Original research article

To Compare the Thyroid Profile, hs-CRP, and Lipid Profile in Newly Diagnosed Hypothyroid Adults to Controls, as well as to Compare the above Parameters in Subclinical and Clinical Hypothyroid Instances

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Abstract

Aim: The aim of the study to analyse the thyroid profile, hs-CRP and lipid profile in newly detected hypothyroid adults in comparison to controls and also to compare the above parameters in subclinical and clinical hypothyroid cases.

Methods: The study was a cross sectional study which was carried in the Department of Medicine ,Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga,Bihar,India. for 1 year. Total 180 patients were divided into 2 groups. Group-1 for newly detected hypothyroid adults and Group 2 as Controls. 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 -20^0 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 36.32±12.31years and 35.97±11.16 years respectively (p=0.67). Approximately 83.33% of cases and 71.11% of controls were females depicting a female preponderance. BMI values in the study were higher in cases (26.89± 4.87kg/m2) compared to controls (24.77± 4.56kg/m2) and was statistically significant (P=0.03). The mean TSH levels (14.77 ± 9.8μIU/ml) of cases were high compared to controls (4.2 ± 0.91μIU/ml) and was statistically significant (p < 0.001) The total cholesterol level in cases (183.31 ± 40.77mg/dl) and control (187.32±28.38mg/dl) were within the reference range and there was no statistical significance (p=0.79). HDL-c in cases (48.29±9.37mg/dl) and control (52.57±6.6mg/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 (145.14±34.12mg/dl) and control (134.05±31.14mg/dl) was high in cases and the difference was statistically significant (p=0.01). The triglyceride levels of cases (158.27±49.87mg/dl) were significantly higher than that of control (145.24±27.27mg/dl) and was statistically significant (p=0.02). As per the Pearson's correlation, there was a significant positive correlation between serum TSH and hs - CRP levels in cases (r=0.237, p < 0.001).

Conclusion: The hypertriglyceridemia and at risk hs-CRP levels though seen in hypothyroid cases were more prominent in CH cases than SCH. Dyslipidemia and inflammatory markers were found to be increased in the cases that helped in prediction and evaluation of patients at risk of cardiovascular disease.

Keywords: hs-CRP, TSH, SCH

Introduction

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). The human thyroid secretes about 80μg of T4, 4μg of T3 and 2μg of RT3 per day.[1] Subclinical hypothyroidism is defined as an elevated serum TSH level associated with normal total or free T4 and T3 values. The overall prevalence has been reported to range from 6 – 8% in women and 3% in men. Because of the frequency with which this condition is encountered, important questions have been raised regarding its clinical relevance and appropriate management. Worldwide, too little iodine in the diet is the most common cause of hypothyroidism. 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. The diagnosis of hypothyroidism, when suspected, can be confirmed with blood tests measuring thyroid-stimulating hormone (TSH) and thyroxine levels.[2] Worldwide about one billion people are estimated to be iodine-deficient; however, it is unknown how often this results in hypothyroidism. In the United States, hypothyroidism occurs in 0.3–0.4% of people. Subclinical hypothyroidism, a milder form of hypothyroidism characterized by normal thyroxine levels and an elevated TSH level, is thought to occur in 4.3–8.5% of people in the United States. Hypothyroidism is more common in women than in men.[3] Hypothyroidism is one of the main causes of abnormal lipid metabolism.[4,5] Patients with overt hypothyroidism are at risk of hypertension, cardiovascular disease, and atherosclerosis.[6] Lipid abnormalities in overt hypothyroidism includes elevated total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and triglycerides (TG).[5] Although the association between subclinical hypothyroidism (SCH) and dyslipidemia is still controversial, changes in lipid profile in these patients have been observed in several studies.[7]

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.[8] Possible role of CRP in atherogenesis might be due to enhanced expression of local endothelial cell surface adhesion molecules, endothelin-1, reduced endothelial nitric oxide bioactivity. To explore the moderate elevations as in screening, performance of hs-CRP is recommended to better identify CRP variations.[9,10] In our study we hypothesized that hypothyroidism is associated with mild dyslipidemia associated with chronic inflammatory state as measured by hs-CRP. The basic aim is to study the same in the newly detected hypothyroid adults.

Material and methods

The study was a cross sectional study which was carried in the Department of Medicine ,Darbhanga Medical College and Hospital , Laheriasarai, Darbhanga,Bihar,India., after taking the approval of the protocol review committee and institutional ethics committee. Total 180 patients were divided into 2 groups. In Group-1: 90 newly detected hypothyroid adults and Group 2: Controls – 90 normal healthy adults within same age group.

Inclusion criteria
- Newly detected hypothyroid cases

Exclusion criteria
- Cardio vascular disorders,
- Diabetes Mellitus,

- kidney failure,
- Liver disorders

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 -20° until analyzed. Anthropometric measurements for BMI, height (cm) and body weight (kg) were measured.

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 .
 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
As shown in Table 1, both cases and controls were age matched. The mean age of cases and controls in our study was found to be 36.32±12.31years and 35.97±11.16 years respectively (p = 0.67). Approximately 83.33% of cases and 71.11% of controls were females depicting a female preponderance. BMI values in the study were higher in cases (26.89± 4.87kg/m2) compared to controls (24.77± 4.56kg/m2) and was statistically significant (P = 0.03) (Table 1) In the study, the mean TSH levels (14.77 ± 9.8µIU/ml) of cases were high compared to controls (4.2 ± 0.91µIU/ml) and was statistically significant (p < 0.001) (Table 2).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 (p = 0.002). The total cholesterol level in cases (183.31 ± 40.77mg/dl) and control (187.32±28.38mg/dl) were within the reference range and there was no statistical significance (p = 0.79). Further it was found that HDL-c in cases (48.29±9.37mg/dl) and control (52.57±6.6mg/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 (145.14±34.12mg/dl) and control (134.05±31.14mg/dl) was high in cases and the difference was statistically significant (p=0.01). The triglyceride levels of cases (158.27±49.87mg/dl) were significantly higher than that of control (145.24±27.27mg/dl) and was statistically significant (p=0.02). As in Table 3, hs -CRP levels were in within reference range for 70 (77.78%)of cases and 84(93.33%)controls whereas above the normal range was seen in 20 (22.22%) cases and only 6(6.67%) controls. (Table 4)As per the Pearson's correlation, there was a significant positive correlation between serum TSH and hs - CRP levels in cases (r = 0.237, p < 0.001).

To analyse the condition, Hypothyroid cases (n=90) in our study was divided into two groups (subclinical hypothyroid and clinical hypothyroid) based on TSH and thyroid hormone levels. Out of 90, 72.22% (n=65) were subclinical hypothyroid (SCH) and 27.78% (n=25) were clinical hypothyroid (CH) cases. A definite female preponderance was observed in the study. In Table 5, the mean age, BMI between the two groups did not differ significantly. There was a significant increase in serum TSH in CH (25.11 ± 8.3µIU/ml) as compared to SCH (11.31±2.7µIU/ml). The difference was statistically significant (p < 0.001). hs-CRP levels though high in CH than SCH were statistically insignificant (p = 0.51). Total cholesterol value

was within the reference range in both the groups (CH and SCH) whereas TG was found to be high in CH compared to SCH and was found to be significant (p < 0.001). There was no significant difference in HDL-c and LDL-c between the two groups (SCH & CH). TSH and hs-CRP when compared between SCH, CH and controls showed a statistically significant difference between groups with p value<0.001. (Table 6)

Table 1: Comparison with age and BMI

	Cases n=90	Controls n=90	P Value
Age	36.32±12.31	35.97±11.16	0.67
BMI (Kg/m2)	26.89± 4.87	24.77± 4.56	= 0.03*

Table 2: Comparison of biochemical parameters

Parameter	Case= 90	Control =90	P value
T H µIU/ml	14.77 ± 9.8	4.2 ± 0.91	<0.001*
FT3 pg/ml	1.8 ± 0.8	2.2± 0.8	= 0.34
FT4 ng/ml	0.8 ± 0.6	0.9 ± 0.07	= 1.12
hs-CRP mg/l	4.3 ± 2.8	2.8 ± 2.6	= 0.002*
Total Cholesterol (mg/dl)	183.31 ± 40.77	187.32±28.38	= 0.79
HDL-c (mg/dl)	48.29±9.37	52.57±6.6	< .001*
LDL-c(mg/dl)	145.14±34.12	134.05±31.14	= 0.01*
TG (mg/dl)	158.27±49.87	145.24±27.27	= 0.02*

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

	Hypothyroid Cases =90	Controls n=90
hs-CRP mg/l < 5 mg/l	70 (77.78%)	84(93.33%)
≥ 5 mg/l	20 (22.22%)	6(6.67%)
Chi square value =7.21, p value = 0.008		

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

Parameters	r value	P value
T H vs hs-CRP	0.237	<0.001

Table 5: Comparison of various parameters among CH and SCH

Parameter	CH =25	SCH n=65	p value
Age (years)	38.22 ± 12.31	36.28 ±12.27	=0 .15
BMI (kgm2)	27.47± 4.38	27.41 ± 5.32	= 0.15
TSH (µIU/ml)	25.11 ± 8.3	11.3 ± 2.7	< .001*
FT3 (pg/ml)	1.6 ± 0.8	2.7 ± 0.6	< .001*
FT4 (ng/ml)	0.8 ± .4	1.3 ± 0.3	< .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 a disorder presenting with different degrees of thyroid failure and metabolic consequences. An increase of serum TSH is a very early biochemical marker of impending thyroid failure resulting from the gradual decline of T4 and at a later stage of T3. SCH is a frequent syndrome and has been defined as a condition with normal circulating levels of T3 and T4 but elevated TSH. Lipid levels and hs-CRP are known cardiovascular risk factors and the following study focuses on these two risk factors and their possible link with SCH.

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). The human thyroid secretes about 80μg of T4, 4μg of T3 and 2μg of RT3 per day.[11] Subclinical hypothyroidism is defined as an elevated serum TSH level associated with normal total or free T4 and T3 values. The overall prevalence has been reported to range from 6–8% in women and 3% in men. Because of the frequency with which this condition is encountered, important questions have been raised regarding its clinical relevance and appropriate management.[12]

This study has investigated the possible association of hypothyroidism with hs-CRP, lipid profile both reportedly associated with risk of CVD. A total of 180 subjects participated in this study. Out of the total 90 subjects were newly detected hypothyroid subjects (cases) and 90 were healthy control. Both the cases and control were age matched. The mean age of cases and controls in our study was found to be 36.32±12.31years and 35.97±11.16 years respectively (p = 0.67). Approximately 83.33% of cases and 71.11% of controls were females depicting a female preponderance. Hypothyroidism is known to inflict females more than males. Devika Tayal et al 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.[13,14] In this study BMI was higher in hypothyroid cases. Study conducted b y Nivedita Nanda et al , Kunal B.K.[15] et al reported similar observation with BMI in hypothyroidism. Thyroid hormones mediate their effects mainly through mechanism that stimulate basal metabolic rate, increase ATP expenditure, modulate adrenergic receptor number and responsiveness to catecholamines. Hypothyroid state characterized by slowing down of basal metabolic rate may be an important factor contributing to increase BMI in these cases. The mean TSH levels (14.77 ± 9.8μIU/ml) of cases were high compared to controls (4.2 ± 0.91μIU/ml) and were statistically significant (p < 0.001). The mean serum FT3 levels (1.8 ± 0.8 vs 2.2 ± 0.8 pg/ml, p = 0.34) and serum FT4 levels (0.8 ± 0.6 vs 0.9 ± 0.07 ng/ml, p = 1.12) in both cases and control respectively were within the

normal range (Table 2). Study done by Mohsin Shafi et al on newly detected hypothyroid patients found that mean TSH levels higher in cases as compared to control (15.27 ± 9.2µIU/L vs 3.1 ± 0.88) and was statistically significant (p < 0.01).[16] Thyroid. hormone plays a crucial role in regulation of immune system and has the potential to dampen inflammatory cytokines such as INF-α, IL-6, IL-10. Several signs and symptoms suggest that hypothyroidism is an inflammatory state resulting from interaction of IL-6 on TNF and IL-1 leading to increase hs - CRP in this state. Recent studies found that moderate elevations of CRP correlate with future cardiovascular events justifying the use of this test to evaluate cardiovascular risk.[17] This study 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 (r = 0.237, p < 0.001). Christ-crain et al (2003) observed an elevation in CRP levels with progressive thyroid failure and a clear association between hypothyroidism and increased hsCRP.[18] Tuzcu et al , Alpaslan T et al [17] in their studies of the association between coronary heart disease and SCH have reported that elevated hs -CRP levels suggest low grade inflammation predictive of CV risk in hypothyroid subjects.[17] In contrary to this, a study conducted by Aksoy DY et al on women could not validate a significant difference in hs-CRP levels between hypothyroid and control.[19] 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.[20] 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.[21,22]

In this study, it was found that total cholesterol values had no statistical significance but HDL-c in cases was found to be lower compared to control and the difference was statistically significant (p < 0.001). The mean LDL-c and triglyceride in cases were higher than control with p = 0.001 and p = 0.02 respectively. Sunanda et al found that there was a strong positive association between TSH and lipid profile in hypothyroid patients and concluded that effect of hypothyroidism on the serum lipids is more pertinent in patients with higher TSH levels.[23] Khan Mah et al) also found a significant dyslipidemia i.e. significant increase in TC, LDL-c and TG levels and decrease in HDL-c levels.[24] Slight elevation in TSH levels, preponderance of subclinical hypothyroid subjects and shorter duration of illness (newly detected cases) might be likelihood causes of mild dyslipidemia observed in the study. In clinical hypothyroidism (CH), a decrease in LPL activity and the clearance of TG-rich lipoproteins[25] are found. Therefore CH patients may also present with elevated TG levels associated with increased levels of VLDL and occasionally fasting chylomicronemia[26] as observed with hypertriglyceridemia in hypothyroid cases in the study. Many previous studies concluded that CH patients have elevated atherogenic and oxidative stress markers. Hence, serum TSH measurement is the essential test for diagnosis of mild thyroid failure when the peripheral thyroid hormone levels are within normal reference range.[27] In this study, a low HDL levels in cases was found. Clinical studies however reported a conflicting result about HDL-cholesterol plasma levels in hypothyroidism. The studies conducted by Caron et al found a reduction in HDL cholesterol and an increase in HDL after subsequent treatment with thyroxine. However, S. Valdemarssonet et al and E. Muls et al found an improvement in the mean HDL levels in the hypothyroidism with a reduction after treatment. Several proteins related with HDL metabolism are affected by thyroid hormones.[28-30] The extent to which various levels of thyroid dysfunction affects CV event need to be debated.[9] Cappola et al in their study of Cardiovascular

Health Study data found that there was no relationship between SCH or CH and prevalence of atherosclerotic disease, cardiovascular mortality o r all causes mortality.[31] For better analysis in this study, hypothyroid cases were divided into subclinical hypothyroid (SCH) and clinical hypothyroid (CH). Majority of the target study group was female. The mean age, BMI values between two groups did not differ significantly. The CH subjects has higher serum TSH levels as compared to the subjects of SCH which was statistically significant (P <0.001). hs-CRP levels were found to be at risk level and was comparable in both CH and SCH but was statistically insignificant (p=0.51). Many studies have shown that high levels hsCRP in women with SCH correlated with parameters of obesity which emphasizes the role of body weight in inflammation and may consider as an additional risk factor for the development of atherosclerosis and CVD.[32,33] Total cholesterol value was found to be within reference range in both the groups (CH and SCH) but TG value was found to be high in CH as compared to SCH which was found to be statistically significant (p < 0.001). There was no significant differences in HDL-c, LDL-c between two groups. The mean values of serum TSH and hs-CRP were higher in CH as compared to SCH and controls. It was observed that the difference was statistically significant (p < 0.001). Studies conducted by Bondi and Cooper have shown that SCH is associated with variable and inconsistent changes in above mentioned parameters in contradictory to CH in which significant changes are normally found.[34]

Conclusion
The present study concluded that the hypertriglyceridemia and at risk hs-CRP levels though seen in hypothyroid cases were more prominent in CH cases than SCH. Dyslipidemia and inflammatory markers were found to be increased in the cases that helped in prediction and evaluation of patients at risk of cardiovascular disease.

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