A Study of Inflammatory Cytokines and Lipid Profile in Hypothyroidism Patients at a Tertiary Care Hospital

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KEYWORDS

Hypothyroidism, inflammatory cytokines, Lipid profile, T3, T4, dyslipidaemia

ABSTRACT

INTRODUCTION: A common endocrine condition called hypothyroidism is caused by an underactive thyroid gland, which lowers the production of thyroid hormones such triiodothyronine (T3) and thyroxine (T4). Furthermore, dyslipidaemia and elevated inflammatory cytokine levels have been associated with hypothyroidism.

AIM AND OBJECTIVE: To find out the association between TSH and pro- inflammatory markers (IL6 and TNF alpha) in hypothyroid patients with dyslipidemia.

MATERIAL & METHODS: This was a one-year Prospective cross-sectional study conducted at a tertiary care hospital, Assam. Total 80 individuals were enrolled in this study in which 40 were case patients with hypothyroidism with dyslipidemia) and 40 were controls age and sex matched hypothyroid without dyslipidemia). Lipid profile and inflammatory cytokines value were recorded.

RESULTS: Out of 40(case group), 19 were male and 21 were females in which 14(35%) belong to age group 31-40 and only 3(7.5%) belong to age group 41-50. BMI values in the study were higher in cases (28.4 ± 4.6 kg/m2) compared to controls (23.8 ± 4.3 kg/m2) and was statistically significant. The hypothyroid patients also presented higher levels of total cholesterol, triglycerides, HDL and LDL than control group(healthy individuals) despite the age and BMI to be similar between groups and also inflammatory cytokines levels were significantly higher in hypothyroid patients with dyslipidemia(Case group), when compared to control group. The proinflammatory markers mainly IL 6 level also found to be higher in the hypothyroid patients with dyslipidemia (Cases) and positively correlated with increased TSH levels.

CONCLUSION: From the present study it can be assumed that inflammation plays an important role in hypothyroidism, and the cause for dyslipidemia can be contributed to this inflammation and because of which there is an additional inflammatory burden on the individual potentially striking towards an increasing risk for cardiovascular events.

INTRODUCTION

Thyroid dysfunction is one of the most prevalent endocrinopathies across the globe [1]. Prevalence of spontaneous hypothyroidism is 1-2% of all the thyroid disorders in the world [2].
In India thyroid disorders are the second most common glandular disorder of the endocrine system and are increasing predominantly among women [3]. ypothyroidism is characterized by deficient thyroid hormone production which can be severe or moderate [4].Common etiologies of hypothyroidism are dietary deficiency of iodine and Hashimotos thyroiditis, an auto-immune disease [5,6].
Hypothyroidism is known for its effects on different organs system, leading to hypometabolism. Thyroid gland regulates a wide array of metabolic parameters of carbohydrate and lipid metabolism and has profound effects on the cardiovascular system [7].
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 [8].
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.[9] It acts predominantly through regulation of gene expression related to lipid metabolism [10].
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 (LDL-c) receptors by gene activation and maintains serum TG by stimulation of tissue lipoprotein lipase 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 11].However, not all lipid parameters are corrected suggesting a more complex cause of dyslipidemia in hypothyroidism [12].
The acute phase response to inflammation is characterized by the combination of hepatocyte-derived plasma proteins induced by the inflammatory cytokines tumor necrosis factor-a (TNF-a) and interleukin-1 (IL-1) as well as those induced by interleukin-6 (IL-6)[13]. A key regulator of the inflammatory response is IL-6, which stimulates the synthesis of acute phase proteins including CRP and fibrinogen.
Moreover, IL-1 has been identified as a chemical mediator released from monocytes/macrophages and exhibits important biologic activity in inflammatory and immunologic responses[14]

TNF-a is another important cytokine mediating the induction of adhesion molecules and other cytokines[13] and modulating of the immunologic reactions produced by interferon-g (IFN-g) of HLA class II molecules in human thyroid follicular cells[15].
Despite the potential influence of hypothyroidism on blood inflammatory biomarkers there are few studies investigating this potential association.
Therefore, we performed case control study to evaluate the inflammatory cytokines and lipid profile in the hypothyroidism patients.

MATERIAL AND METHODS

Study design & Study setting: Hospital based Prospective Cross-sectionl study conducted in the the Multidiscipliary Research Unit(MRU), Assam Medical College, Dibrugarh, Assam. The study was approved by institutional ethics committee, and informed consent was obtained from all the participants.

Study population:
Total 80 participants were included in this study, which divided into two groups:

- **CASE GROUP (n=40):** TSH > 10 mIU/L, low T3 and T4 values, and clinical symptoms were used to diagnosis patients with primary hypothyroidism of age group 18-60 with dyslipidemia.

- **CONTROL GROUP (n=40):** Hypothyroid patients of same age group without dyslipidemia.

Inclusion criteria: Newly diagnosed hypothyroidism patients of age group 18- 60 years.
Exclusion criteria:
- Hypothyroidism patients on other medications or treatment.
- Individuals having diabetes mellitus, Kidney failure, liver disease, pregnancy and other chronic illness.

Data collection:
Blood samples were collected after 12 hr overnight fasting with all the aseptic precautions.
- **Demographic and Clinical Data:** Age, sex, BMI, and clinical symptoms were recorded.
- **Laboratory Analysis:**
    - **Thyroid Function Tests:** TSH, T3, and T4 levels were measured using chemiluminescent immunoassay.
    - **Lipid Profile:** Total cholesterol, triglycerides (TG), HDL, and LDL were analyzed using enzymatic colorimetric methods.
    - **Inflammatory Cytokines:** IL-6, TNF-α, and CRP levels were measured using enzyme-linked immunosorbent assay (ELISA) kits.

Statistical Analysis

Data were analyzed using SPSS version 25.0. Results were expressed as mean ± standard deviation. A p-value < 0.05 was considered statistically significant.

RESULTS

Out of 40(case group), 19 were male and 21 were females in which 14(35%) belong to age group 31-40 and only 3(7.5%) belong to age group 41-50. In control group(n=40), there were 11 males and 29 females, and maximum number of individual belong to age group 31-40 and least belong to age group of 18-30.(Table 1) (Figure 1). BMI values in the study were higher in cases(28.4 ± 4.6 kg/m2) compared to controls (23.8 ± 4.3 kg/m2) and was statistically significant (P = 0.04) (Table 1)

Table 1: Comparison of cases and controls according to age and BMI

VARIABLES	CASE GROUP(n=40)	CONTROL GROUP(n=40)	P value
Age			
18-30	11(27.5%)	4(10%)	
31-40	14(35%)	23(57.5%)	
41-50	3(7.5%)	5(12.5%)	
51-60	12(30%)	8(20%)	
BMI	28.4 ± 4.6 kg/m^2	23.8 ± 4.3 kg/m^2	= 0.04

Figure 1: Gender wise distribution of case and control group.

Table 2 showed that, the case group(hypothyroidism patients) have higher TSH and lower T3 and T4 levels. The hypothyroid patients also presented higher levels of total cholesterol, triglycerides, HDL and LDL than control group(healthy individuals) despite the age and BMI to be similar between groups.

Table 2: Comparison of laboratory data of case and control group.

	CASE GROUP	CONTROL GROUP
TSH(mlU/L)	13.24±2.65	1.65 ± 10.3
T3(nmol/L)	0.51±0.12	1.61 ± 1.06
T4(pmol/L)	18.6±0.82	84.23±26.30
Total cholesterol(mg/dl)	272.5±35.91	159.3±25.75
Triglycerides(mg/dl)	146.5±47.69	104±28.03
HDL(mg/dl)	48.5±10.12	65.52±14.35
LDL(mg/dl)	197.8±36.79	77.69±24.70

As seen in table 3, inflammatory cytokines levels were significantly higher in hypothyroidism patients(Case group), when compared to control group.

Table 3: Comparison of Inflammatory cytokines level in Case and control group.

	CASE GROUP	CONTROL GROUP
IL-6(pg/ml)	92.10±5.92	52.43±5.02
TNF-α(pg/ml)	139.8±8.78	86.23±5.89

Correlation between IL-6 and lipids in Hypothyroid patients was evaluated in table 4. There was a positive correlation was observed in IL-6 with total cholesterol.

Table 4: Correlation between IL-6 and lipids in Hypothyroid patients.

VARIABLES	**IL-6(pg/ml) (p value)**
Total cholesterol(mg/dl)	0.003
HDL cholesterol(mg/dl)	-

LDL cholesterol(mg/dl)	0.009
Triglycerides(mg/dl)	-

DISCUSSION

Hypothyroidism is by far the most prevalent form of thyroid disorder and is more common in women [16]. 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 [17]. This study has investigated the association of hypothyroidism with inflammatory cytokines and lipid profile.

A total 80 individuals participated in this study. Out of the total, 40 individuals were newly detected hypothyroidism with dyslipidemia and 40 were hypothyroid without dyslipidemia. Both the controls and case group have age and gender were almost matched. Thyroid dysfunction is a common endocrine disorder with its prevalence increasing with age. Hypothyroidism is known to inflict females more than males (Figure 1).

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.[18,19].

In this study BMI was higher in hypothyroid cases. Study conducted by Nivedita Nanda et al (2012) , Kunal B.K[20] et al (2012) 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.

We found higher levels of total cholesterol, LDL cholesterol and triglycerides and lower levels of HDL cholesterol in the case group. These findings are in agreement with results of other recent investigations, which have showed dyslipidemia associated with hypothyroid status[21-23].

A causal mechanism to explain the association between lipid profile alteration and case group is related to the fact that thyroid hormones upregulate the LDL- receptor expression which may have an inflammatory basis. Thus, the low levels of T3 and T4 found in hypothyroidism promote a reduction in catabolism of lipoproteins leading to hypercholesterolemia[24,25].

The levels of inflammatory cytokines (IL-1, IL-6, TNF-α, and IFN-γ) were performed between case and control group. The results showed higher levels of these biomarkers in OH subjects indicating the occurrence of a low-grade inflammatory state that is in consonance with atherosclerosis development.

It is widely recognized that OH is associated with increased risk of atherosclerosis. Hyperlipidemia is one of the major risk factors leading to early atherosclerotic vascular diseases. Atherosclerosis has been considered a chronic inflammatory disease, involving both the innate and adaptive immune systems, which modulate the initiation and progression of the lesions, and potentially devastate thrombotic complications[26,27]. TNF-a along with IFN-g and IL-1 stimulate IL-6 production by smooth muscle cells. IL-6 gene transcripts are expressed in human atheromatous lesions, and IL-6 is the main hepatic stimulus for CRP production[28].

Hypothyroidism can predispose systolic and diastolic cardiac dysfunction, increased peripheral vascular resistance, endothelial dysfunction, altered coagulopathy, and dyslipidemia resulting in atherosclerosis [29]. Thyroid hormones can influence homocysteine metabolism by regulating the methylenetetrahydrofolate reductase (M THR) [30,31].

Therefore, the potential causal relationship between inflammatory cytokines and hypothyroidism requires further investigation. Most of the evidence on the relationship between inflammatory cytokines and hypothyroidism comes from observational studies, which are prone to reverse causality, selection bias, and confounding factors. Therefore, more research using innovative methods is needed [32].

Our data suggest that higher lipid concentrations are associated inflammatory status observed in hypothyroidism. It is also essential to assess the progression to the clinical state and to finalize the course of treatment.

CONCLUSION

This study demonstrates that hypothyroidism is associated with significant dyslipidemia and elevated inflammatory cytokines. Regular monitoring of lipid profiles and inflammatory markers, along with timely thyroid hormone replacement therapy, is essential for reducing cardiovascular risk in hypothyroid patients. Further research on larger populations is warranted to explore the mechanisms underlying these changes and the benefits of therapeutic interventions.

Declarations:

Conflicts of interest: There is not any conflict of interest associated with this study

Consent to participate: There is consent to participate.

Consent for publication: There is consent for the publication of this paper.

Authors contributions: Author equally contributed the work.

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