# SCREENING OR AGGRESSIVE CASE FINDING FOR HYPOTHYROID PATIENTS. WHAT IS THE EVIDENCE?

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**ABSTRACT :**

***Backgound :*** *Hypothyroidism enhances atherosclerosis in multiple ways. Carotid intima media thickness(CIMT) as measured by B-Mode ultrasound and color Doppler, is a risk determinant of atherosclerosis. hsCRP is a marker of inflammation and has been incriminated as a risk factor for future cardiovascular events. Our study aims at generating evidence for increased risk of cardiovascular risk factors in hypothyroid patients and thus need for population- based screening for hypothyroidism.*

***Methods :*** *We included 25 consecutive patients in to each of two groups of our study. (n=50) Hypothyroid group had patients with Thyroid stimulating hormone (TSH) >10miu/l, subclinical hypothyroid(SCH) group patients with TSH 6-10miu/l. We compared CIMT and hsCRP in 2 groups along with other atherosclerotic risk factors.*

***Results :*** *We found that in the subclinical hypothyroid patients the mean value of total cholesterol(TC)(208.8.84±**6.14**), LDL-C levels(**157.88±33.51**), total cholesterol/ LDL cholesterol ratio(5.29±1.31), LDL cholesterol ratio/ HDL cholesterol ratio(3.93±1.25) and plasma hsCRP(**2.13±0.69**) levels were higher than the normal values. In hypothyroid patients we found that these values and the CIMT values were statistically significantly higher than the subclinical hypothyroid patients, in addition diastolic hypertension (95.84±**11.06** ) and higher than normal waist-hip ratio (1.03±**0.19**) was also seen in hypothyroid group. CIMT and hsCRP also showed positive correlation with other atherosclerotic risk factors. (Waist-hip ratio, diastolic hypertension and LDL cholesterol)*

***Conclusion :*** *Cardiovascular risk factors were increased in sub clinical as well as in clinical hypothyroidism so efforts should be made to detect and treat hypothyroidism at an early stage by aggressive case finding in high risk population.*

## Introduction :

Cardiovascular disease is the leading cause of death and disability in developed nations and is increasing rapidly in the developing world .The role of hypothyroidism in increasing the risk of cardiovascular diseases has been well established via increase in circulating levels of highly atherogenic low-density lipoprotein (LDL), induction of diastolic hypertension , altered coagulability , and direct effects on vascular smooth muscle.[1]

Furthermore in recent years in addition to the classical risk factors several novel risk factors for cardiovascular diseases have been identified, including, elevated hsCRP(highly sensitive c-reactive protein) levels, elevated fibrinogen levels and endothelial dysfunction as seen by CIMT measured by B-Mode ultrasound and color Doppler and many researchers have related these new risk factors to hypothyroidism.[2]

In regard to the hypothyroidism induced risk in cardiovascular (CV) system, cardiac dysfunction and heart damage may be induced via an increment of highly atherogenic low-density lipoproteincholesterol (LDL-C) particles, induction of diastolic hypertension, stiffening of central arteries with endothelial dysfunction, and altered coagulation parameters[3-6].Thus association of hypothyroidism in its overt form (TSH > 10 miu/L) with the cardiovascular risk factors by inducing atherosclerosis is incontrovertible , but does the risk starts when the disease is subclinical is yet to be established. Some studies have associated the subclinical disease (TSH values between 5 - 10 miu/L) with the cardiovascular risk factors [1, 2]. In landmark studies the first case-control study by Vanhaelst *et al.* [7] compared autopsy findings in 25 patients with hypothyroidism with 50 age-matched controls and found a greater prevalence and severity of coronary atherosclerosis in the hypothyroid group. Similar results were found in autopsy finding in another study by Steinberg AD though in hypothyroid patients with hypertension. [8]

Two studies have shown that LDL is more susceptible to oxidation in patients with hypothyroidism, with normalization after restoration of the euthyroid state [8,9]. Several studies have shown decreases in the Lp(a) concentration after T4 treatment of hypothyroid patients [10-13]. A study by Walsh J P, O'Leary P et al [14], found a significant 10% decrease in mean intima-media thickness after 6 months of thyroxine replacement, with a decrease of similar magnitude in the 18 participants with TSH less than 10 mU/ L.

Various studies all over the world have suggested that abnormal levels of serum thyrotropin (TSH) may represent a novel cardiovascular risk factor. It has also been seen that restoration of euthyroid state reduces the cardiovascular risk.

Thus we undertook this study with the objective to study the association of conventional(waist-hip ratio, diastolic hypertension, lipid profile) and novel risk factors(Carotid intima media thickness i. e CIMT, high sensitivity c-reactive protein i.e hsCRP and fibrinogen) in young patients of hypothyroidism and their correlation with the severity and duration of hypothyroidism, so as to gather evidence for increased risk of cardiovascular risk factors in hypothyroid patients and thus need for population- based screening for hypothyroidism and it's treatment to prevent atherosclerosis and cardiovascular events.

**Materials and Methods:**

The present cross-section observational study was carried out in the Department of Medicine, Era's Lucknow Medical College and Hospital, Lucknow.

Patients with symptoms or signs suggestive of hypothyroidism were advised to get their TSH done. **All patients** newly diagnosed to have hypothyroidism with TSH > 5.0 miu/L irrespective of the etiology (like chronic hashimoto's thyroiditis, atrophic thyroiditis, hypothyroidism due to treatment with radioactive lithium or surgery or postpartum thyroiditis)or patients who were known to have hypothyroidism but had inadequate treatment due to either irregularity or insufficient dose of levothyroxine replacement and were aged between 18 - 40 years, were included in the study.

The patients who were smokers, with history of diabetes mellitus, obese (BMI>30 kg/m²), inflammatory or infectious diseases, with a previous cardio-vascular event, on drugs (like estrogen, oral contraceptives and hypolipidemic drugs) and pregnant women were not included in the present study.

Each patient in the study group was examined and investigated according to a predesigned examination Performa. Consecutive twenty five patients with TSH values between 5 10 miu/L, normal thyroxine and triiodothyronine levels were included in sub-clinical hypothyroidism group and consecutive twenty five patients with TSH values =10 were in hypothyroidism group. **A total of 50 patients were included in the present study.**

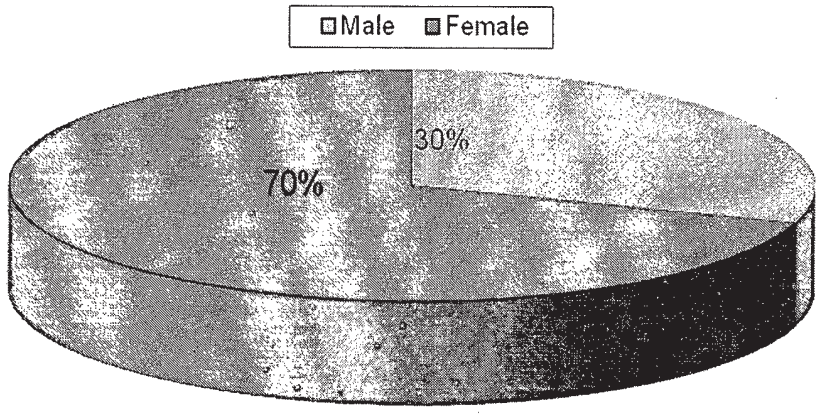
**Results:**

**Baseline demographic characteristics of the patients:** The baseline demographic characteristics of the 50 patients enrolled in two study groups are shown in table-1. There was no statistically significant difference in them except in duration of symptoms which can be explained by their increased TSH values indicating more severe values. **The mean age of sub-clinical hypothyroidism patients was 31.88 (±8.57) years and it was** 31.36 (±5.57) **years in hypothyroidism patients, there was no statistical difference between them. Majority in both sub-clinical hypothyroidism (76%) and hypothyroidism patients (64%) groups were females (Fig.1). The waist-hip ration of sub-clinical hypothyroidism patients was** 0.93 (±0.09) **and it was** 1.03 (±0.19) **in hypothyroidism patients. The mean duration of symptoms of sub-clinical hypothyroidism patients was** 53.5 (±21.1) **days and it was** 781.5 (±51.6) **days in hypothyroidism patients.**

**Table 1**

| | Sub-clinical hypothyroidism (n=25) | Hypothyroidism (n=25) | P-value |
|---|---|---|---|
| Age-years | 31.88±8.57 | 31.36±5.57 | 0.80 |
| Female sex% | 76.0 | 64.0 | 0.36 |
| Average duration of symptoms-Days | 53.5±21.1 | 781.5±51.6 | 0.0001 |

**Fig.1: Distribution of sex**



**Clinical Profile of patients :**

The clinical profile of sub-clinical hypothyroidism and hypothyroidism patients is depicted in the Table-2. There was statistically significant difference ($p<0.05$) in waist-hip ratio between sub-clinical hypothyroidism patients (0.93±0.09) as compared to hypothyroidism patients (1.03±0.19). Systolic blood pressure was higher in hypothyroid patients (133.20±12.14) in comparison to hypothyroid patients (133.20±12.14) though it was statistically insignificant ($p>0.05$), but there was a statistically significant difference ($p<0.05$) in diastolic blood pressure between sub-clinical hypothyroidism patients (88.24±13.50) as compared to hypothyroidism patients (95.84±11.06).The pulse rate was almost equal in both sub-clinical hypothyroidism patients (74.72±7.35) and hypothyroid patients (74.32±8.08).

The total cholesterol level was significantly ($p= 0.001$) lower in sub-clinical hypothyroidism patients (208.84±6.14) as compared to hypothyroid patients (246.80±54.32). The LDL was significantly ($p= 0.005$) lower in sub-clinical hypothyroidism patients (157.88±33.51) as compared to hypothyroid patients (197.20±58.35). There was statistically significant difference ($p<0.05$) in Total cholesterol/HDL-C ratio between sub-clinical hypothyroidism patients (5.29±1.31) as compared to hypothyroidism patients (7.90±3.26) who had statistically significant (3.07, 0.001) difference with higher ratio for hypothyroidism patients. Similar statistically significant (3.68, 0.001) higher values were found for LDL-C/ HDL-C ratio in hypothyroidism patients(6.44±3.18) as compared to subclinical hypothyroid patients (3.93±1.25).

However, the HDL was insignificantly ($p>0.05$) higher in sub-clinical hypothyroidism patients (36.85±7.17) as compared to hypothyroid patients (33.98±9.77). The level of VLDL was almost similar ($p>0.05$) in both sub-clinical hypothyroidism patients (13.16±2.95) and hypothyroid patients (13.28±3.08). The triglycerides level was insignificantly ($p>0.05$) lower in sub-clinical hypothyroidism patients (68.40±16.5) as compared to hypothyroid patients (75.40±17.61).

There was statistically significant difference ($p < 0.05$) in CIMT between sub-clinical hypothyroidism patients (0.67±0.10) as compared to hypothyroidism patients (0.74±0.14) who had statistically significant (2.10,$p= 0.04$) difference with higher values for hypothyroidism patients. Similar statistically significant (5.75, 0.0001) higher values were found for hsCRP in hypothyroidism patients (3.42±0.90) as compared to subclinical hypothyroid patients (2.13±0.69).

The values of fibrinogen was insignificantly ($p>0.05$) lower in sub-clinical hypothyroidism patients (3.68±0.50) as compared to hypothyroid patients. (4.00±0.83).

**Table 2**

**CLINICAL PROFILE OF PATIENTS (MEAN ± SD)**

| | Sub-clinical hypothyroidism (n=25) | Hypothyroidism (n=25) | P-value |
|---|---|---|---|
| Waist-hip ratio | 0.93±0.09 | 1.03±0.19 | 2.29, 0.03* |
| Pulse rate | 74.72±7.35 | 74.32±8.08 | 0.18, 0.86 |
| **Blood pressure** | | | |
| Systolic | 128.88±17.03 | 135.28±15.60 | 1.39, 0.17 |
| Diastolic | 88.24±13.50 | 95.84±11.06 | 2.18, 0.03 |
| Total cholesterol | 208.84±6.14 | 246.80±54.32 | 3.47,0.001* |
| HDL-C | 36.85±7.17 | 33.98±9.77 | 1.18, 0.24 |
| LDL-C | 157.88±33.51 | 197.20±58.35 | 2.92,0.005* |
| VLDL-C | 13.16±2.95 | 13.28±3.08 | 0.14, 0.89 |
| Total cholesterol/HDL-C | 5.29±1.31 | 7.90±3.26 | 3.07, 0.001* |
| LDL-C/ HDL-C | 3.93±1.25 | 6.44±3.18 | 3.68, 0.001* |
| Triglycerides | 68.40±16.5 | 75.40±17.61 | 1.45, 0.15 |
| CIMT | 0.67±0.10 | 0.74±0.15 | 2.10, 0.04* |
| Fibrinogen | 3.68±0.50 | 4.00±0.83 | 1.66, 0.11 |
| hsCRP | 2.13±0.69 | 3.42±0.90 | 5.75, 0.0001* |

*Statistically significant

**Quintiles and CIMT values :**

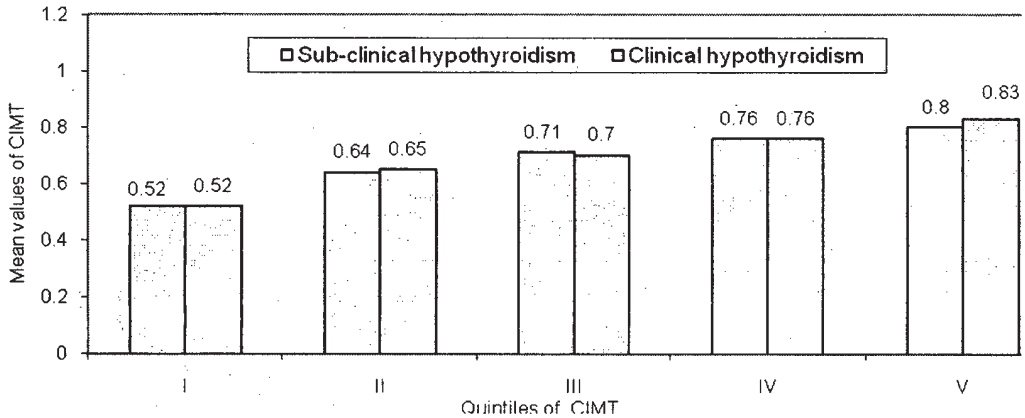
For better data presentation of newer risk factors namely CIMT, hsCRP and fibrinogen we made quintiles of all the patients with 5 groups of 20% each according to their CIMT values by arranging them in ascending order of CIMT values. The thinnest CIMT patients were in 1st Quintile and the thickest CIMT patients were in Vth Quintile, with serial arrangement of patients in ascending order according to the increasing CIMT from 1st quintile to the Vth. If more than one patient had same CIMT, than the patient with shorter duration of complaint was kept in low risk or thinner CIMT quintile and patient with longer duration of complaints in high risk or thicker CIMT quintile. The quintile-wise values of CIMT is given in the Table-3 and Fig.2. There was no significant difference in the values of CIMT in each of the quintiles of **sub-clinical hypothyroidism patients as compared to respective quintile of hypothyroid patients. However, within sub-clinical hypothyroidism patients, the CIMT values were significantly higher (p<0.0001) in quintile V (0.80±0.001) as compared to IV (0.76±0.02), III (0.71±0.02), II (0.64±0.02) and I (0.52±0.08). Similarly, within clinical hypothyroidism patients, the CIMT values were significantly higher (p<0.0001) in quintile V (0.83±0.03) as compared to IV (0.76±0.02), III (0.70±0.02), II (0.65±0.01) and I (0.52±0.05).**

**Table 3**

**QUINTILE-WISE DISTRIBUTION OF PATIENTS ACCORDING TO CIMT**

| Quintiles | Sub-clinical Hypothyroidism | | Clinical Hypothyroidism | | T-Test, P-Value |
|---|---|---|---|---|---|
| | N | CIMT | N | CIMT | |
| I | 6 | 0.52±0.08 | 4 | 0.52±0.05 | 0.11, 0.99 |
| II | 5 | 0.64±0.02 | 5 | 0.65±0.01 | 0.86, 0.43 |
| III | 7 | 0.71±0.02 | 3 | 0.70±0.02 | 0.87, 0.44 |
| IV | 5 | 0.76±0.02 | 5 | 0.76±0.02 | 0.11, 0.99 |
| V | 2 | 0.80±0.001 | 8 | 0.90±0.02 | 2.48, 0.03* |
| ANOVA-F and p-value | | 33.49, <0.0001* | | 109.01, <0.0001* | |

**Fig.2: Quintile-wise distribution of patients according to CIMT**




**Quintiles and TSH :**

The quintile-wise values of TSH is given in the Table-4 and Fig.3. The values of TSH was significantly (p<0.01) lower in sub-clinical hypothyroidism (5.98±0.65) patients as compared to hypothyroid patients (15.79±4.68) in quintile I. Similar pattern was observed for higher quintiles.

Within sub-clinical hypothyroidism patients, the TSH values were significantly higher (p<0.001) in quintile V (9.75±0.21) as compared to IV (8.76±0.30), III (8.28±0.77), II (7.20±0.36) and I (5.98±0.65). Similarly, within hypothyroidism patients, the TSH values were significantly higher (p<0.0001) in quintile V (70.38±2.58) as compared to IV (55.56±4.37), III (37.51±9.82), II (24.65±2.84) and I (15.79±4.68).

Table 4

QUINTILE-WISE DISTRIBUTION OF PATIENTS ACCORDING TO TSH

| Quintiles | Sub-clinical Hypothyroidism | | Clinical Hypothyroidism | | T-Test, P-Value |
|---|---|---|---|---|---|
| | N | CIMT | N | CIMT | |
| I | 6 | 5.98±0.65 | 4 | 15.79±4.68 | 5.23, 0.001* |
| II | 5 | 7.20±0.36 | 5 | 24.65±2.84 | 13.61, 0.001* |
| III | 7 | 8.28±0.77 | 3 | 37.51±9.82 | 12.77, 0.001* |
| IV | 5 | 8.76±0.30 | 5 | 55.56±4.37 | 23.89, 0.0001* |
| V | 2 | 9.75±0.21 | 8 | 70.38±2.58 | 31.77, 0.0001* |
| ANOVA-F and p-value | | 26.89, 0.0001* | | 137.33, 0.0001* | |

**Discussion :**

In the present study we have demonstrated that there is a increasing cardiovascular risk associated with rising TSH value and that this risk starts with low TSH value i.e in patients with subclinical hypothyroidism as well. We found that in the subclinical hypothyroid patients the mean value of total cholesterol(208.8,84±**6.14**), LDL-C levels(**157.88±33.51**), total cholesterol/ LDL cholesterol ratio(5.29±1.31), LDL cholesterol ratio/ HDL cholesterol ratio(3.93±1.25) and plasma hsCRP(**2.13±0.69**) levels were higher than the normal values. In hypothyroid patients we found that these values and the CIMT values were statistically significantly higher than the subclinical hypothyroid patients, in addition diastolic hypertension ( 95.84±**11.06** ) and higher than normal waist-hip ratio (1.03±**0**.19) was also seen in hypothyroid group.(p= <0.05)

Our patients mean total cholesterol value was 208.84±**6.14 for subclinical hypothyroid patients and 246.80±54.32 for hypothyroid patients (3.71,p= 0.001).** Similar results were seen in the Colorado thyroid disease prevalence study of 25,862 subjects, 9.5% had SCH (defined as a TSH >5.1mU=L) (15). In this survey, serum TC averaged 214, 224, and 251mg=dL in euthyroid, SCH, and hypothyroid patients, respectively, with these differences being statistically significant (p < 0.001). Elevated levels of total cholesterol and LDL cholesterol are well documented features of overt hypothyroidism, but our study substantiates the evidence regarding their raised levels in subclinical hypothyroid patients.(16)

Average waist-hip ratio in our hypothyroid patients(1.03±**0**.19) was higher then normal and significantly higher than subclinical hypothyroid patients. **(p= 0.03)** In 87 euthyroid obese patients with BMI >40 kg=m2, serum TSH levels were found higher than in women with BMI <40 kg=m2 and were positively correlated with BMI, leptin, leptin=BMI ratio, body surface area, and insulin sensitivity (HOMA) (17). It was therefore suggested that TSH may represent a marker of energy balance in markedly obese euthyroid patients.

In quintile analysis it was observed that TSH & hsCRP of the patients increased as we moved from 1st quintile to the Vth in both the subclinical and the hypothyroid patients thus indicating that CIMT was directly proportional to TSH in both the groups(Fig 3), and hsCRP was directly proportional to TSH.(Fig.4)

In these patients percentage was determined for no. of hypothyroid patients in each quintile, out of all hypothyroid patients; similarly percentage was also determined for no. of subclinical hypothyroid patients in each quintile, out of all subclinical hypothyroid patients. (Fig. 5) In hypothyroid group the risk increased from 16 % in 1st quintile to 32 % in Vth quintile. In subclinical group of patients 8 % were in highest risk group, thus supporting evidence for cardiovascular risk in subclinical hypothyroid patients. Our findings thus were consistent with previous studies indicating presence of atherosclerosis in hypothyroid as well as subclinical hypothyroid patients.(6,7)

Rossi et al in their study in 2006(18) found that Levothyroxine replacement therapy of sub-clinical hypothyroidism was able to improve both the carotid IMT and atherogenic lipid profile. In one study by Prats(19), A total of 100 patients with SHT treated with levothyroxine were included in the study. No significant differences were detected in TC or in LDL-c after treatment with levothyroxine,this might have occurred as it was a retrospective study and selection bias may have occured as obesity was an exclusion criteria. Recently, Kim et al (2009) determined Thyroid hormone replacement significantly decreased the C-IMT (0.67+/- 0.11 to 0.60+/- 0.10 mm; P = 0.021) and improved the lipid profile. Thyroid hormone replacement resulted in regression of the increased C-IMT, which was attributed to the improvement in the lipid profile (20).

In a review by Martin.I.Surks et al it was recommended that aggressive case finding for subclinical and clinical

hypothyroidism in high-risk groups should be taken up. (21) Our study adds weight to their recommendations.

**Conclusion :**

The hypercholesterolemia and, more specifically, the elevated TC/HDL-C and LDL-C/HDL-C ratios that are often observed in SCH constitute risk factors for CVD that are probably increased by the coexistence of hypertension, being overweight, particularly in middle-aged women. Compelling data show that plasma TC and LDL-C concentrations are elevated in subclinical hypothyroid disease as well. Cardiovascular risk factors some of which induce atherosclerosis, and atherosclerosis in itself were significantly increased as demonstrated by high CIMT values in clinical hypothyroid patients as well as in subclinical hypothyroidism. In high risk population, like those with previous radiation treatment of the thyroid gland (radioactive iodine or therapeutic external beam radiation), those who have had previous thyroid surgery or thyroid dysfunction, and those who have type 1 diabetes mellitus, a personal history of autoimmune disease, a family history of thyroid disease, or atrial fibrillation, TSH in itself acts like a risk factor so efforts should be made to detect and treat hypothyroidism at an early stage (preferably subclinical hypothyroidism) by aggressive case finding in such high risk population.

**Fig.3: Quintile-wise distribution of patients according to TSH**

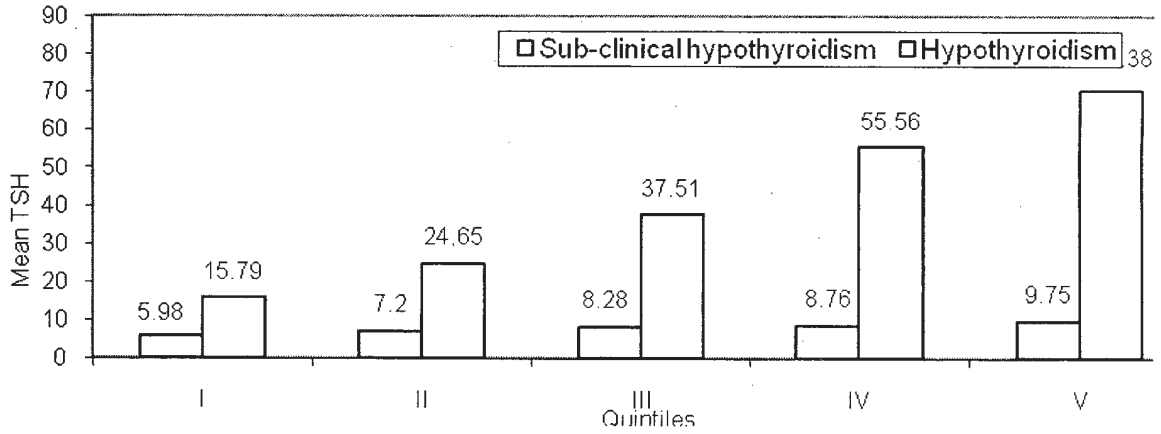



**Fig.4: Quintile-wise distribution of patients according to hsCRP**

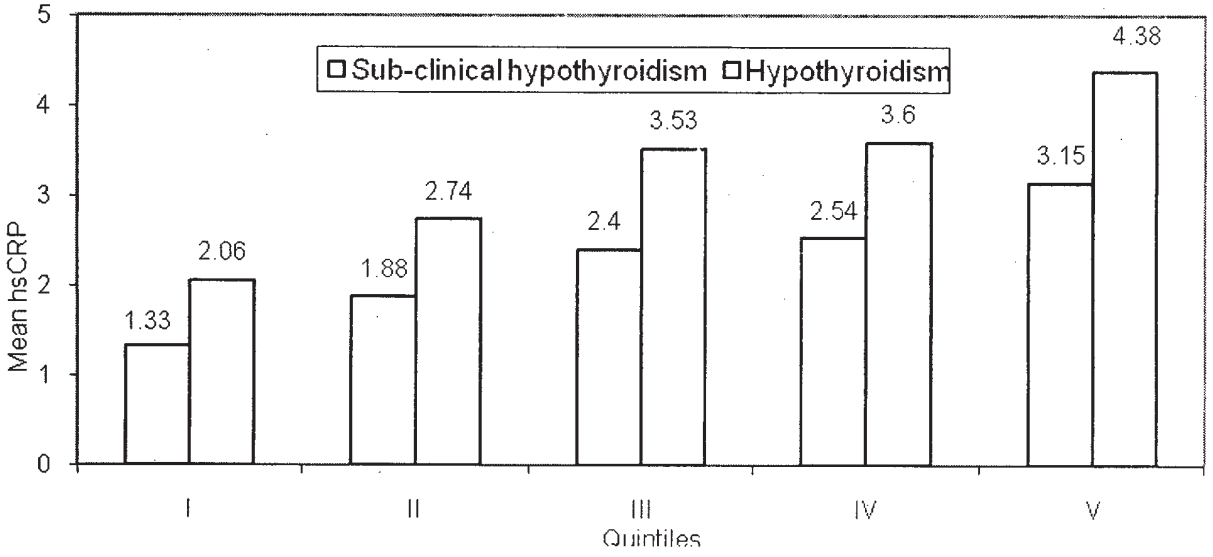
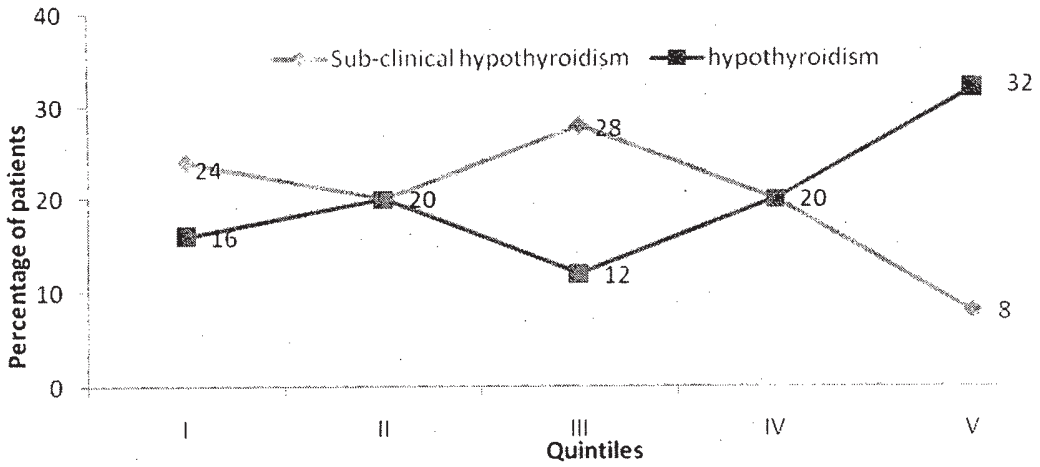


Fig.5: Quintile-wise distribution of patients according to CIMT

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