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A hospital based assessment of the thyroid profile, HS-CRP and lipid profile in newly detected hypothyroid adults: Case control study

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Abstract
Aim: To determine and compare the thyroid profile, lipid parameters and high sensitive C- reactive protein in the study subjects.
Methodology: The study was a cross sectional study which was carried in the Department of Medicine, Department of General Medicine, Mamatha Medical College, Khammam, Telangana, India. Total 100 patients were divided into 2 groups. In Group-1: 50 newly detected hypothyroid adults and Group 2: Controls-50 normal healthy adults within same age group. Serum TSH, FT3 and FT4 by CLIA, Serum high sensitive C reactive protein by Immunoturbidimetric assay and Lipid parameters analyzed in Erba EM360 autoanalyzer, Serum TG: GPO Method, HDL and LDL cholesterol by precipitation method, Total cholesterol by cholesterol oxidase – peroxidase method were investigated. Blood samples were collected with full aseptic precautions after obtaining informed consent. Clot activator that contains vacuum evacuated tubes for analysis of serum TSH, FT3, FT4, TC, HDL-c, LDL-c, TG, hs-CRP. Then after collection, serum samples were stored at -20º until analyzed. Anthropometric measurements for BMI, height (cm) and body weight (kg) were measured.
Results: The mean age of cases and controls in our study was found to be 32.45±13.54 years and 33.54±12.03 years respectively (p= 0.67). Approximately 80% of cases and 74% of controls were females depicting a female preponderance. BMI values in the study were higher in cases (32.57± 8.23 kg/m^2) compared to controls (29.46± 9.36 kg/m^2) and was statistically significant (P = 0.02). In the study, the mean TSH levels (15.34 ± 8.3 µIU/ml) of cases were high compared to controls (3.9 ± 1.54µIU/ml) and was statistically significant (p< 0.001). The mean serum hs - CRP levels in both the study groups was within the reference range, but it was high and statistically significant in cases than in control.
The total cholesterol level in cases (179.34 ±45.58 mg/dl) and control (191.67±31.76 mg/dl) were within the reference range and there was no statistical significance (p = 0.79). Further it was found that HDL-c in cases (49.64±10.47 mg/dl) and control (55.75±4.8 mg/dl) were found to be lower in cases compared to controls and the difference was statistically significant (p< 0.001). The mean LDLc value in cases (150.47± 38.68 mg/dl) and control (139.68±36.56 mg/dl) was high in cases and the difference was statistically significant (p=0.01).
Conclusion: From this study, it can be concluded that the hypertriglyceridemia and at risk hs-CRP levels though seen in hypothyroid cases were more prominent in CH cases than SCH. ANOVA test showed that the difference in the mean between TSH and hs–CRP was found to be statistically significant. Hypothyroidism (CH & SCH) is common among females and is associated with mild dyslipidemia and low-grade inflammation. Moreover subclinical hypothyroidism is more common than clinical hypothyroidism.

Keywords: Hypothyroidism, hypertriglyceridemia, thyroxin, lipids

Introduction
Thyroid dysfunction is one of the most prevalent endocrinopathies across the globe [1]. The thyroid gland maintains the level of metabolism in the tissues that is optimal for their normal function. The principal hormones secreted by the thyroid are thyroxine (T4) and triiodothyronine (T3). Hypothyroidism is characterized by deficient thyroid hormone production which can be severe or moderate [2]. Common etiologies of hypothyroidism are dietary deficiency of iodine and Hashimotos thyroiditis, an auto-immune disease [3].
Severe deficit of thyroid hormones defines clinical hypothyroidism (CH) and is biochemically characterized by TSH concentration (usually >10 µIU/L) with low levels of free thyroxine (FT4) and or Free Triiodothyronine (FT3). The moderate form, called subclinical hypothyroidism (SCH) is defined biochemically as serum TSH concentration

above the upper limit of reference range (> 4.5 - 10 µIU/L) with thyroid hormone levels that remain within the reference range [4]. Subclinical hypothyroidism is defined as an elevated serum TSH level associated with normal total or free T4 and T3 values.

The human thyroid secretes about 80µg of T4, 4µg of T3 and 2µg of RT3 per day [5]. The prevalence of spontaneous hypothyroidism is 1-2% of all the thyroid disorders in the world [6]. The overall prevalence has been reported to range from 6 – 8% in women and 3% in men. In India thyroid disorders are the second most common glandular disorder of the endocrine system and are increasing predominantly among women [7].

Hashimoto's thyroiditis is the most common cause of hypothyroidism in countries with sufficient dietary iodine. Less common causes include previous treatment with radioactive iodine, injury to the hypothalamus or the anterior pituitary gland, certain medications, a lack of a functioning thyroid at birth, or previous thyroid surgery. Hypothyroidism is one of the main causes of abnormal lipid metabolism [8, 9]. Patients with overt hypothyroidism are at risk of hypertension, cardiovascular disease, and atherosclerosis [10]. Lipid abnormalities in overt hypothyroidism includes elevated total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and triglycerides (TG) [9].

The effect of serum thyroid hormones on lipid profile is a complex phenomenon. Thyroid hormones have various effects on both synthesis and degradation of lipids in vivo [11]. It acts predominantly through regulation of gene expression related to lipid metabolism [12]. Thyroid hormones through its nuclear receptors, induce HMG- Co enzyme a reductase, which is the first as well as the regulatory step in cholesterol biosynthesis, upregulates low density lipoprotein (LDLc) receptors by gene activation and maintains serum TG by stimulation of tissue lipoproteinlipase enzyme. It also reduces the plasma HDL by increasing the activity of cholesteryl-ester transfer protein (CETP), hepatic lipase, expression of HDL receptors in the liver and helps reverse cholesterol transport through increased excretion of bile acids in the liver [13].

High sensitive C-reactive protein (hs -CRP) is a marker of chronic subclinical inflammation. Increased hs -CRP levels might be a key molecule linking inflammation to oxidative stress in atherosclerosis (Singh et al) leading to CV risk [14, 15]. Beyond that, hs-CRP is a predictor of future cardiovascular events and probably participates directly in the pathogenesis of atherosclerosis through activation of endothelial cells and coronary artery smooth muscle cells [16].

Material and methods

The study was a case control study which was carried in the Department of Medicine, Department of General Medicine, Mamatha Medical College, Khammam, Telangana, India. Total 100 patients were divided into 2 groups. In Group-1: 50 newly detected hypothyroid adults and Group 2: Controls – 50 normal healthy adults within same age group.

Inclusion criteria

• Newly detected hypothyroid cases.

Exclusion criteria

- Cardio vascular disorders
- Diabetes Mellitus
- Kidney failure
- Liver disorders

Methodology

Serum TSH, FT3 and FT4 by CLIA, Serum high sensitive C reactive protein by Immunoturbidimetric assay and Lipid parameters analyzed in Erba EM360 autoanalyzer, Serum TG: GPO Method, HDL and LDL cholesterol by precipitation method, Total cholesterol by cholesterol oxidase – peroxidase method were investigated.

Blood samples were collected with full aseptic precautions after obtaining informed consent. Clot activator that contains vacuum evacuated tubes for analysis of serum TSH, FT3, FT4, TC, HDL-c, LDL-c, TG, hs-CRP. Then after collection, serum samples were stored at -20º until analyzed. Anthropometric measurements for BMI, height (cm) and body weight (kg) were measured.

Statistical analysis

Analysis was done using SPSS version-20 software. The mean and standard deviation for quantitative variables were calculated for the study. Chi-square test, ANOVA test, students t test were applied whenever necessary. Pearson correlation coefficient was obtained to find out correlation between different parameters. p value < 0.05 was considered to be significant.

Results

The mean age of cases and controls in our study was found to be 32.45±13.54 years and 33.54±12.03 years respectively (p= 0.67). Approximately 80% of cases and 74% of controls were females depicting a female preponderance. BMI values in the study were higher in cases (32.57± 8.23 kg/m^2) compared to controls (29.46± 9.36 kg/m^2) and was statistically significant (P = 0.02)

Table 1: Comparison with age and BMI

Variables	Cases (n=50)	Controls (n=50)
Age	32.45±13.54	33.54±12.03
BMI (Kg/m^2)	32.57± 8.23	29.46± 9.36

In the study, the mean TSH levels (15.34 ± 8.3 µIU/ml) of cases were high compared to controls (3.9 ± 1.54µIU/ml) and was statistically significant (p< 0.001). The mean serum hs - CRP levels in both the study groups was within the reference range, but it was high and statistically significant in cases than in control. The total cholesterol level in cases (179.34 ±*45.58* mg/dl) and control (191.67±31.76 mg/dl) were within the reference range and there was no statistical significance (p = 0.79). Further it was found that HDL-c in cases (49.64±10.47 mg/dl) and control (55.75±4.8 mg/dl) were found to be lower in cases compared to controls and the difference was statistically significant (p< 0.001). The mean LDLc value in cases (150.47± 38.68 mg/dl) and control (139.68±36.56 mg/dl) was high in cases and the difference was statistically significant (p=0.01).

Table 2: Comparison of biochemical parameters

Parameter	Cases	Controls	P value
TSH µIU/ml	15.34 ± 8.3	3.9 ± 1.54	<0.001*
FT3 pg/ml	2.0 ± 1.2	2.4± 1.0	0.34
FT4 ng/ml	0.7 ± 0.4	1.0 ± 0.1	1.12
hs-CRP mg/l	4.2 ± 3.0	2.9 ± 3.2	0.002
Total Cholesterol (mg/dl)	179.34 ±*45.58*	191.67±31.76	0.79
HDL-c (mg/dl)	49.64±10.47	55.75±4.8	< *0*.001
LDL-c(mg/dl)	150.47± 38.68	139.68±36.56	= 0.01
TG (mg/dl)	160.65±*31.38*	142.45±29.37	= 0.02

Hs -CRP levels were in within reference range for 38 (76%) of cases and 44 (88%) controls whereas above the normal range was seen in 12 (36%) cases and only 6(12%) controls.

Table 3: Distribution of cases and controls according to their hs-CR

Variables	Cases	Controls
hs-CRP mg/l <5 mg/l	38 (76%)	44(88%)
≥ 5 mg/l	12 (36%)	6(12%)
Chi square value =7.19, p value = 0.009		

As per the Pearson's correlation, there was a significant positive correlation between serum TSH and hs - CRP levels in cases (r = 0.253, p< 0.001).

Table 4: Pearson's correlation coefficient between TH vs hs-CRP

Parameters	r value	P value
T H vs hs-CRP	0.253	<0.001

Table 5: Comparison of various parameters among CH and SCH

Parameter	CH =25	SCH n=65	p value
Age (years)	34.37 ± 13.27	29.38 ±15.27	0 .15
BMI (kgm^2)	28.98± 4.76	26.44 ± 5.05	0.15
TSH (µIU/ml)	23.5 ± 9.6	10.6 ± 3.8	<.001
FT3 (pg/ml)	1.6 ± 0.8	2.7 ± 0.6	<.001
FT4 (ng/ml)	0.7 ± 0.5	1.5 ± 0.7	<.001
hs-CRP (mg/l)	4.6± 3.8	4.3 ± 2.5	0.51
TC (mg/dl)	173.4± 32.6	186.7 ± 45.7	0.17
HDL-C (mg/dl)	45.3 ± 8.9	46.2 ± 8.5	0.55
LDL-C (mg/dl)	151.24 ± 36.8	140.8 ± 33.2	= 0.36
TG (mg/dl)	107.54 ± 21.4	156.13 ± 51.4	<.001*

Table 6: Anova of various parameters of SCH, CH and control

Variables	SCH (n=65)	CH (n=25)	Controls	Total	F value	P value
T H	11.31± 2.3	25.31± 9.4	1.82±0.84	8.52±8.35	315.77	<.001
hs- CRP	3.81±2.15	4.33±3.32	2.27±2.9	3.26±2.72	11.33	<.001

Discussion

Hypothyroidism is by far the most prevalent form of thyroid disorder and is more common in women [17]. It is characterized by a broad clinical spectrum ranging from an asymptomatic/subclinical condition to over the state of myxoedema, end organ effects and multi organ failure [18]. This study has investigated the possible association of hypothyroidism with hs-CRP, lipid profile both reportedly associated with risk of CVD.

Hypothyroidism is known to inflict females more than males. Devika Tayal et al. (2012) in their study observed a similar female predominance with a female to male ratio of 2.86 (females 5542 vs Males 1933) A redox imbalance elicited by estrogen could be responsible for increased prevalence in female [19, 20]. In our study also, approximately 80% of cases and 74% of controls were females depicting a female preponderance.

Data about the association between hs-CRP and thyroid function are not very consistent. Two cross-sectional analyses with a design similar to this study found conflicting results [21, 22]. First, a cross-sectional analysis of a cohort of 2,494 participants recruited in Taiwan from 2006 to 2008 showed an association between SCH (TSH >5.6 µIU/ml) and elevated hs-CRP, defined as above the fourth quartile (>24.67 nmol/l), i.e. results consistent with ours [21].

Similar to the NHANES data, other studies with different designs were not able to show a consistent association between SCH and increased hs-CRP. One Swiss double-blind placebo-controlled clinical trial showed that hs-CRP values increased progressively with thyroid failure in 63 subjects with SCH (p = 0.022), and particularly in 61 subjects with overt hypothyroidism (p = 0.016), in comparison to 40 euthyroid matched controls. However, levothyroxine therapy over 48 weeks did not result in decreased hs-CRP in 31 subjects with SCH compared to 32 subjects with SCH randomized to the placebo group [23]. Consistent with this clinical trial, one retrospective South Korean study that followed individuals with SCH who were treated or not with levothyroxine did not find decreased serum hs-CRP levels in either group [24].

In the study, the mean TSH levels (15.34 ± 8.3 µIU/ml) of cases were high compared to controls (3.9 ± 1.54µIU/ml) and was statistically significant (p< 0.001) .The mean serum hs - CRP levels in both the study groups was within the

reference range, but it was high and statistically significant in cases than in control. The total cholesterol level in cases (179.34 ±45.58 mg/dl) and control (191.67±31.76 mg/dl) were within the reference range and there was no statistical significance (p = 0.79). The interaction of IL-6 on TNF-α and IL-1 results in the raised CRP levels in hypothyroidism. Lack of thyroid hormones may impair the rate of CRP clearance which may be one reason in increase in serum CRP level. Similarly, slow CRP uptake in target cells might also add to this phenomenon. The low grade inflammation which may be accountable for increased risk of developing CVD in hypothyroidism [25]. Thyroid disorders are known to influence lipid metabolism and other CV risk factors predominantly. Dyslipidaemia is a well-recognized association of thyroid dysfunction which should be considered in the process of evaluating and treating dyslipidemic patients [26, 27]. This study also showed that mean serum hs -CRP levels in both study groups were within reference range but the mean serum hs-CRP levels in cases was significantly higher (p=0.005) than in control. A significant positive correlation was also found between serum TSH and hs-CRP levels in cases.

Conclusion

From this study, it can be concluded that the hypertriglyceridemia and at risk hs-CRP levels though seen in hypothyroid cases were more prominent in CH cases than SCH. ANOVA test showed that the difference in the mean between TSH and hs–CRP was found to be statistically significant. Hypothyroidism (CH & SCH) is common among females and is associated with mild dyslipidemia and low-grade inflammation. Moreover subclinical hypothyroidism is more common than clinical hypothyroidism.

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