

# Coronary artery calcium scoring is a better predictor of cardiac risk in subclinical hypothyroidism patients with low-risk Framingham score

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## ABSTRACT

**Context:** Overt hypothyroidism accelerates the cardiovascular disease. Subclinical hypothyroidism (SCH), being considered as a preclinical state, impacts on cardiovascular status is not clear. **Aims:** This study was aimed at assessing cardiac risk stratification by Framingham risk scoring (FRS) and coronary artery calcium score (CACS) by noncontrast cardiac computed tomography in SCH. **Study Design:** Observational study. **Subjects and Methods:** We enrolled thirty treatment-naive SCH patients (aged 30–60 years with no serious concurrent medical conditions), thirty euthyroid (age, sex, and body mass index-matched) controls, and ten healthy controls. All cases were evaluated for coronary artery calcium scoring and Framingham risk score. **Statistical Analysis:** Qualitative data were analyzed using the Chi-square test. In addition, demographics and CACS are summarized graphically or in a table. **Results:** SCH cases had higher thyroglobulin, while there was a trend toward an increase in total cholesterol, low-density lipoprotein (LDL), very LDL, and decrease in HDL levels. All participants had low-risk FRS (10-year FRS < 10%). The mean CACS in SCH was significantly higher than simple obese and healthy controls (47.17 vs. 2.67 vs. 0.00). **Conclusion:** This study suggests that SCH is an independent risk factor for coronary artery disease in apparently healthy controls. The risk of occult coronary artery disease is increased in SCH cases.

**Key words:** Framingham risk score, modified Agatston score, obesity, subclinical hypothyroidism

## INTRODUCTION

Cardiovascular system is one of the major target organ systems of thyroid hormone action. Thyroid dysfunction results in some important alteration in cardiovascular hemodynamics.<sup>[1,2]</sup> Coronary atherosclerosis is associated more frequently with overt hypothyroidism (OVH)<sup>[3]</sup> and

acceleration of coronary atherosclerosis is known to occur on OVH. The proposed mechanisms by which OVH causes cardiovascular disease (CVD) are rise in low-density lipoprotein-cholesterol (LDL-C), hypertension, coagulation abnormalities, and increased homocysteine and CRP levels. Subclinical hypothyroidism (SCH) is characterized by elevated level of thyroid stimulating hormone (TSH) but with normal concentration of FT4. SCH is considered a preclinical state of OVH, so a similar CVD pathogenesis may be expected although at a different pace.

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The investigation of choice for diagnosis of CAD is coronary angiography, but it has a major limitation of being invasive in nature. With the advancement of noninvasive multidetector technology of computed tomography (CT), it is possible to explore coronary artery anatomy and pathophysiology in a detailed fashion.<sup>[4]</sup> The calcium present in atherosclerotic plaques of coronary arteries can be quantified with the help of noninvasive CT scanning. This calcification can be used as a marker of atherosclerotic CAD. Coronary artery calcium score (CACS) is an accepted prognostic indicator of CAD.<sup>[5]</sup> Patients of low risk of CAD evaluated on clinical assessment can still have increased risk which can be evaluated by CACS.<sup>[6]</sup>

The data pertaining to cardiovascular risk and coronary artery calcium score in SCH are limited in world literature and have not been studied in Indian cases. The study will be able to identify the cardiovascular risk in SCH and underline the need of thyroxine supplementation in subclinical hypothyroid cases with respect to the occurrence of CAD.

## SUBJECTS AND METHODS

The study was conducted after informed consent on seventy volunteers, aged 30–60 years and without serious concurrent medical conditions in the Department of Endocrinology and Metabolism, Institute Medical Sciences, Banaras Hindu University, Varanasi, from February 2014 to January 2016. They were divided into three groups: Group 1 was comprised thirty patients (treatment-naïve SCH with no serious concurrent medical conditions as per exclusion criteria), Group 2 was comprised thirty age-, sex-, and body mass index (BMI)-matched simple obesity patients, and Group 3 was comprised ten age-matched healthy controls. SCH was confirmed twice within a period of 3–6 months. The study was approved by the Institute's Ethics Committee.

Patients with clinical hypothyroidism (untreated/partially treated/treated) and age below 30 and above 60 years, and/or those with a concurrent medical illness which may increase the coronary artery calcium scoring (hypertension, diabetes, and renal disease) were excluded from the study. The study population was subjected to clinical (including anthropometry) and laboratory evaluation (fasting plasma glucose, plasma glucose 2 h postoral glucose tolerance test (OGTT), glycated hemoglobin, blood urea, serum creatinine, serum liver function test, fasting lipid profile, serum free T4, serum TSH, and serum antithyroid-peroxidase [TPO] antibody). Thyroid function tests and serum anti-TPO antibody measurements were performed by chemiluminescent method (Access 2,

Beckman Coulter, USA). The Framingham risk score was calculated by the available online calculator ([www.cvdrisk.nhlbi.gov](http://www.cvdrisk.nhlbi.gov)). The parameters of scoring were age, gender, total cholesterol (TC), HDL cholesterol, history of smoking, and any treatment for hypertension.

### Coronary artery calcium scoring

All study controls were radiologically evaluated for coronary artery calcium scoring. Coronary artery calcium scoring (CACS) was performed using a 64-slice CT scanner (LightSpeed VCT G.E. Healthcare, USA). The patient did not require any specific premedication for the purpose, while counseling and anxiolysis were done in selected patients to ensure optimum patient cooperation. Noncontrast scans were acquired with a high-resolution volume mode with prospective electrocardiography-gating and the patient in supine position. Breath-hold scans were acquired from the carina to the base of heart with 2.5 mm slice thickness in volume mode (such that to generate at least twenty contiguous slices without gap). The acquisitions were planned such that the scanning is triggered at 80% of the R-R interval. The data so gathered was postprocessed on an offline workstation available with the scanner, preloaded with tailored software for calculation of “modified Agatston score.” All foci of suspected coronary calcification were manually traced to calculate the area using a free tracing technique. Only areas having a CT density of >90 HU and a size of >1 mm<sup>2</sup> were included for final analysis. The final summation was done after taking in account the weighting factor for each focus using a “step-algorithm.” The value so generated was labeled as the CACS of that particular individual and was used for patient-specific risk stratification, in terms of “percentile ranking” on standard nomograms [Figure 1]. The CACS evaluation was blinded for reducing observer bias by the radiologist.

### Statistical analysis

The statistical analysis was done using statistical software SPSS Inc, SPSS for Windows, Version 16.0, Chicago, SPSS Inc. Chi-square test was used for nonparametric variables, Student's *t*-test was used for continuous variables, and one-way ANOVA test was used for multiple group comparison. *P* < 0.05 was stated as statistically significant.

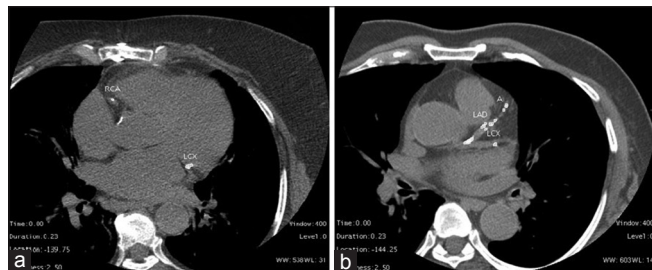
## RESULTS

Baseline characteristics of three groups are shown in Table 1. In Groups 1 and 2, there were five males and 25 females, while Group 3 had five males and five females.

The most important clinical presentation of which cases were investigated was the presence of goiter. It was present

in six cases in Group 1, whereas no goiter was there in other two groups. The family history of hypothyroidism was present in six cases of Group 1 and one control of Group 2. There was no family history of hypothyroidism in Group 3. The  $P = 0.044$  which was statistically significant.

The blood pressure, plasma glucose (fasting and OGTT), blood urea, creatinine, and liver function test (except alkaline phosphatase) were similar and normal in all three groups. Serum alkaline phosphatase in Group 1 (SCH) was



**Figure 1:** (a) A 51-year-old female with subclinical hypothyroidism (coronary artery calcium score = 59) (b) A 52-year-old male with subclinical hypothyroidism (coronary artery calcium score = 294)

$80.30 \pm 21.13$  U/L, Group 2 was  $99.77 \pm 34.84$  U/L, and Group 3 was  $97.10 \pm 22.81$  U/L with significant  $P = 0.027$  in Group 1 versus Group 2 and Group 1 versus Group 3 which was statistically significant and insignificant  $P$  value in Group 2 versus Group 3.

The mean TC, HDL, LDL, and very LDL (VLDL) were normal in all three groups; however, there was an increasing trend for TC, LDL, and VLDL, and decreasing trend of HDL levels from Group 3 to Group 1. The mean plasma triglyceride levels in Groups 1, 2, and 3 were  $161.88 \pm 69.88$  mg/dl,  $123.01 \pm 54.93$  mg/dl, and  $114.10 \pm 18.91$  mg/dl, respectively, with a significant  $P = 0.039$  among Group 1 versus Group 2, and 0.045 among Group 1 versus Group 3, and insignificant  $P$  value among Group 2 versus Group 3.

The coronary artery calcium score (CACS) was classified into five groups according to Agatston scoring system (0, 1–10, 11–100, 101–400, and > 400) [Table 2]. The  $P = 0.073$  which was statistically insignificant.

**Table 1: Clinical, anthropometric, and biochemical parameters**

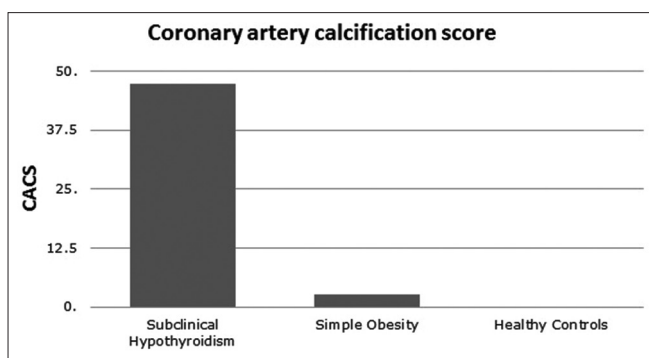
| Parameter                            | Mean±SD             |                                |                                  | P      |
|--------------------------------------|---------------------|--------------------------------|----------------------------------|--------|
|                                      | Group 1 (SCH, n=30) | Group 2 (simple obesity, n=30) | Group 3 (healthy controls, n=10) |        |
| Age (years)                          | 42.7±10.3           | 42.5±7.5                       | 47.6±7.9                         | 0.26   |
| Height (cm)                          | 155.99±8.19         | 153.38±6.42                    | 157.29±8.162                     | 0.25   |
| Weight (kg)                          | 70.49±11.56         | 65.93±10.62                    | 51.42±5.43                       | 0      |
| BMI (kg/m <sup>2</sup> )             | 29.0±4.22           | 28.0±4.37                      | 20.74±1.13                       | 0      |
| Waist (male)                         | 91.70±6.04          | 92.33±2.51                     | 80.90±7.74                       | 0.036  |
| Waist (female)                       | 94.51±11.51         | 91.57±12.09                    | 65.78±4.95                       | <0.001 |
| SBP (mmHg)                           | 121.47±5.63         | 120.80±5.72                    | 120.00±5.25                      | 0.757  |
| DBP (mmHg)                           | 82.77±8.91          | 81.47±10.41                    | 79.80±5.03                       | 0.658  |
| Fasting plasma glucose (mg/dl)       | 93.52±9.47          | 90.33±11.77                    | 92.38±8.89                       | 0.498  |
| Plasma glucose 2 h post-OGTT (mg/dl) | 116.54±15.10        | 116.48±13.39                   | 121.36±10.05                     | 0.590  |
| HbA1c (%)                            | 5.09±0.36           | 5.07±0.56                      | 5.03±0.29                        | 0.914  |
| Urea (mg/dl)                         | 23.44±6.43          | 24.48±7.24                     | 22.50±4.93                       | 0.676  |
| Creatinine (mg/dl)                   | 0.88±0.16           | 0.87±0.17                      | 1.01±0.39                        | 0.150  |
| AST (U/L)                            | 30.00±4.78          | 29.47±6.39                     | 32.50±3.31                       | 0.306  |
| ALT (U/L)                            | 29.27±6.53          | 30.75±6.77                     | 27.50±6.39                       | 0.377  |
| Total bilirubin (mg/dl)              | 0.76±0.27           | 0.71±0.23                      | 0.87±0.17                        | 0.190  |
| Direct bilirubin (mg/dl)             | 0.21±0.11           | 0.21±0.10                      | 0.24±0.07                        | 0.663  |
| Alkaline phosphatase (U/L)           | 80.30±21.13         | 99.77±34.84                    | 97.10±22.81                      | 0.006  |
| Total proteins (g/dl)                | 7.86±0.62           | 7.64±0.82                      | 7.76±0.42                        | 0.495  |
| Albumin (g/dl)                       | 4.42±0.37           | 4.43±0.39                      | 4.45±0.41                        | 0.975  |
| Total cholesterol (mg/dl)            | 194.40±36.54        | 188.47±32.65                   | 177.90±30.15                     | 0.410  |
| Triglyceride (mg/dl)                 | 161.86±69.88        | 123.01±54.93                   | 114.10±18.91                     | 0.018  |
| HDL (mg/dl)                          | 47.44±11.59         | 48.150±11.52                   | 56.30±9.20                       | 0.092  |
| LDL (mg/dl)                          | 133.39±47.57        | 121.12±32.84                   | 103.60±19.39                     | 0.103  |
| VLDL (mg/dl)                         | 31.34±8.19          | 26.38±10.38                    | 21.50±4.55                       | 0.007  |
| Free T4 (ng/dl)                      | 1.23±0.22           | 1.12±0.23                      | 1.09±0.13                        | 0.086  |
| TSH (μIU/ml)                         | 7.53±1.67           | 2.99±1.60188                   | 3.59±2.14                        | 0      |
| Serum anti-TPO antibody (IU/ml)      | 367.46±70.84        | 54.44±24.12                    | 24.20±18.03                      | 0      |

SD: Standard deviation, SCH: Subclinical hypothyroidism, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, OGTT: Oral glucose tolerance test, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, TSH: Thyroid stimulating hormone, TPO: Thyroid peroxidase, HbA1c: Glycated hemoglobin, Free T4: Free thyroxine

**Table 2: Distribution of coronary artery calcium score**

| Parameter             | Mean±SD                                    |                                | Group 3 (healthy controls, n=10) |
|-----------------------|--|--------------------------------|----------------------------------|
|                       | Group 1 (subclinical hypothyroidism, n=30) | Group 2 (simple obesity, n=30) |                                  |
| Framingham risk score | 1.40±1.653                                 | 1.07±0.254                     | 1.00±0                           |
| CACS                  |  |                                |                                  |
| Score, n (%)          |  |                                |                                  |
| 0                     | 19 (63.3)                                  | 25 (83.3)                      | 10 (100)                         |
| 1-10                  | 2 (6.7)                                    | 2 (6.7)                        | 0                                |
| 11-100                | 3 (10.0)                                   | 3 (10.0)                       | 0                                |
| 101-400               | 6 (20.0)                                   | 0                              | 0                                |
| >400                  | 0  | 0                              | 0                                |
| Total                 | 30 (100)                                   | 30 (100)                       | 10 (100)                         |
| Mean CACS             | 47.17±16.55                                | 2.67±1.72                      | 0                                |

SD: Standard deviation, CACS: Coronary artery calcium score



|                               | Subclinical hypothyroidism | Simple obesity | Healthy controls |
|-------------------------------|----------------------------|----------------|------------------|
| Coronary artery calcium score | 47.17                      | 2.67           | 0                |

**Figure 2:** Coronary artery calcium score in subclinical hypothyroidism, simple obesity, and healthy controls

## DISCUSSION

The present study included cases were between 30 and 60 years of age. This age group may not have established atherosclerosis and may show the early atherosclerotic changes. The mean age of subclinical hypothyroid (Group 1) was 42.7 years, while it was 42.5 years for simple obesity (Group 2) and 47.6 years for healthy controls (Group 3). There were five males and 25 females in each Group 1 and 2, and five males and five females in Group 3.

The parameters of obesity (weight, waist circumference [WC], and BMI) were comparable between the subclinical hypothyroid group and simple obesity group, whereas the controls were normal. In our study, the mean BMI of study controls of Group 1 was 29.01 kg/m<sup>2</sup>, so we enrolled BMI-matched controls of Group 2 to study the effect of obesity on various parameters.

The mean WC in males 91.70 cm, 92.33 cm, and 80.90 cm for Group 1, 2, and 3, respectively. The mean WC in females was 94.51 cm, 91.57 cm, and 65.78 cm for Group 1, 2, and 3, respectively. The WC (male and female) was significantly higher in SCH and simple obesity than controls. In a recent study Anjaneya *et al.*<sup>[7]</sup> demonstrated that the prevalence of SCH is higher in females and increases with body weight.

The most important clinical presentation of which cases were investigated was the presence of goiter. It was present in six cases (20%) in Group 1, whereas no goiter was there in other two groups. Carlé *et al.*<sup>[8]</sup> reported an incidence of 20.8% for the presence of the thyroid enlargement in patients with autoimmune thyroid disease, which is consistent with the findings of our study data.

The family history of hypothyroidism was present in six cases of Group 1 and one case of Group 2. There was no family history of hypothyroidism in Group 3. The  $P = 0.044$  which was statistically significant. Tomer and Davies<sup>[9]</sup> have demonstrated that Hashimoto thyroiditis, an autoimmune disease, has a strong hereditary component. Certain polymorphisms in a couple of genes, in particular, are associated with the development of Hashimoto's disease; one is the cytotoxic T-lymphocyte-associated antigen-4 gene, and another is the protein tyrosine phosphatase-22 gene. Autoimmune thyroid diseases (both Graves' disease and Hashimoto's disease) can occur within the same families, and they may share human leukocyte antigen and other genetic susceptibility haplotypes.<sup>[10]</sup> Both types of patients can have autoantibodies to thyroglobulin (TG), TPO, and the TSH receptor. SCH due to autoimmune thyroid disease is considered as a continuum to OVH.<sup>[11,12]</sup> The patients with SCH can have a familial pattern of inheritance as supported from above-mentioned studies.

All the baseline biochemical investigations such as renal function tests, OGTT, glycosylated hemoglobin, and liver function tests (other than serum alkaline phosphatase) were comparable in all the groups. Serum alkaline phosphatase in Group 1 was normal but significantly lower than the other groups. There is no study mentioning decreased ALP levels and its implications in SCH in the available literature. As the absolute value did not fall outside the normal range (30–120 U/L), this may be due to lower bone activity in SCH.

The relationship between SCH and serum lipids remains controversial.<sup>[3]</sup> In several cross-sectional studies, SCH was found to be associated with a variable and somewhat inconsistent increase in TC and in LDL-C,<sup>[13]</sup> higher plasma oxidized LDL-C levels,<sup>[14]</sup> and inconsistent changes in serum levels of HDL-C.<sup>[15]</sup> In the Busselton study, serum TC was significantly higher in cases with SCH than in euthyroid controls, but the difference was barely significant after adjustment for age and sex.<sup>[16]</sup> The TC in our study Group 1 was somewhat higher than from control groups; it was statistically insignificant.

In the Whickham survey, SCH was not related to hyperlipidemia.<sup>[17]</sup> In the Rotterdam study, TC was lower in women with SCH than in euthyroid women.<sup>[18]</sup> In the NHANES III, mean cholesterol levels and rates of elevated cholesterol levels were higher in people with SCH than in euthyroid controls, there were no differences in LDL or HDL levels.<sup>[19]</sup> However, when adjusted for age, race, sex, and the use of lipid-lowering drugs, SCH was not related to increased cholesterol levels. In the New Mexico Elder Health Survey, there were no differences in TC, HDL-C, or triglycerides between patients with a serum TSH level below 4.6 mIU/L and those with a serum TSH level between 4.7 mIU/L and 10 mIU/L.<sup>[20]</sup> Both HDL and LDL cholesterol levels were comparable in all groups in this study. These findings were in accordance with the above-mentioned study.

In a Danish study, SCH was associated with a higher concentration of triglycerides and CRP.<sup>[21]</sup> The mean plasma triglyceride levels were significantly higher in SCH group than simple obesity and healthy controls; the latter two groups had similar TG levels. These findings were in accordance with the above-mentioned studies.

The difference in mean VLDL was statistically insignificant between SCH and simple obesity but was statistically significant between SCH and controls.

Thus, our study showed higher TG, while there was a trend toward an increase in TC, LDL, VLDL, and decrease in HDL levels in SCH cases. In literature, there are conflicting results about lipid pattern and SCH. This might reflect

differences in the population studied (e.g., cause of SCH, duration of thyroid dysfunction, and TSH levels), as well as differences in age, gender, and ethnicity of the controls tested.<sup>[22]</sup>

The mean serum anti-TPO antibody in Group 1, 2, and 3 was 367.46 IU/ml, 54.44 IU/ml, and 24.20 IU/ml, respectively; the difference was statistically significant between Group 1 versus Group 2 and Group 1 versus Group 3, but insignificant between Group 2 versus Group 3. Mohanty *et al.*<sup>[23]</sup> have reported a mean anti-TPO antibody level of 269.19 IU/ml in patients of SCH. This finding is consistent with our study and indicates autoimmune nature of the disease.

### Framingham risks score

The Framingham risk score values of Group 1 were 1.4; Group 2 were 1.07, and Group 3 were 1.0 with no statistical difference between each group. In our study, the participants fell under low-risk profiles (10-year risk < 10%) who would have benefited from further examinations to facilitate risk stratification in our assessment of the relationship between SCH and CAD.

### Subclinical hypothyroidism and coronary artery disease risk stratification by coronary artery calcium score

The relationship between CAD and OVH is well known through several mechanisms, namely increase in arterial stiffness and systemic vascular resistance resulting in high blood pressure<sup>[24]</sup> and dyslipidemia. However, the association between SCH and CAD is still somewhat controversial.

In the present study, we performed CT cardiac evaluations to detect CAD. CACS has already been accepted as an effective prognostic indicator of CAD that is independent of traditional risk factors.<sup>[25-27]</sup> In our study, mean coronary artery calcium score (CACS) in SCH was 47.17, simple obesity was 2.67, and in controls was 0.00. The  $P = 0.016$  between SCH and simple obesity was statistically significant.

The Busselton health study reported that SCH is an independent risk factor for coronary heart disease.<sup>[16]</sup> Moreover, several studies have shown an association between SCH and either specific age ranges or TSH levels. The Rotterdam study in the year 2004 showed a higher prevalence of atherosclerotic CVD in female SCH patients who were 55 years of age or older, but in our study, the mean age in SCH group was 42 years. However, Ochs *et al.*<sup>[28]</sup> found in their meta-analysis using population-based cohort studies that the relative risk of SCH for CAD was significantly higher in participants younger than 65 years but not in participants with age 65 years and older. This

observation is in accordance with results of our study as the enrolled patients' age ranged between 30 and 60 years. Detection of atherosclerotic changes (CACs) in young SCH population is important in the light of increasing prevalence of premature CAD.

Razvi *et al.*<sup>[29]</sup> also reported the results from a meta-analysis showing that SCH is associated with increased CAD in cases from younger populations only. In addition, the Wickham survey, a large-scale, long-term, follow-up study, found no evidence to suggest that SCH is associated with an increased risk of ischemic heart disease (IHD).<sup>[30]</sup> These discrepancies may have originated from the heterogeneity of the study controls with regard to age and sex distribution, number, and the characteristics of the selected cases, such as inpatient or community setting.

Russo *et al.*<sup>[31]</sup> recently reported that CACS and coronary CT angiography findings, such as obstructive CAD and presence of noncalcified or mixed plaques, were predictors of a coronary event. The fact that even after adjustment for CVD risk factors (including the age, sex, and BMI, which are known risk factors for CAD), SCH was still significantly associated with the presence of CAD suggests that even mild thyroid failure may influence the occurrence of occult CAD and can be a useful marker to predict future major adverse cardiovascular events as reported by Hulthen *et al.*<sup>[32]</sup> In our study cases, the presence of CAD, representative of the presence of occult CAD, was significantly associated with SCH.

In a recent paper, Razvi *et al.*<sup>[29]</sup> reported data from a Wickham Reanalysis. They showed that there was an association between IHD- and IHD-related mortality in patients with SCH over 20 years of follow-up, which is in contrast to the data from the original Wickham survey report.<sup>[30]</sup> These results could also support our study results showing an association between SCH and occult CAD.

In a retrospective analysis, Park *et al.*<sup>[33]</sup> enrolled 2404 asymptomatic cases with an intermediate to high risk (Framingham 10-year risk  $\geq 10\%$ ) of developing CAD but with no known CAD or thyroid disease. Of these, 49 cases had SCH. CACS was assessed by cardiac CT, and it was concluded that SCH cases were significantly more likely to exhibit occult CAD than euthyroid cases suggesting that mild thyroid failure also independently contributes to the development of CAD.

Although the CACS in our study group of SCH was 47.17 and was statistically significant as compared to other

groups, this range falls under a moderate risk for occurrence of CAD [Figure 2].

## CONCLUSION

This study suggests that SCH is an independent risk factor for coronary artery disease in apparently healthy controls. The lipid profile pointed that it could be a pro-atherogenic state. The risk of occult coronary artery disease is increased in SCH cases. We can speculate that levothyroxine replacement may be beneficial for coronary artery disease risk reduction in SCH. Our study is the first report in India for examining the association between SCH and CAD using cardiac CT, which is a very accurate and sensitive method for detecting CAD in a noninvasive manner. Further studies with a larger number of cases are needed to strengthen these findings.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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