

Association of subclinical hypothyroidism with atherosclerosis in central India

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Abstract

Introduction: Overt hypothyroidism is widely recognized as a risk factor for atherosclerosis and cardiovascular disease, but recently subclinical hypothyroidism has also shown as an independent risk for it. Subclinical hypothyroidism also has close association with dyslipidemia and low grade inflammation leading to atherosclerosis which can be assessed by carotid intimal medial thickness. **Objective:** The objective of the study was to explore the correlation of subclinical hypothyroidism with atherosclerosis in the form of dyslipidemia, C Reactive Protein and Carotid Intimal Medial Thickness in patients of central India. **Methods:** This study was conducted at department of medicine in GMC, Bhopal. It was a case control study among which 100 patients with raised TSH and normal T3/T4 values were included as cases in the study and 50 controls with normal TSH/T3/T4 were taken. Three groups were made according to TSH values as euthyroids (<5.5), Subclinical Hypothyroids group 1(5.5-10) & group 2 (>10) and their fasting lipid profile, C Reactive Protein levels and Carotid Intimal Medial Thickness were measured. **Results:** We compared the Subclinical Hypothyroids with euthyroids subjects in which lipid profile was highly significant (<0.01) and showed positive correlation in both groups of Subclinical Hypothyroids except for high density lipoprotein. In cases where TSH (>5.5) the CRP was found to be significantly associated showing presence of low grade inflammation in these patients. The study also showed that mean Carotid Intimal Medial Thickness was higher in Subclinical group as compared to euthyroids but only when TSH(>10). **Conclusion:** This study concludes that subclinical hypothyroidism is characterized by dyslipidemia with increased Carotid medial intimal thickness value and positive C Reactive Protein suggesting the future development of cardiovascular disease in these patients.

Keywords: Dyslipidemia, CRP, Subclinical hypothyroidism, Thyroid stimulating hormone, CIMT

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Introduction

Subclinical hypothyroidism refers to biochemical evidence of thyroid hormone deficiency in the form of raised TSH and normal T3 & T4 and can also be described as patients who have few or no apparent clinical features of hypothyroidism with mild thyroid failure [1]. In general population the prevalence of SCH is quite common with prevalence ranging from 4 to 15% [2,3]. Over thyrohypothyroidism is widely recognized as a risk factor for atherosclerosis and cardiovascular disease due to its association seen with deranged

lipid profile and inflammation[4]. The incidence of SCH increases as age is increased which is explained by thyroid failure is evident in increasing age [2]. SCH frequently occurs in females comparative to males and elderly females are more affected [5].

Early clinical and autopsy studies have suggested an association between subclinical hypothyroidism and coronary heart disease[4]. In recent population based surveys subclinical hypothyroidism has spurt as one of the risk factor for aortic atherosclerosis and myocardial infarction leading to cardiovascular morbidity[6].

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Lipid metabolism needs thyroid hormone for proper functioning as its needed for the catabolism and synthesis of lipids and its deficiency may create alteration in lipid metabolism mostly degradation rather than synthesis [7].

Previous studies have revealed that cardiovascular disease risk might be present in subclinical hypothyroidism but the effect of TSH range is not clear [8,9]. Therefore, lipid metabolic changes affected by the severity of disease in terms of elevation in the TSH range are topic of debate. There are limited number of studies done on SCH in India and the relationship of lipid profile abnormalities to SCH is not certain.

Systemic inflammation is measured by CRP which is seen increased in atherosclerosis and hypothyroidism is associated with low grade inflammation and thus leads to possibility of CVS morbidity. Carotid artery intimal medial thickness (CIMT) is increasingly used as a surrogate marker of early atherosclerosis, and in a recent review it was shown that CIMT is a strong predictor of future vascular events such as myocardial infarction and stroke [10].

It has been shown that CIMT bears a relation to the incidence and prevalence of atherosclerosis in all its clinical forms and cardiovascular risk factors are predictors of CIMT. In various studies association of SCH with CIMT is shown which was assessed in our study to find its relevance. In central Indian population there are no studies that have answered these questions.

While the effect of deficiency of thyroid hormones on the cardiovascular system is of particular interest to this study with main emphasis on atherosclerosis, inflammation and the derangement of lipid profile.

Materials and Methods

This study was conducted in Gandhi Medical College & Hamidia Hospital, Bhopal from May 2014 to April 2016 for a period of 2 years. It is an observational case control study and 100 cases of newly diagnosed subclinical hypothyroidism from the medical and endocrine OPD of HH were selected which were divided in two groups based on TSH range: SCH-I (5.5-10 μ IU/ml) & SCH-II (>10 μ IU/ml). Along with it, 50 control cases

(euthyroids) were also selected to compare the findings. All the patients of age >18 years were included in the study. Those patients were excluded from the study who were having thyroid disease, diabetes, hypertension and any cardiovascular risk and patients on thyroxine, hypolipidemic drugs or drugs causing dyslipidemia were also excluded.

Thyroid profile, lipid profile and qualitative CRP (positive and negative) were estimated in all the participants of study group by taking fasting samples. Thyroid stimulating hormone (TSH), T3 & T4 were measured by using enzyme linked immunosorbent assay (ELISA) technique and the patients with TSH range (>5.5 μ IU/ml), T3 & T4 within reference range were said to having SCH.

CIMT was measured by recording ultra sonographic images of both the left and right common carotid artery with a 12MHz linear array transducer. Patients were examined in the supine position, with the head turned 45° from the side during the scanning procedure.

The reference point for the measurement of IMT was the beginning of the dilatation of the carotid bulb, with loss of the parallel configuration of the near and far walls of the common carotid artery. The mean IMT of the four measurements was calculated in each patient.

Total cholesterol (<200 mg/dl), Triglycerides (<150 mg/dl) and High-density lipoprotein cholesterol (40-60 mg/dl) were measured by using CHOD/POD method, GPO-PAP method, and CHOD/POD/ Phospho tungstate method respectively. LDL cholesterol (<130 mg/dl) was estimated by Friedewald formula. Total cholesterol/HDL-C and LDL-C/HDL-C ratio were also calculated by dividing TC and LDL-C with HDL-C respectively [11].

A SPSS (statistical package of social sciences) version 20.0 of IBM for windows was used for statistical analysis. All the variables were expressed in Mean \pm SD. The variables of divided groups of subclinical hypothyroidism were analyzed by using one way ANOVA. Pearson correlation coefficient was performed between TSH and other parameters (TG, TC, TC/HDL-C ratio and LDL/HDL ratio). A p value <0.05 was considered statistically significant.

Results

In our study we made 3 groups among which one was of euthyroid which were controls and 2 groups of SCH cases TSH (5.5-10) & TSH(>10) and these 2 groups were compared with the controls. Out of 100 cases 72 were females and 28 were male whereas in control grp 35 were females and 15 were males so sex matched cases and control were selected (see table 1). In group2 TSH (5.5-10), 46 patients were found among which 33 (71.7%) females & 13 (28.2%) males were present and in group 3 TSH (>10), 54 patients were there which had 39 (72.2%) females & 15 (27.7%) males.

There was no statistically significant relationship exists between the two groups (P value- 0.72). There was more number of females in SCH group which was also found in Colorado study where also females were the majority of SCH patients [2].

Mean age in the Euthyroid group was 52.7±12.6 years and in the SCH group 2 TSH(5.5-10) is 53.15±12.7 years and group 3 TSH(>10) is 53.65±13.94 years which shows a increasing incidence of thyroid failure as age advances (see table 2&3). In our study population, TSH in the euthyroid group was 2.70±1.47 μ IU/ml and in group 2 was 7.59±1.43 μ IU/ml and in group 3 was 13.89±3.89 μ IU/ml and it was found to statistically significant as p value (<.001)

Table-1: Correlation of sex with SCH.

Groups [TSH level] (μ IU/ml)	Sex		Total	P value
	F	M		
<5.5 [Controls]	34	16	50	
5.5-10	33	13	46	0.69
>10	39	15	54	0.63
Total	106	44	150	

Table-2: Correlation of SCH with age (years).

	Controls TSH <5.5 [n=50]		TSH 5.5-10 [n=46]		TSH >10 [n=54]		P value	
	Mean	\pm SD	Mean	\pm SD	Mean	\pm SD	Controls vs TSH 5.5-10	Controls vs TSH >10
Age	52.70	12.78	53.15	12.66	54.65	13.94	0.71	0.72
TSH	2.70	1.47	7.59	1.33	13.89	3.14	<0.001	<0.001
T3	1.54	1.15	1.13	0.34	1.39	0.92	0.02	0.45
T4	8.00	2.13	8.04	2.08	8.46	2.24	0.92	0.28

Table-3: Prevalence of SCH with Age.

Groups [TSH Level- μ IU/ml]	Age groups [years]						Total
	<30	31-40	41-50	51-60	61-70	>70	
<5.5 [Controls]	3	6	10	13	15	3	50
5.5-10	4	6	10	11	14	1	46
>10	3	8	10	15	11	7	54
Total	10	20	30	39	40	11	150

Table-4: Correlation of lipid profile with SCH.

Variables (mg/dl)	Controls TSH <5.5 [n=50]		TSH 5.5-10 [n=46]		TSH >10 [n=54]		P value	
	Mean	± SD	Mean	± SD	Mean	± SD	Controls vs TSH 5.5-10	Controls vs TSH >10
Total cholesterol	193.66	30.55	244.02	30.09	250.43	28.65	<0.001	<0.001
Triglycerides	142.22	17.38	152.37	16.42	155.85	20.89	0.004	<0.001
LDL	126.12	14.90	149.50	20.88	161.78	23.77	<0.001	<0.001
HDL	59.52	7.75	56.83	9.12	52.83	7.11	0.068	<0.001
VLDL	21.54	5.30	29.20	5.94	32.59	35.85	<0.001	0.033
TC/HDL ratio	3.22	0.84	4.46	0.78	4.43	0.72	<0.001	<0.001
LDL/HDL ratio	2.10	.364	2.74	.612	2.89	.634	<0.001	<0.001
CIMT(mm)	.54	.503	.81	.444	.89	.483	.043	.041

Table-5: Correlation between TSH and other variables [§].

Parameters	r value
TSH – TG	0.147*
TSH-TC	0.44*
TSH-LDL	0.525*
TSH-HDL	-0.119*
TSH-TC/HDL ratio	0.42 **
TSH- LDL/HDL ratio	0.37 **

§ By pearson correlation coefficient.

* p value Significant at 0.05 level.

** p value Significant at 0.01 level.

Table-6: Correlation of Mean CIMT with SCH.

Groups [TSH Level]µIU/ml	CIMT		Total	P value compared with controls
	1 [#]	2 [§]		
<5.5 [Controls]	8	42	50	
5.5-10	27	19	46	<0.001
>10	32	22	54	<0.001
Total	67	83	150	

- significant § - insignificant

Table-7: Correlation of CRP with SCH

Groups [TSH Level-µIU/ml]	CRP		Total	P value compared with controls
	1 [#]	2 [§]		
<5.5 [Controls]	12	38	50	
5.5-10	23	23	46	0.008
>10	31	23	54	0.0005
Total	66	84	150	

- positive § - negative

In our study the total cholesterol in the euthyroid group was 193 ± 30.55 mg/dl but in the SCH group 2 (5.5-10) was 234 ± 30.09 mg/dl and in SCH group (>10) was 250.43 ± 28.65 mg/dl and this total cholesterol was found to be statistically significant with p value $<.001$ in both the groups. In present study there is a significant positive correlation of TSH with total cholesterol as evident by pearson correlation $[r]=0.44$.

Similarly, the triglycerides levels were compared, the mean values of triglycerides in control group 1 are 142.22 ± 17.38 ; in SCH group 2 is 152.37 ± 16.42 and in the group 3 is 155.38 ± 20.69 . In control group, 20% (10) subjects had TG value >150 mg% whereas in SCH group 1 52.17% (24) patients and in group 2 57.4% (31) patients which is also statistical significant as p value came to be $<.001$. A significant positive correlation was also found between TSH values and TG values pearson coefficient $[r]$ is 0.147.

Coming to another variable of lipid profile, LDL, its mean values in the euthyroid group is 126.12 ± 14.90 ; in SCH group 1 is 149.50 ± 20.88 and in the group 2 is 155.89 ± 20.89 and these values were found to be significant when compared with euthyroid group as p value was $<.001$ which correlated with other studies in which it was significantly associated. In control group, 10% (5) patients had increased LDL whereas in SCH group 2 63% (29) patients and in the SCH group 3 72% (39) patients.

These were found to be statistically significant and a significant positive correlation was also found of LDL value with the TSH values with pearson coefficient $[r]$ being 0.525. HDL in the present study was found to be having significant negative correlation with TSH values $[r]= -0.119$ which shows that as the value of TSH increases the values of HDL decreases. Mean value of HDL in group 1 SCH is 56.83 ± 9.3 which compared to euthyroid group was not significant as p value was .17 but in group 2 SCH it was statistically significant as mean value was 52.83 ± 7.9 as compared with controls (p value <0.001) which shows that patients of SCH whose TSH >10 are more prone for risk of dyslipidemia (see table 4 & 5).

We also evaluated the lipid ratios i.e. Total Cholesterol to HDL ratio and LDL to HDL ratio as these are better markers of cardiovascular morbidity. TC/HDL ratio is having significant association as in group 2 SCH, mean was 4.43 ± 0.72 as compared to euthyroid group in which mean value was 3.22 ± 0.84 and p value was significant. Similarly, in the group 3 SCH the mean value was 4.46 ± 0.78 which was also statistically significant. LDL/HDL ratio when compared with euthyroid group the mean values in control group is 2.1 ± 0.36 ; in group 1 is 2.74 ± 0.61 and in group 2, 2.89 ± 0.63 and p values $<.001$ which shows its significant association though the LDL/HDL ratio did not surpass the cut off value for risk of cardiovascular morbidity in SCH group but definitely comparing with the euthyroids the ratio was significantly increased (see table 4&5).

In the present study we also evaluated the subjects in all the groups to see if any relationship with atherosclerosis is present in SCH by making subjects to go for carotid intimal medial thickness. We found out that in the control group mean of CIMT was 0.54 ± 0.50 ; in group 1 SCH was 0.81 ± 0.44 and group 2 SCH the mean was 0.89 ± 0.48 and in both group of SCH it was statistically significant p value $<.001$. In the euthyroid group 16% (8) subjects had increased CIMT whereas in group 1 SCH, 58.66% (27) subjects and in group 2 SCH, 59.25% had increased CIMT which when compared with the control group had significant p value $<.001$. (see table 6)

In the present study relationship of SCH with the inflammation was also explored in the form of qualitative CRP measurement as for atherosclerosis to occur low grade inflammation is necessary. The study revealed that in euthyroid group 24% (12) patients had positive CRP and when it was compared with group 1 SCH which had 50% (23) subjects with positive CRP showed a significant association (p value .008).

Similarly in group 2 SCH which had 57.4% (31) subjects with positive CRP significant relationship was seen (p value .0005). (see table 7) Thus all variables of lipid profiles were significantly associated in both groups of subclinical hypothyroidism except HDL-Cholesterol. TC/HDL and LDL/HDL ratios were also significantly related in each group of SCH and consistently increasing along with the range of TSH. CRP and CIMT also showed the similar association with subclinical hypothyroidism as compared to controls which were euthyroid.

Discussion

In most patients with hypothyroidism, the relative greater decrease in catabolism and the resulting increased synthesis results in high cholesterol concentrations. Hyperlipidemia, especially hypercholesterolemia is a major risk factor for Atherosclerosis. Low-density lipoprotein (LDL), a major component of the total serum cholesterol associated with increased risk of atherosclerosis. Thyroid function significantly affects lipoprotein metabolism as well as some cardiovascular risk factors [12]. There is positive linear correlation between TSH and total cholesterol(TC), low-density lipoprotein (LDL) and triglycerides (TG) and negative linear correlation between TSH and high-density lipoprotein (HDL) levels [13]. Therefore, hypothyroidism is one of the significant common causes of hyperlipidemia which is linked to atherosclerosis. Nature and degree of dyslipidemia in overt hypothyroidism has been demonstrated in many studies and there is no doubt about the beneficial effects of thyroid substitution on serum lipids and on the risk for cardiovascular diseases. Although the relationship between SCH and an atherogenic lipoprotein profile is still under debate [13], a meta-analysis of 13 intervention studies showed that levothyroxine therapy led to a significant reduction in both serum total cholesterol and LDL cholesterol levels[14].

Subclinical hypothyroidism has a major influence on derangement of lipid profile leading to early atherosclerosis. One of the largest study, the Colorado study conducted on thyroid dysfunction also showed that there is derangement of lipid profile with increasing TSH values[2]. Tanis et al also concluded that SCH is independently associated with atherosclerosis and cardiovascular morbidity which can be attributed to dyslipidemia and substitution with exogenous thyroid replacement reverses the lipid changes[15]. In our study we also found that there is statistically significant increase in the Total cholesterol, triglycerides and LDL levels in SCH. As the level of thyroid failure increases the derangement of lipid profile also increases along with positive CRP which indicates ongoing inflammation making patient prone for atherosclerosis. Celik C et al observed to support this study that SCH are characterised by dyslipidemia[16]. Luboshitzky R et al also supported the findings of our study and

they have also concluded that dyslipidemia and hypertension was associated with SCH in middle aged women[17]. Similar findings were also noted in the EPIC-Norfolk prospective study which found significantly increased concentrations of serum total cholesterol (TC), LDL cholesterol and triglyceride in SCH women only[18].

Monzani et al also showed that the SCH group had increased CIMT values 0.75 ± 0.13 as compared with control group 0.63 ± 0.01 and was significantly associated[19]. Nagasaki et al also found the similar association in their study which showed increased and significant CIMT values in hypothyroid and SCH group when compared with control group and replacement with thyroxine decreased the CIMT values on follow up[20]. Kim et al (2009) had a similar outcome in their study[21]. However, not all studies showed an association between TSH and CIMT. In the study of Chiche *et al.* among a population of hyperlipidemic patient's investigators found that neither prevalence nor severity of carotid plaques nor CIMT were significantly different between hypothyroid patients and controls. Likewise, in another study with 21 subclinical hypothyroid patient CIMT is found normal[22].

Knvetny et al also showed the similar positive finding of increased crp in SCH male patients below 50 years of age and predict increased risk of cardiovascular disease[23]. Christ-crain too found out that in overt as well as subclinical hypothyroidism have increased CRP values and shows a positive correlation of thyroid failure with inflammation[24]. Tuzcu et al noticed mean hsCRP levels which were 3.04 ± 0.8 , 2.56 ± 0.65 , and 1.81 ± 0.88 in 3 groups respectively, which was also found to be significant ($p < 0.001$)[25]. Tian *et al.* showed that SCH is associated with preclinical vascular alteration, characterized by increased CIMT, which had been shown to be related to the high sensitive CRP and TSH[26].

In Indian scenario, Senthilkumaran S et al also found that SCH is more common in female compared to overt hypothyroidism[27]. We have also found that Total cholesterol, triglycerides and LDL cholesterol have positive correlation with severity of disease as the elevation of TSH range.

Karthik N et al observed a significant dyslipidemic changes in SCH women compared to control group[28]. Similarly, when we compared the LDL/TC and HDL/TC ratios which are better indicator of cardiovascular morbidity, we found that these were positively correlated with TSH concentration.

There is some controversy regarding the presence or the severity of SCH induced dyslipidemia as some studies have found no correlation between TSH concentration and dyslipidemia. Legrys et al did not find any evidence that SCH was associated with increased risk of myocardial infarction in postmenopausal women[29].

Data from NHANES III revealed increased levels of TC in SCH patients vs controls, however when adjusted for age, race, sex and use of lipid lowering drugs, no difference was observed between SCH and controls regarding lipid profile[3].

Among dyslipidemia, increased level of Total cholesterol, triglycerides and LDL-cholesterol might suggest a future development of cardiovascular diseases. There was also positive correlation of thyroid stimulating hormone with total cholesterol and triglycerides and as the value of TSH increases their concentration also increases.

Similarly, the LDL/TC and HDL/TC ratio which are better predictor of cardiovascular morbidity also found to be significantly associated with SCH and positive correlation with TSH values were also seen in our study and points towards the higher risk for atherogenicity.

Similarly, when we compared the data of CRP which is a inflammation marker foe atherosclerosis which was seen increased in subclinical group as compared with euthyroids suggesting its role.

CIMT, which is the well proved marker of atherosclerosis is seen increased in our subclinical hypothyroids groups as compared with controls implicating again the increased probability of atherosclerosis in subclinical group Therefore this study specifies that SCH patients have increased chances of cardiovascular morbidity and among them SCH with TSH>10 μ IU/ml have higher risk of developing cardiovascular risk in comparison to women having TSH<10 μ IU/ml.

Conclusion

The present study have found that subclinical hypothyroidism is associated with an atherogenic lipid and lipoprotein profile, characterized by an increase in concentration of total cholesterol, LDL and triglycerides and by decrease in HDL levels. In patients of subclinical hypothyroidism lipid abnormalities exhibited great individual variability.

There might be a potential link between subclinical hypothyroidism and atherosclerosis which was further strengthened by the fact that this study also found a positive significant association of increased CIMT and CRP. This study had limitation too as patients fasting lipid profile sample were not taken, and we only took qualitative CRP and quantification of CRP levels were not done. Similarly, its a small-scale study and large scale study is required to validate these findings on a larger scale and TPO antibodies were not examined in the group as these antibodies significantly increased the risk of cardiovascular morbidity and have different effects on body organs.

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