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Effect of High Normal Thyroid Stimulating Hormone Levels on Lipid Parameters in Non-diabetic Subjects

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Authors' contributions

This work was carried out in collaboration between all authors. Authors PAM, SR and MSR were responsible for study design, critical revision of manuscript for important intellectual content. Authors PAM and CM were responsible for study design, concept, critical revision of the manuscript, data interpretation, reviewed the draft and study supervision. Author TJ initiated the project, acquisition of data, data analysis and interpretation of the data, wrote the manuscript and had full access to all the data in the study and takes responsibility for integrity of data and the accuracy of the data. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To investigate relationship between serum TSH and lipid parameters in subjects with different levels of TSH.
Study Design: Cross-sectional study.
Place and Duration of Study: Clinical Biochemistry Department of Kasturba Medical College, Hospital Mangalore, between January 2014 to June 2014.
Methodology: 348 subjects were screened of which 194 were selected. Lipid parameters, TSH, T_3, T_4 and glycemic status were determined. Association between TSH and serum lipids were studied by categorizing subjects into three groups based on their thyroid status. Group 1 [TSH= 0.27-2.5 mIU/L], Group 2 [TSH= 2.6-4.12 mIU/L] and Group 3 [TSH= 4.13-9.9mIU/L].Statistical

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analysis was performed by ANOVA followed by Tukey's multiple comparison test. The relationships between TSH and different parameters were evaluated by Pearson's correlation analysis.

Results: TSH showed a significant positive linear correlation with total cholesterol (r=0.288; P = 0.001), Triglycerides (r=0.129; P=0.016), LDL cholesterol (r=0.305; P =0.001) and negative correlation with HDL (r = - 0.129; P=0.750). Increasing TSH showed a consistent linear association with altered lipids quite evident from the uppermost part of the reference range that is considered clinically normal and there on.

Conclusion: A subtle variations of TSH alone in clinically normal thyroid state can alter serum lipids and hence asserts the role of TSH in maintaining lipid homeostasis.

Keywords: Dyslipidemia; euthyroid; TSH; subclinical hypothyroidism.

1. INTRODUCTION

Atherogenic lipid abnormalities, a typical observation in hypothyroidism has always been attributed to altered thyroid hormone levels [1]. On the contrary subclinical hypothyroidism [SCH] characterized with normal T_3 and T_4, with elevated thyroid stimulating hormone [TSH] is also associated with unfavourable serum lipids, especially if TSH is greater than 9.9 mIU/L [2,3]. Available data linking subclinical hypothyroidism to hyperlipidemia when TSH ranges between 4 and 10 mIU/L is controversial and highly conflicting mainly due to disparity among the subjects studied in relation to age, gender, race, life style, iodine intake, etiology, duration of the disease, TSH reference range and difference in the sensitivity of assays employed [4,5]. Clinical guidelines recommend treatment for this group in case of dyslipidemia or other cardiovascular risk [6]. Recent laboratory guidelines of NACB [National Academy of Clinical Biochemistry] recommend the lowering of the upper normal limit of TSH from 4.5 down to 2.5 mIU/L as more than 95% of normal Caucasian subjects had TSH levels < 2.5 mU/L [7]. Hypothyroidism being a less common condition in general population and more than 80-90% of subjects with SCH have TSH levels less than 10 mIU/L, [8,9] the relationship between TSH and lipid profile has gathered much interest on the possible extra thyroidal effects of TSH.

Recently, there is growing amount of evidence indicating that dyslipidemia is partially contributed by the direct effect of TSH even in euthyroid state [10,11]. Hyperlipidemia and subclinical hypothyroidism is relatively common in general population. This study focuses on the better understanding of thyroid hormone independent effects of TSH on lipid parameters at different levels of TSH in Indian population.

2. MATERIALS AND METHODS

This cross-sectional study was conducted in the clinical Biochemistry laboratory of Medical College Hospital from January 2014 to June 2014 among the subjects who came for general health check-up package. Written informed consent was taken from all subjects. The study was approved by the institutional ethical committee. Fasting blood samples were obtained and blood sugar (FBS), Total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL), low density lipoprotein direct (LDL-D) levels were estimated using fully automated biochemistry analyser. Estimation of T_3, T_4 and TSH was carried out using ECLIA technique.HbA1c was quantified in Biorad D10 using HPLC technique.

2.1 Statistical Analysis

ANOVA followed by Tukey's multiple comparison tests for subgroups. The relationships between TSH and different parameters were evaluated by Pearson's correlation analysis. The level of statistical significance was set at $P< 0.05$. All the above analyses were performed using SPSS software, version 16.0.

3. RESULTS

A total of 348 subjects were screened, of which those subjects on treatment for thyroid complications, hypertension, dyslipidemia and age less than 20 or greater than 50 years were excluded. Finally 194 subjects were selected with TSH value between 0.27-9.9 mIU/L. Based on their thyroid status, participants were classified into three groups as Group 1 [TSH= 0.27-2.5 mIU/L], Group 2 [TSH= 2.6-4.12 mIU/L] and Group 3 [TSH= 4.13-9.9mIU/L] [Fig. 1].

Among the included study population 132 [68%] were males and 62 [32%] females. Although thyroid dysfunction has been considered as a

highly prevalent condition in females, in the current study period 55% of those detected with elevated TSH were males.

The mean age, FBS, HbA1c, Total T_3 and T_4 among three groups were comparable. Impaired fasting glucose [IFG] was seen in 76 [35.5%] subjects. The percentage of individuals with IFG in Group 1, 2 and 3 was 33% (n=29), 46% (n=23) and 44% (n=24) respectively [Table 1].

On multiple comparisons among the groups, [Table 1] there was a significant variation in the individual lipid components namely TC, TG and LDL between Group 1 and 3, whereas only LDL varied significantly between Groups 1 and 2. There was no statistically evident difference in the mean values of any of the lipid components between Groups 2 and 3. The percentage increase in mean value of TC, TG and LDL is depicted in [Fig. 2] showing a consistent linear trend with increasing concentration of TSH. However HDL cholesterol showed a modest decrease across the groups. Elevation of TSH levels was associated with hypercholesterolemia, hypertriglyceridemia and high LDL.The subjects in Group 3 showed the highest prevalence of these lipid abnormalities [Fig. 3].

On overall comparison [Fig. 4], TSH correlated significantly and positively with LDL (r=0.305; *P* =0.001) followed by total cholesterol (r=0.288; *P*=0.001) and TG (r=0.129; *P*=0.016) and negatively correlated with HDL(r= -0.129; *P*=0.750).

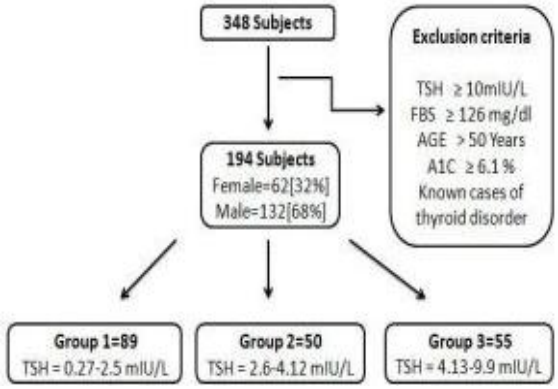

Fig. 1. Study design and selection of subjects

4. DISCUSSION

Controversy still prevails on association of adverse lipid profile in subclinical hypothyroid state. In the present study we observed a significant increase in deleterious lipid levels with increasing level of TSH which was consistent and quite evident in the uppermost part of the reference range that is considered clinically normal. Several studies have reported similar association of TSH with less favourable lipid levels in elderly euthyroid population (Asvoldet al. 2007-The HUNT Study [12], Chin et al. 2014 [13]. In contrast the current study included relatively younger subjects aged 20-50 years.

Table 1. Clinical characteristic of subjects stratified according to serum TSH concentration

Parameters	Group 1 TSH= 0.27-2.5 mIU/L	Group 2 TSH= 2.6-4.12 mIU/L	Group 3 TSH= 4.13-9.9 mIU/L
Age [years]	38±8	38±7	37±8
Gender [Male: Female]	68:21	32:18	32:23
TSH [mIU/L]	1.5±0.51	3.3±0.5	5.8±2
T_3 [ng/ml]	1.3±0.6	1.2±0.16 *P* <0.620	1.2±0.16 *P* <0.515
T_4 [µg/dl]	7.5±1.2	7.5±1.3 *P* <0.999	7.3±1.4 *P* <0.605
FBS [mg/dl]	97±8 (IFG=33%)	98±7 (IFG=46%) *P* <0.603	98±7 (IFG=44%) *P* <0.848
A1C [%]	5.4±0.3	5.4±0.3 *P* <0.551	5.3 ±0.4 *P* <0.999
TC [mg/dl]	176±30	189±22 *P* <0.072	199±33† *P* <0.001
TG [mg/dl]	115±45	130±44 *P* <0.215	142±62† *P* <0.005
HDL-C [mg/dl]	46±9	45±8 *P* <0.946	44±10 *P* <0.799
LDL-C [mg/dl]	114±22	126±22* *P* <0.008	134±28† *P* <0.001

*Values are mean ± SD; * P< 0.05 Group 1 Vs Group 2; †P< 0.05 Group 1 Vs Group 3.IFG: Impaired fasting glucose*

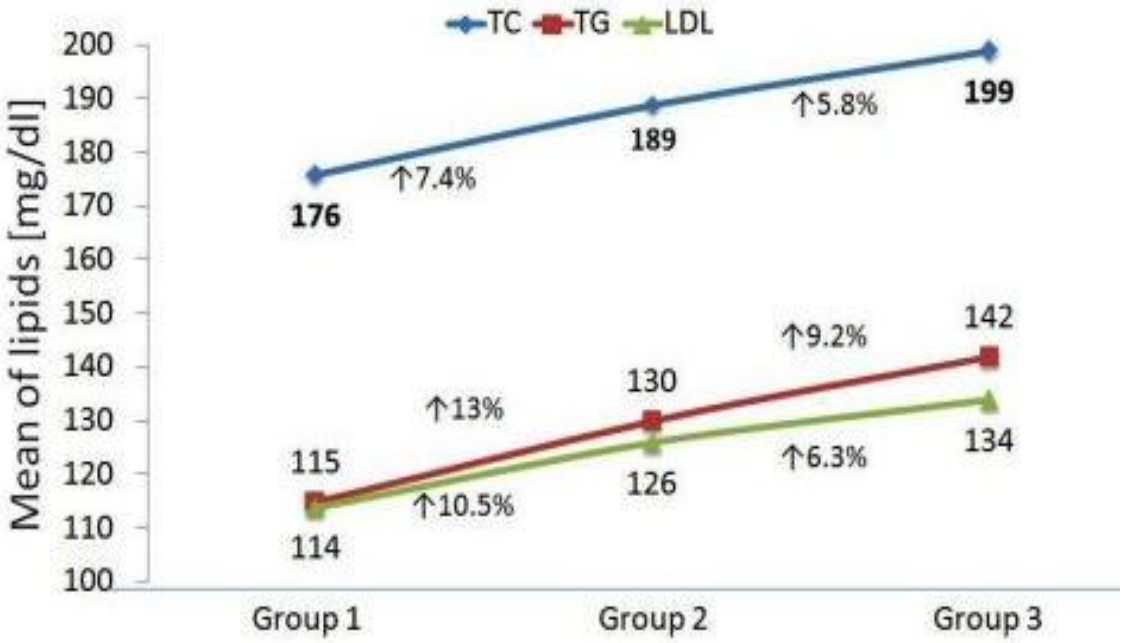

Fig. 2. Mean plot of triglycerides [TG], total cholesterol [TC] and LDL cholesterol
The data presented as mean and the percentage increase of lipids along the TSH sub groups

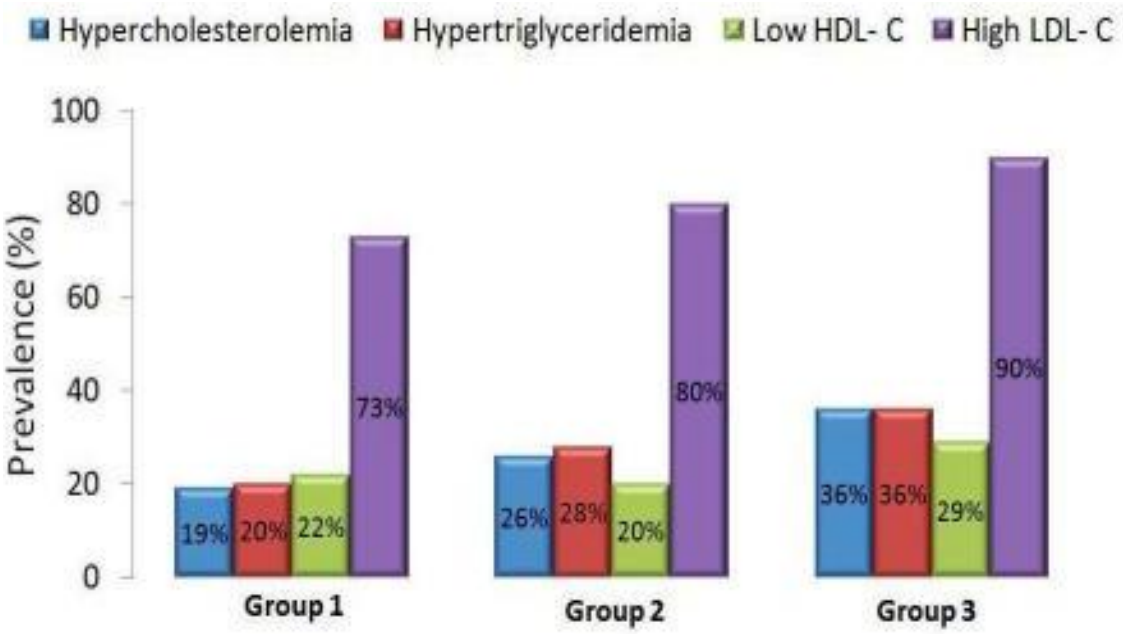

Fig. 3. The prevalence of altered lipids in TSH subgroups
The data are presented as percentage of individuals in each group

Another significant observation was the TSH was positively associated with TC, TG and LDL. This was consistent with the observations of previous studies [14,15]. Some studies have observed this association only in relation to TG [16]. Contrary to this, a study by Ho et al. [17] did not find significant correlation between TSH and lipid parameters in euthyroid state. An atherogenic

lipid abnormality in SCH state is a topic of debate with conflicting results. In several population based studies [18,19] SCH subjects were found to have elevated lipid levels while few of the studies in contrast, did not observe any significant difference in lipid levels in SCH [20,21]. In the present study, subjects with SCH had significantly higher levels of lipids as compared to control groups, but within the normal reference range. This result is in agreement with earlier studies in Indian population which observed atherogenic lipid abnormalities in adult SCH subjects especially when TSH was greater than 9.9 mIU/L [22,23].

Dyslipidemia in hypothyroidism is attributed to altered thyroid hormones.T_3 regulates lipids mainly by controlling the activity of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate limiting enzyme in cholesterol metabolism [24] and additionally, up-regulates LDL receptors by controlling the catabolism of LDL and IDL and protecting LDL from oxidation [25,26]. Thyroid hormones influence HDL metabolism by increasing cholesteryl ester transfer protein (CETP), which increases the reverse cholesterol transport [27]. Together with this T_3 also stimulate lipoprotein lipase (LPL) activity to increase the clearance of TG-rich lipoproteins and hepatic lipase (HL) activity to reduce the catabolism of HDL [28].

In subclinical hypothyroidism, it has been found that thyroid hormones and their function are low in target tissue which is believed to influence lipids by the same mechanism as seen in clinically hypothyroid state [29]. The plausible explanations for the direct effects of TSH on lipid metabolism in euthyroid state are even more complex and the exact reason for this phenomenon has not been fully elucidated. Data from preclinical studies suggest the presence of TSH receptors [TSHR] in hepatocytes.TSH thereby independent of thyroid hormones might up regulate the expression of HMG-CoA reductase resulting in increased cholesterol synthesis which might have deleterious effects in the long run [30] . A higher incidence of thyroid malignancy has also been reported among subjects with normal to high TSH levels. Hence monitoring of TSH levels is important not only for dyslipidemia but also for the diagnosis of malignancies [31,32]. The limitation of this study is its cross-sectional design due to which a cause-effect relationship cannot be established. Furthermore the influence of other confounding factors like smoking, alcohol consumption and lack of physical exercise were not considered.

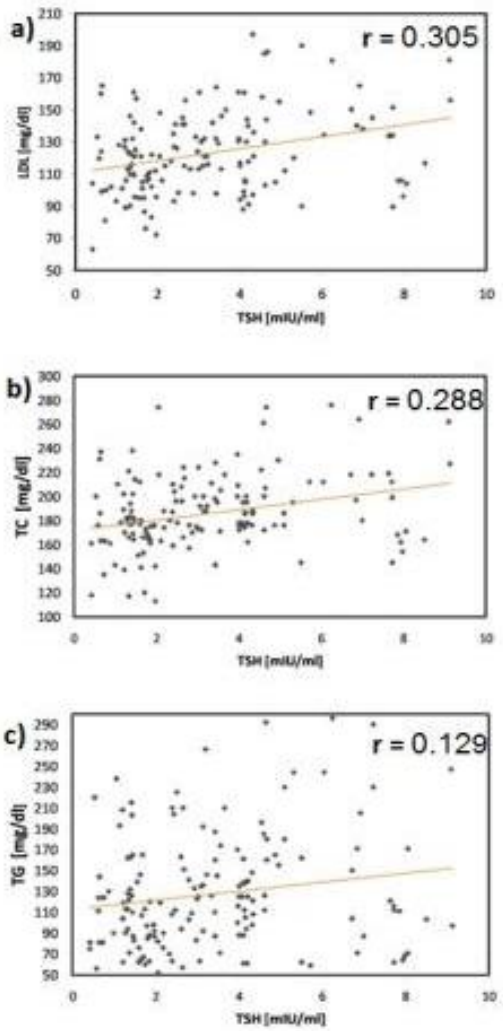

Fig. 4. Positive and linear association between TSH level and lipids (a) LDL; low-density lipoprotein (b) TC; Total cholesterol (C) TG; triglycerides

5. CONCLUSION

A consistent linear trend of lipids was seen with increasing concentration of TSH. Mean LDL, TC and TG in that order showed a significant positive linear correlation. This study confirms the association of lipid abnormalities with thyroid function in both SCH and in the euthyroid considered under the upper normal limit and hence asserts the role of TSH in maintaining lipid homeostasis.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for participating in this study.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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