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Research Article

ASSESSMENT OF CARDIOVASCULAR RISK IN SUBCLINICAL HYPOTHYROIDISM

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A B S T R A C T

Patients with subclinical disease have few or no definitive clinical signs or symptoms of thyroid dysfunction. The clinical importance of and therapy for mild elevation of serum TSH (<10 mIU/L) and the exact upper limit of normal for the serum TSH level remain subjects of debate. We evaluated 100 euthyroid and subclinical hypothyroid patients and found that subclinical hypothyroidism is associated with a more atherogenic lipid profile which contributes to the increased cardiovascular disease risk in SCH patients.

INTRODUCTION

Subclinical hypothyroidism (SCH) is defined as a serum TSH concentration above the statistically defined upper limit of the reference range when serum free T4 (FT4) concentration is within its reference range. Subclinical hypothyroidism or mild thyroid failure is a common problem, with a prevalence of 3% to 8% in the population without known thyroid disease.

Patients with subclinical disease have few or no definitive clinical signs or symptoms of thyroid dysfunction. Before diagnosis of SCH, other causes of an elevated TSH level, such as recovery from nonthyroidal illness, assay variability, presence of heterophile antibodies interfering with the TSH assay, and certain cases of central hypothyroidism with biologically inactive TSH and thyroid hormone resistance, should be excluded. However, the most common cause of elevated TSH is autoimmune thyroid disease.

The clinical importance of and therapy for mild elevation of serum TSH (<10 mIU/L) and the exact upper limit of normal for the serum TSH level remain subjects of debate. When the TSH level is above 10 mIU/L, levothyroxine therapy is generally agreed to be appropriate

A few trials have found that persons with subclinical hypothyroidism who are given L-thyroxine experience some improvements in their energy level and feelings of well-being. Cardiovascular diseases (CVDs) are the most common cause of mortality, primarily affecting older adults. Heart disease causes nearly 700 000 deaths annually in the United States. Although established risk factors explain most cardiac risks, significant attention has been focused on alternative biochemical markers to assist in identifying those at risk of a clinical cardiac event.

If one can prove clearly that a SCH is definitely associated with lipid abnormalities, then one can go for general screening and treatment of patients with SCH with levothyroxine and thereby preventing the overt hypothyroidism and thereby the cardiovascular complications at a very early stage. There are few population-based studies that have compared lipid levels in patients who have subclinical hypothyroidism with lipid levels in euthyroid persons. So the purpose of this study is to determine whether the known risk factors for the CAD such as hypertension, increase in fasting blood glucose and lipid abnormalities are more significant in patients with subclinical hypothyroidism when compared with those in euthyroid individuals and to assess cardiovascular risk among subclinical hypothyroid patients when compared with age and sex matched euthyroid controls

Aims and Objectives

The study will be conducted in Department of Medicine (OPD as well as IPD), Department of Endocrinology (OPD as well as IPD) and Clinical and Pathological Lab of L.L.R.M. Medical College and associated S.V.B.P. Hospital with following aims
Assessment of cardiovascular risk in patients with subclinical hypothyroidism as compared to age and sex matched euthyroid controls using Framingham 10 year CVD risk score.

MATERIALS AND METHODS

The present study was conducted in the Department of Medicine, Department of Endocrinology, LLRM Medical College, Meerut during the period of one year after obtaining

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ethical clearance. Study design is Observational Cross-sectional Study. A total 100 patients were enrolled in the study. In 100 patients, there were 2 categories. Group A with 50 Euthyroid subjects as controls.& Group B with 50 Subclinical hypothyroid subjects as cases.

Inclusion Criteria: Euthyroid controls having normal TSH values (0.35-4.94 UIU/ml), Subclinical hypothyroid cases having TSH above 4.94 UIU/ml with normal free T3 (1.71-3.71 pg/ml) and free T4 10.70-1.48 ng/dl levels, Age more than 18 years

Exclusion Criteria: are age less than 18 years, Obese (BMI >= 30 kg/m2) subjects, Smokers, Subjects with known hypothyroidism, Subjects with history of previous radioactive iodine therapy, thyroidectomy, external radiation, consumption of drugs known to cause SCH, Subjects with history of primary or secondary dyslipidemia.

The subjects' BMI was determined from height and weight. BMI (Kg/m2) = Weight/ (Height)2. Venous blood samples were drawn at 8 AM following a 12 hours fast, in a plain bulb from the subjects, with all the aseptic precautions. Blood samples were centrifuged within 30 minutes at 3000 rpm for 5 min. and serum was separated. Serum samples was stored at -20° C until assayed. Serum T3, T4 and TSH levels were measured by ELISA method using immunoassay analyzer, Serum fasting glucose was estimated by Spectrophotometer, Serum total cholesterol (TC) and triglycerides (TG), High-density lipoprotein cholesterol (HDL-C), Low-density lipoprotein cholesterol (LDL-C) was determined by Spectrophotometer, Framingham 10 year cardiovascular risk scoring system is used to assess the cardiovascular risk among cases and controls by using Framingham risk score calculator by HIOX.

Risk categories

	Framingham 10 year CVD risk (%)
Category 1 (mild risk)	<10%
Category 2 (Moderate risk)	10 - 20%
Category 3 (Severe risk)	> 20%

OBSERVATIONS AND RESULTS

Populations characteristics

Table 2 : Distribution of patients according to mean age in two groups

S.No.	Group	No. of patients	Mean age in years	P-value
1	A	50	51.46±5.234	0.922
2	B	50	51.56±4.995	

Table no. 2 and fig no.3 shows that mean age in group A is 51.46±5.234 and mean age in group B is 51.56±4.995. (Insignificant age difference among both groups can be seen as p >0.05)

Fig 3 : Distribution of patients according to mean age in two groups

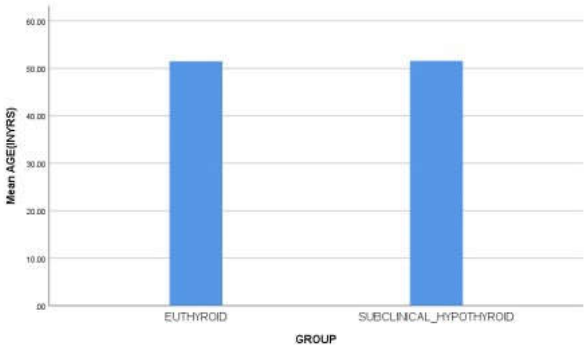

Table 3 : Distribution of patients according to gender in two groups:

S. No.	Group	No. of patients	Male	Female	P-value
1	A	50	9 (18%)	41 (82%)	0.799
2	A	50	10 (20%)	40 (80%)	

Table no.3 and fig no.4 shows that in group A out of 50 patients , 18% were male and 82% were female and in group B out of 50 patients, 20% were male and 80% were female.

(Insignificant gender difference among both groups can be seen as P >0.05)

Fig. 4 : Distribution of patients according to gender in two groups

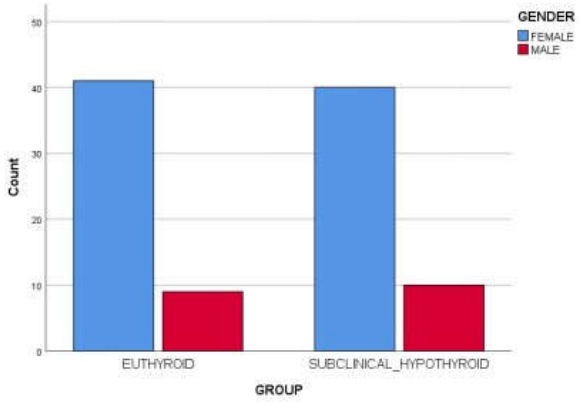

Table 4 : Distribution of patients according to mean BMI in two groups

S.No.	Group	Mean BMI (Kg/m^2)	P-value
1	A	22.6786±1.24246	0.005
2	B	23.3260±1.02196	

Table No.4 and fig no.5 shows that mean BMI in group B (23.3260±1.02196) is significantly higher than group A (22.6786±1.24246) (p value 0.005 is statistically significant)

Fig.5 : Distribution of patients according to mean BMI in two groups

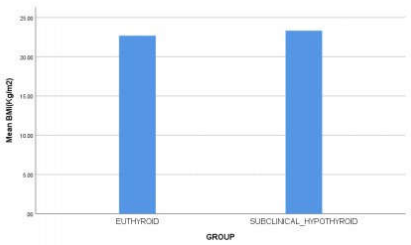

Table 5 : Distribution of patients according to mean FBS in two groups

S.No.	Gro6p	Mean FBS (mg/dl)	P-value
1	A	90.12±6.915	0.046
2	B	93.00±7.343	

Table no.5 and Fig. no.6 shows that mean FBS in group B (93.00±7.343) is significantly higher than group A (90.12±6.915) (p value 0.046 is statistically significant).

Fig.6 : Distribution of patients according to mean FBS in two groups

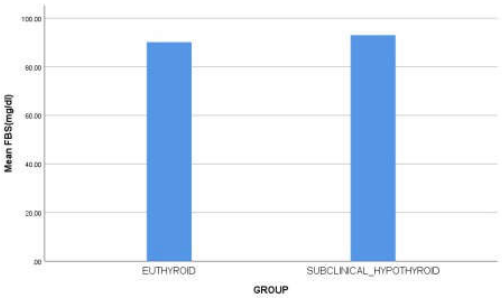

Table 6 : Distribution of patients according to mean SBP in two groups

S.No.	Group	Mean SBP (mmHg)	P-value
1	A	122.12±11.047	0.000
2	B	139.32±19.582	

Table No.6 and Fig No.7 shows that mean SBP in group B (139.32±19.582) is significantly higher than group A (122.12±11.047) (p value 0.000 is statistically significant)

Fig.7 : Distribution of patients according to mean SBP in two groups

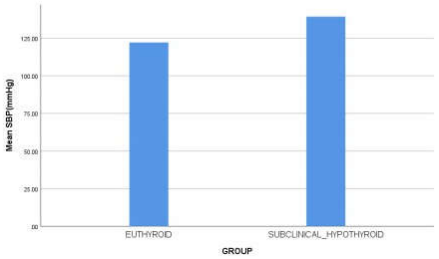

Table 7 : Distribution of patients according to mean DBP in two groups

S.No.	Group	Mean DBP (mmHg)	P-value
1	A	78.18±4.632	0.063
2	B	80.04±5.087	

Table No.7 and Fig. no.8 shows that mean DBP in group A is 78.18±4.632 and group B is 80.04±5.087 (Insignificant DBP difference among two groups as p value >0.05)

Fig.8 : Distribution of patients according to mean DBP in two groups

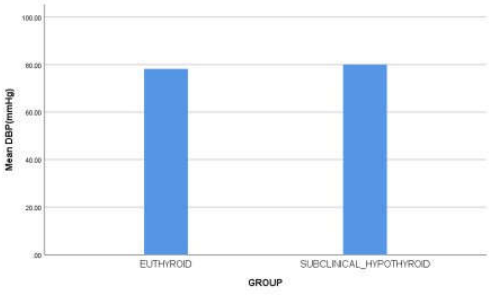

Table 8 : Distribution of patients according to mean FT3 among two groups

S.No.	Group	Mean FT3 (pg/ml)
1	A	2.4186±0.39294
2	B	2.4342±0.39467

Table No.8 and Fig No.9 shows that mean FT3 levels in Group A is 2.4186±0.39294 and group B is 2.4342±0.39467. Suggestive of normal FT3 levels in both groups

Fig.9 : **Distribution of patients according to mean FT3 among two groups**

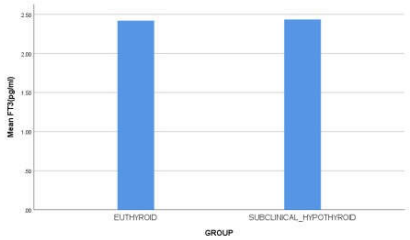

Table 9 : Distribution of patients according to mean FT4 among two groups

S.No.	Group	Mean FT4 (ng/dl)
1	A	1.1230±0.15908
2	B	0.9366±0.15531

Table No.9 and Fig. no.10 shows that mean FT4 levels in group A is 1.1230±0.15908 and group B is 0.9366±0.15531 suggestive of normal FT4 levels in both the groups.

Fig.10 : Distribution of patients according to mean FT4 among two groups

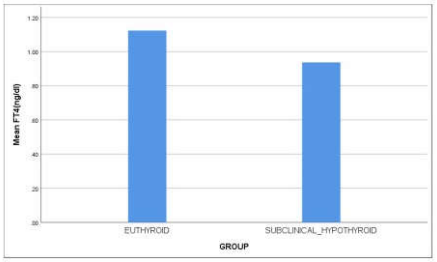

Table 10 : Distribution of patients according to mean FTSH among two groups

S.No.	Group	Mean FTSH (uIU/ml)	P-value
1	A	1.8976±0.51868	0.000
2	B	9.4978±2.96669	

Table No.10 and Fig no.11 shows that mean FTSH levels is significantly higher in group B (9.4978±2.96669) as compare to group A (1.8976±0.51868)

(Significant FTSH levels difference among two groups as p value of 0.000 is statistically significant)

Fig.11 : Distribution of patients according to mean FTSH among two groups

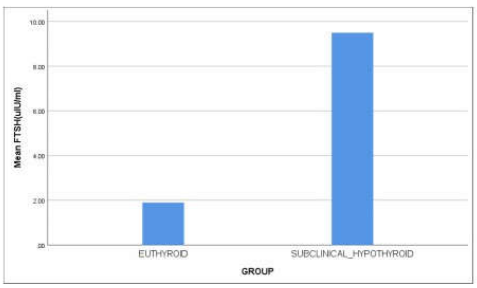

Table 11 : Distribution of patients according to mean LDL among two groups

S.No.	Group	Mean LDL (mg/dl)	P-value
1	A	88.44±27.126	0.000
2	B	140.40±50.464	

Table no.11 and Fig.no.12 shows that mean LDL levels in group B (140.40±50.464) is significantly higher than group A (88.44±27.126)

(Significant LDL difference between two groups as p value of 0.000 is statistically significant)

Fig.12 : Distribution of patients according to mean LDL among two groups

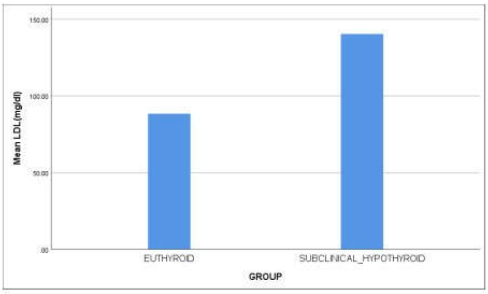

Table 12 : Distribution of patients according to mean HDL among two groups

S.No.	Group	Mean HDL (mg/dl)	P-value
1	A	46.92±4.981	0.022
2	B	43.08±10.577	

Table No.12 and Fig. No.13 shows that mean HDL levels in group A (46.92±4.981) is significantly higher than group B (43.08±10.577)

(Significant HDL difference between two groups as p value of 0.022 is statistically significant)

Fig.13 : Distribution of patients according to mean HDL among two groups

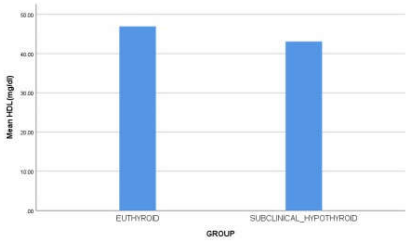

Table 13 : Distribution of patients according to mean VLDL among two groups

S.No.	Group	Mean VLDL (mg/dl)	P-value
1	A	17.06±4.093	0.000
2	B	23.78±4.867	

Table No.13 and Fig No.14 shows that mean VLDL levels in group B (23.78±4.867) is significantly higher than group A (17.06±4.093)

(Significant VLDL difference between two groups as p value of 0.000 is statistically significant)

Fig.14 : Distribution of patients according to mean VLDL among two groups

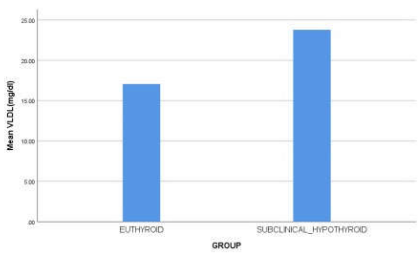

Table 14 : Distribution of patients according to mean triglyceride among two groups

S.No.	Group	Mean Triglycerides (mg/dl)	P-value
1	A	85.30±19.652	0.000
2	B	120.84±24.573	

Table no.14 and Fig no15. shows that mean triglycerides levels in group B (120.84±24.573) is significantly higher than group A (85.30±19.652) (Significant triglycerides difference between two groups as p value of 0.000 is statistically significant).

Fig.15 : Distribution of patients according to mean triglyceride among two groups

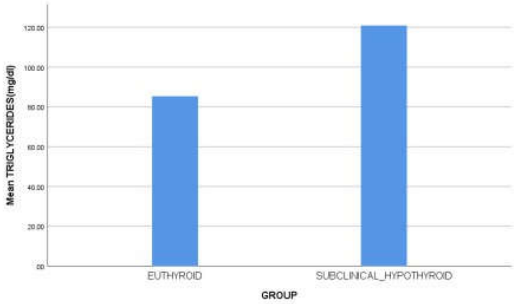

Table 15 : Distribution to patients according to mean total cholesterol among two groups

S.No.	Group	Mean TC (mg/dl)	P-value
1	A	152.50±28.441	0.000
2	B	207.26±48.760	

Table No.15 and Fig. No.16.a shows that mean TC levels in group B (207.26±48.760) is significantly higher than group A (152.50±28.441) Significant TC difference between two group as p value of 0.000 is statistically significant.

Fig.16.a : Distribution to patients according to mean total cholesterol among two groups

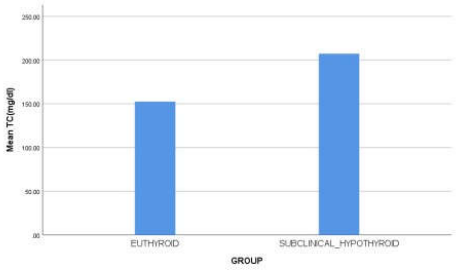

Fig.16.b : Distribution to patients according to mean total cholesterol among two groups

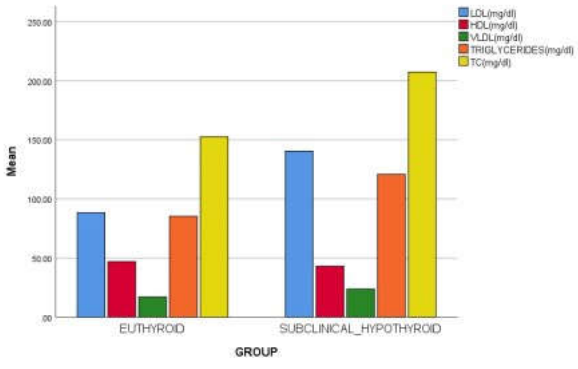

Table 16 : Distribution of patients according to Framingham 10 year CVD score among two groups

S.No.	Group	No. of patients	Framingham 10 year CVD score	P-value
1	A	50	7.40±3.642	0.000
2	B	50	11.92±5.506	

Table no.16 and Fig. no.17 shows that Framingham 10 year CVD score is higher in Group B (11.92±5.506) as compared to group A (7.40±3.642)

(Significant Framingham score difference between two groups as p value of 0.000 is statistically significant)

Fig.17 : Distribution of patients according to Framingham 10 year CVD score among two groups

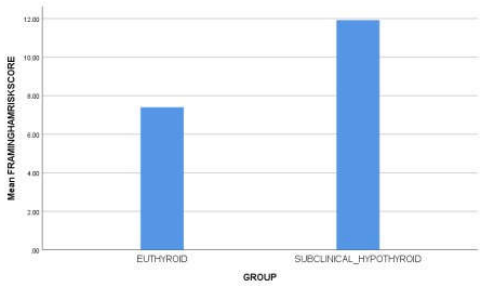

Table 17 : Distribution of patients according to Framingham 10 year CVD score risk category among two groups

S.No.	Group	No. of patients in mild risk cat.	No. of patients in moderate cat.	No. of patients in severe risk cat.	P value
1	A	49 (98%)	1 (2%)	0	0.001
2	B	38 (76%)	12 (24%)	0	

Table No.17 and Fig no.18 shows that no. of patients in moderate risk category is higher in group B (24%) as compared to group A (2%) Which signifies increased CVD Risk in group B as compare to Group A and there is no patient in severe category group.

(Significant difference in cardiovascular risk between two groups as p value 0.001 is statistically significant.)

Fig.18 : Distribution of patients according to Framingham 10 year CVD score risk category among two groups

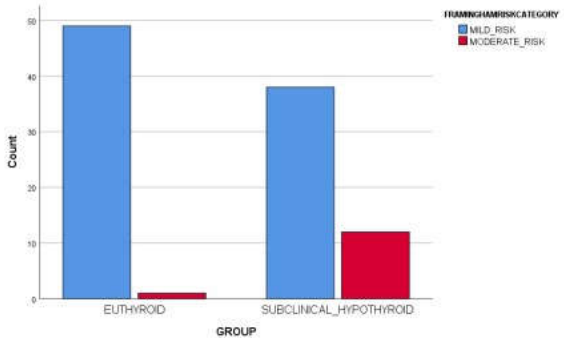

Table 18 : Correlation of FTSH levels with LDL, HDL, VLDL, TG, TC, Framingham Risk Score.

		LDL	HDL	VLDL	TG's	TC	Fr. Score
FTSH	Pearson correlation	0.745	-0.26	0.59	0.16	0.756	0.744
	p value	`0.000	`0.007	0.00	0.00	0.000	0.000

DISCUSSION

Cardiovascular diseases are the major cause of death worldwide and it has significant health related costs. A number of CVD risk factors can be modified thereby decreasing the CVD risk. Wickham survey58 and the colorado study59 have been shown to have prevalence of SCH in 7.5% males and 3.1% females. Subclinical hypothyroidism has clinical importance because of its high prevalence (4-20%), the risk of progression to overt hypothyroidism and consequences associated with cardiac and lipid abnormalities.

Study by Khan SS *et al* 61 demonstrated that obesity was associated with increased risk of cardiovascular morbidity and mortality compared with normal BMI. Elevated TSH is found to be associated with increased BMI in SCH patients. In our study, we observed that mean BMI is significantly higher in SCH group as compared to Euthyroid group (p value is 0.005). Study by Levitzsky YS *et al* 62 demonstrated that impaired fasting glucose is associated with increased CVD events. Sapna Vyakaranam *et al* 63 reported that SCH is associated with Insulin resistance. In our study, we observed that mean FBS is significantly higher in SCH group as compared to Euthyroid group (p value is 0.046).

Claudio Borghi *et al* 64 demonstrated consistent, graded and strong association between SBP and cardiovascular event. Yunfei Cai *et al* 65 observed that SCH is associated with increased SBP and DBP. In our study, we observed that mean SBP is significantly higher in SCH group as compared to Euthyroid group (P value is 0.000) whereas mean DBP in both groups is comparable and there is insignificant DBP differences between two groups (P value is 0.06).

Study by Sharma *et al* 66 demonstrated that patients with SCH had significantly higher levels or TC and LDL-C when compared to same parameters of controls. In our study, we observed that mean LDL is significantly higher in SCH group as compared to Euthyroid group (P value is 0.000). Also, mean TC is significantly higher in SCH group as compared to Euthyroid group (P value is 0.022).

Many studies have reported higher fasting TG levels in patients with SCH. Our study also shows that mean TG level is significantly higher in SCH group as compared to Euthryoid group (P value is 0.000) Also, mean VLDL level is significantly raised in SCH group as compared to Euthyroid group (P value is 0.000).

HDL-C levels are reported as either lower or unchanged in SCH compared with controls. Our study also shows that mean HDL is significantly lower in SCH group as compared to Euthyroid group (P value is 0.022).

Our study also shows that mean TC level is significantly higher in SCH group as compared to Euthyroid group (P value is 0.000).

Hence, from our study it could be clearly seen that LDL,VLDL,TG,TC levels are significantly increased in SCH patients when compared with that of Euthyoid group. Thus displaying a more atherogenic lipid profile in SCH patients. Study by Hee Joong Lim *et al* 68 shows that SCH is associated with increased 10 years CVD risk in comparison with Euthyroidism in Korean female population aged more than 30 years. Our study also shows that Framingham 10 years CVD score is significantly higher in SCH group when compared

with that of Euthyroid control group (P value is 0.000). Also, it is clear from our study that TSH levels are significantly positively correlated with Framingham score (Pearson correlation coefficient is 0.744 with P value of 0.000).

CONCLUSION

Cardiovascular diseases account for the largest single share of morbidity among developed nations and many developing nations including India. By combating modifiable risk factors through primary prevention, the burden of cardiovascular disease can be reduced.

On the basis of data obtained This study shows that mean BMI, mean FBS, Mean SBP, Mean LDL, Mean TG, Mean VLDL, Mean TC are significantly higher in SCH group as compared to Euthyroid group (P value is <0.05).Mean HDL is significantly higher in Euthyroid group as compared to SCH group (P value is <0.05).Mean Framingham 10 year CVD risk score is also significantly higher in SCH group as compared to Euthyroid group predicting increased CVD risk in subclinical hypothyroidism. There is also a significant and positive correlation between FTSH levels with LDL, VLDL,TG, TC and Framingham score. Also a negative and significant correlation between FTSH levels and HDL is observed in this study. In summary, subclinical hypothyroidism is associated with a more atherogenic lipid profile which contributes to the increased cardiovascular disease risk in SCH patients

Also, increasing levels of TSH are associated with increased cardiovascular risk. Hence, our results demonstrate that screening and treatment for SCH may be warranted because of its adverse effects on glucose and lipid metabolism. We recommend large scale, multi-centric trails to further authenticate the findings of this study.

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