



Original Research Article

Subclinical hypothyroidism – A state of hypercoagulability and impending risk of atherosclerosis

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ABSTRACT

Introduction: Subclinical Hypothyroidism (SH) represents a condition of mild to moderate thyroid failure characterized by normal levels of serum thyroid hormones with mildly elevated serum TSH concentrations. The possibility of an increased prevalence of non-traditional risk factors (endothelial dysfunction, low grade inflammation, and alterations in coagulation parameters) in SH remains to be clarified.

The present study was undertaken to evaluate if hypercoagulability exists in subclinical hypothyroid patients.

Materials and Methods: The study was conducted for a period of three months in Government Omandurar Medical College antenatal and Medicine OPDs. The subjects diagnosed as subclinical hypothyroid based on TSH levels were recruited into the study group based on the inclusion and exclusion criteria. The total number of subjects is 60 subjects and were divided into group A (30 subjects with SH - cases) and B (30 subjects euthyroid - controls). 5 ml fasting blood samples were collected.

Free T3, free T4, TSH, fibrinogen, Homocysteine and Hs-CRP were estimated. All statistical analyses were carried out for two tailed significance and p value ≤ 0.05 was considered as statistically significant using SPSS v16.0.

Results: FT3, FT4 values were normal in both cases and controls, whilst TSH values differed significantly (with a mean of 2.59 mIU/L in controls and 7.76 mIU/L in cases) Fibrinogen (282.37 ± 81.91 in controls vs 321.95 ± 85.44 mg/dl in cases).

HsCRP levels (1013.5 in controls vs 3367.87 ng/ml in cases) were significantly higher in the Subclinical Hypothyroid subjects when compared to healthy controls. However the levels of Homocysteine were not significantly different in Subclinical Hypothyroid patients when compared to the control group.

Conclusion: This study found out that the risk factors for hypercoagulable state like fibrinogen and inflammatory state like hsCRP were significantly elevated in subclinical hypothyroids (TSH elevated with normal FT3, FT4) when compared to controls indicating a disturbance in coagulation, inflammation processes escalating the risk for atherosclerosis.

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1. Introduction

Subclinical Hypothyroidism (SH) represents a condition of mild to moderate thyroid failure characterized by normal levels of serum thyroid hormones with mildly elevated serum Thyroid stimulating hormone (TSH) concentrations.¹ The medical definition of SH is it's a hypothyroid condition usually asymptomatic in which free thyroxine (FT4) is normal and thyroid stimulating hormone (TSH) level is

between 5 and 25 mU/L, or, if a thyrotropin-releasing hormone test is conducted, there's a greater than normal elevation in TSH response. The prevalence of SH has been reported to be between 4 and 10% of adult population samples in the United States of America.² The prevalence of the same in the south Indian population is 9.4% according to a study done in Kerala.³ The cardiovascular system is a major target of thyroid hormone action. The most consistent cardiac abnormality reported in patients with SH is impaired left ventricular diastolic function, which is characterized

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by slowed myocardial relaxation and impaired ventricular filling.⁴ The Rotterdam study also proved the association of cardiovascular diseases with increasing TSH levels.⁵ The aim of the study was to compare the fibrinogen, hsCRP and homocysteine levels between euthyroid and subclinical hypothyroid subjects.

2. Materials and Methods

The study was conducted in Department of Biochemistry in collaboration with the Department of Obstetrics and Gynaecology and Department of Medicine, Government Omandurar Medical College, India. The study was approved by Institutional Ethics Committee.

This is a case control study. Subjects were enrolled in the study based on inclusion and exclusion criteria. Two groups were created group A and Group B. Females of the age between 25-45 years were included in both groups. A total of 60 subjects were recruited - For group A 30 patients with TSH levels higher than normal with serum thyroid hormone levels within the normal range, categorized as SH were selected. For group B 30 normal healthy euthyroid subjects were recruited. Subjects with overt hypothyroidism or hyperthyroidism and other secondary causes of thyroid abnormalities, endocrine diseases etc were excluded from study. Also subjects on any kind of medication interfering thyroid function and people who have undergone or undergoing radiotherapy for head and neck region were excluded from the study. Male Subjects were excluded. All subjects were requested to report to the hospital in the morning after overnight fasting of at least 12 hours. Five millilitres of blood sample was collected for the investigations. Estimations of free T3, free T4, TSH and Homocysteine were by chemiluminescence. Hs-CRP was estimated by ELISA using commercial kits.

3. Statistical analysis

Sample size was estimated using the statistical formula based on the difference between two means. The sample size was estimated at 5% level of significance. The distribution of continuous variables were tested by Kolmogorov Smirnov normality assessment and all normally distributed variables were expressed as mean with SD and median with interquartile range were used for expressing non gaussian variables. Independent students t test was used to compare all continuous variables between groups. All statistical analyses were carried out for two tailed significance and p value ≤ 0.05 was considered as statistically significant using SPSS v16.0.

4. Results

The present study was undertaken to compare the thyroid function hsCRP, Fibrinogen and homocysteine levels between Euthyroid and Subclinical Hypothyroid

subjects. The data obtained from the study is presented as follows – Demographic variables are presented in Table 1 and Thyroid profile and coagulative parameters fibrinogen, homocysteine and inflammation marker hsCRP are presented in Table 2 – statistical significance was observed in TSH, hsCRP and fibrinogen levels.

5. Discussion

In our study on analyzing the demographic variables there was no significant difference in the age, body weight, Height and hence BMI values between Euthyroid people and Subclinical Hypothyroid cases. These findings were in accordance to a study conducted in Kuwaiti women by Al Sayed et al.⁶

CRP is a marker of systemic inflammation and is used as a biomarker to assess cardiovascular risk in healthy subjects as well as in people with various disorders. It stimulates the release of inflammatory cytokines in monocytes. Elevated hs-CRP levels have been reported in SH.⁷ It can be concluded that SH is associated with a low grade chronic inflammation and SH might be a contributing risk factor for development of cardiovascular disease.

In a recent study including large number of patients with SH, Kvetny et al. found slightly, but not statistical significantly, increased levels of plasma fibrinogen, PAI-1 and von willebrand Factor antigen.⁸

Numerous retrospective and prospective studies have consistently found a relationship between mild hyperhomocysteinemia (fasting or after oral methionine loading) and cardiovascular disease or all cause mortality. Starting at a plasma total Homocysteine concentration of approximately 10 μ mol/L, an associated risk increase follows a linear dose response relationship with no specific threshold level.⁹ Several studies have been published where subjects with SH were compared against normal euthyroid subjects to determine if there was a continuum of change in serum total homocysteine concentrations in those with SH as opposed to an increase that occurs only when overt hypothyroidism exists. Aldasouqi et al found no association between SH and hyperhomocysteinemia.¹⁰

Canturk et al¹¹ concluded that SH was a hypofibrinolytic hypercoagulable state, which was suggested by their data regarding increased fibrinogen. Also SH affects carotid intima media thickness (CIMT), diastolic function, peripheral vascular resistance, endothelial function, and lipid profile. SH is associated with increased risk of atrial fibrillation (AF) (HR 1.68, 95% CI 1.16 – 2.43) and CHD events (HR 1.21, 95% CI 0.99 – 1.46).¹² According to Baris Akinci et al¹³ SH is a hypofibrinolytic platform due to decreased fibrinolysis capacity thus it's a hypercoagulable state with potential cardiovascular risk because of alterations in secondary hemostasis and thrombosis. In a study carried out in South Indian population in Thiruvananthapuram, it was observed that

Table 1: Comparison of various demographic variables in control and subjects with subclinical hypothyroidism

Variable	Euthyroid (n = 30)	Subclinical Hypothyroid (n = 30)	p Value
Age (years)	38.8 ± 9.67	33.07 ± 10.02	0.74
Body Weight (kg)	56.9 (54–59.9)	57 (54–61)	0.32
Height (cm)	149 (146 – 152)	148 (146–154)	0.97
BMI (kg/m ²)	25.44 ± 2.38	26.02 ± 2.94	0.32

Values are expressed as mean±SD in case of normally distributed data and median (IQR) in case of non normally distributed data

Table 2: Comparison of glucose, thyroid profile, coagulative and cardiovascular risk factors in control and subjects with subclinical hypothyroidism

Variable	Euthyroids (n = 30)	Subclinical hypothyroids (n = 30)	p Value
fT3 (pg/ml)	2.92 ± 0.35	2.75 ± 0.46	0.06
fT4 (ng/dL)	1.14 ± 0.14	1.1 ± 0.17	0.26
TSH (mIU/L)	2.59 (1.86 – 3.48)	7.76 (6.87 – 9.22)	0.001
Fibrinogen (mg/dL)	282.37 ± 81.91	321.95 ± 85.44	0.04
Hs CRP (ng/ml)	1013.5 (742 – 1633.5)	3367.87 (1435.67-6637.29)	0.001
Homocysteine (μmol/L)	11.13(8.93-13.60)	11.70(9.46-15.84)	0.218

Values are expressed as mean±SD in case of normally distributed data and median (IQR) in case of non normally distributed data

on angiographic profile SH patients had higher incident of multivessel disease (LAD in particular) compared to euthyroid subjects.¹⁴ However it was observed that there was no risk in evolving carotid plaques which is a surrogate marker for carotid atherosclerosis in subjects with SH.¹⁵

6. Conclusion

This study observes that in subjects with SH (elevated TSH levels) increased hsCRP and fibrinogen levels exist proving that SH is associated with cardiovascular risk and is a reflection of continuing exposure to a plethora of cardiovascular risk factors including procoagulant, proinflammatory changes amounting to endothelial dysfunction disturbances in hemostasis and hence atherosclerosis. Most of the indices are positively correlated with TSH indicating that altered TSH levels in SH could be the possible mainstay behind all these pathogenic mechanisms.

7. Limitations of the study

This study despite best possible measures to avoid confounding factors is carried out with limited sample size and findings when extrapolated to a bigger population might present a different picture. A follow up study is mandatory to observe the effects of SH on the subjects included in the study

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10. Conflict of interest

No conflict of interest of any sorts exists among the above authors

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