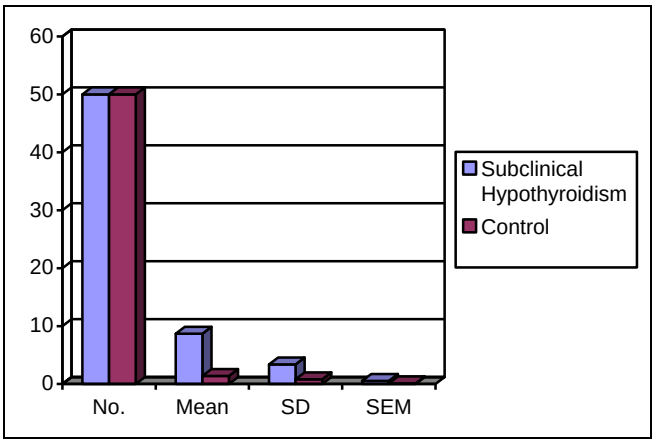

Fig. 1: *Number of cases, mean, SD and SEM values of TSH in study and control groups.*

Chart 2: *Descriptive Statistics of HDL-C (mg/dl).*

	Study Groups	
	Cases of SCH	**Control Group**
N	50	50
Mean	39.74	43.48
SD	4.85	6.14
SEM	0.69	0.87

p-value = 0.001(significant)

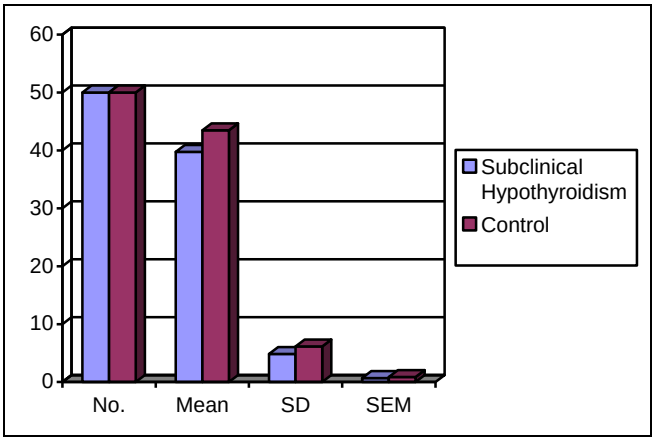

Fig. 2: Number of cases, mean, SD and SEM values of HDL-C in study and control groups.

Chart 2: *Descriptive Statistics of LDL-C (mg/dl).*

	Study Groups	
	Cases of SCH	**Control Group**
N	50	50
Mean	182.82	161.24
SD	201.87	154.07
SEM	6.34	21.78

p-value = 0.0002(significant)

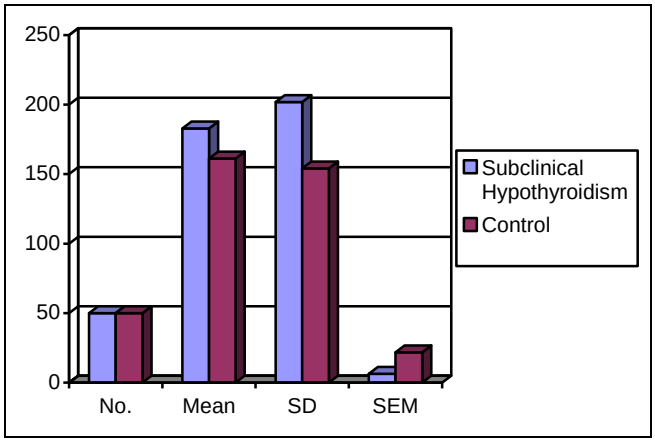

Fig. 3: *Number of cases, mean, SD and SEM values of LDL-C in study and control groups.*

Discussion

In this study, TSH raised subject's show the HDL-C is low, while in the healthy subjects the HDL-C is raised with TSH within normal limits. HDL-C 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-C 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.

This study revealed that the control cases with TSH with normal range, the LDL-C is at a constant normal range level. While with increasing TSH, the LDL-C levels increase is noted. Increase in TSH and decline in free T_3 and free T_4 levels depict a hypothyroid pattern. It is a well-established fact now that elevated TH levels activate fat mobilization which would add up fatty acids in the plasma. Total Cholesterol and Triglyceride in plasma are inversely correlated with TH levels, if TH levels are low Dyslipidemia occurs if the TH levels are raised and high the Lipids tend to be low. As a matter of fact the physicians immediately think of thyroid functions if the lipid profile is overtly high. Thyroid hormone stimulates expression of the LDL receptor. T_3 binds to the thyroid hormone receptor on the nuclear membrane, the pair A 'dimer' is then transported into the nucleus, where it acts as a transcription factor, causing LDL-C receptors to be generated to the cell membrane. So higher levels of free T_3 would mean more LDL-C receptors that would pull more LDL-C particles into the cells and strip off their fatty cargo. So raised T_3 tend to reduce serum LDL-C levels, but give cells more energy providing fats. Conversely, raised TSH levels and low T_3 would tend to raise serum cholesterol, but deprive cells of energy.

The same facts as stated above are mentioned in textbooks, if the TH levels are enhanced they would certainly alter the lipid and Total Cholesterol and Triglyceride levels, bring them towards lower ranges. Inverse to this if the levels of TH are low then the Triglyceride, Lipid and Cholesterol would be increased.[12]

In another study it was mentioned that 10 million Americans did not have any idea that their raised Lipid levels were due to unrevealed low levels of Thyroid Hormone. It was further added that Unknown TH deficiency with no signs and symptoms i.e. SCH and never getting the Thyroid Profile checked could be a cause of high lipid levels in blood.[13] Some experts have gone to an extent by issuing warning statements that, undermining the importance of thyroid hormone levels and their effects on lipids, is extremely dangerous as it could ultimately become a major contributing cause in establishing atherosclerosis.

January 2012 was declared as 'Thyroid Awareness Month' in USA. American Association of Clinical Endocrinologists (AACE) published results of a survey for the benefit of general public, in which a Thyroid-Cholesterol linking was exhibited. It was elaborated that SCH (Chemical changes in blood having low levels of TH with no signs and symptoms) was responsible for initiating a dangerous rise in LDL-C and VLDL-C, which were culprit lipids involved in atherosclerosis. It was further alarming to note that more than half of the population surveyed, who had high lipids , did not know the relationship of TH with lipid profile. Furthermore more than 90% of the sur-

veyed population was not aware of the impact of or relationship of TH with Lipids in blood. The drug company's manufacturing lipid lowering agents as Statins have also started to advise the patients of high Cholesterol levels to get their Thyroid profiles checked, before starting the drug intake.

In a study it was expressed that hypothyroid patients have a raised levels of Cholesterol and Lipids, Triglyceride which would lead to atherosclerosis and narrowing of the cardiac blood vessels, enhancing the risk of heart disease many fold. This relationship between TH and Lipids was seen more in females as compared to males.[14]

I a study multiple effects of TH on cholesterol synthesis and metabolism were considered. Thyroid hormone may have a beneficial role in the treatment of cholesterol in hypothyroid patients. The replacement therapy with Thyroxin to the diagnosed patients of Hypothyroidism exhibited significant lowering of lipid levels.[15]

In another study it was stated that there were no signs and symptoms of low TH levels in patients labeled as 'SCH', they could only be diagnosed by serum TH and TSH evaluation, conforming to the results we have shown in our study.[16]

In another study which was cross sectional it was stated that it was clear that total Cholesterol and Lipids were high in cases who were explicitly hypothyroid, but the status of lipid profile and total serum Cholesterol did not show much difference when compared between sub-clinical Hypothyroid subjects and control group.[17] Contrary to this in another study it was stated that TC was meaningfully raised in SCH subjects, this study was conducted population based sample of 2799 elderly black and white population.[18] In another study which was declared to be one of the largest studies undertaken on the current subject. 25,862 subjects were recruited to be blood sampled for Thyroid functions, in Colorado. TSH levels were found to be high in 9% population. Almost all of this 9%, found to have high TSH had normal or near normal T3 & T4 levels, which showed they were suffering from SCH, unaware of their current status. If the condition persisted the thyroid function would continue to decline till it becomes overt hypothyroidism and play its due role in increasing the lipids and Cholesterol and hence risks of developing atherosclerosis would increase many fold.[21]

The state of affair in our society is very different. We have made no surveys, and conventional way of thinking prevails everywhere. That is why all the people who have heart problems as a result of atherosclerosis, or associated ailments e.g. strokes are instantly advised drugs to lower the lipids, based on strong marketing tactics of the pharmaceutical industry. We don't try to search for the cause. For this reason this study was under taken. It seems that our physicians are not very sensitive to the role of Thyroid in Lipid metabolism and risks it is exposing the unaware public; with lower thyroid levels without any signs or symptoms (SCH) which might silently becausing dyslipidemias and ultimately be a major contributing factor in atherosclerosis. As a matter of fact the physician should not ignore females who give vague complaints of tiresomeness, obesity despite diet control, mood variations and order for Thyroid functions tests to rule out SCH, and save them from disastrous out comes with replacement therapy.

Conclusion

The subclinical hypothyroidism has statistically significant effect in lowering HDL-C and increasing LDL-C levels.

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