International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2016): 79.57 | Impact Factor (2017): 7.296

Correlation of Subclinical Hypothyroidism and its Relation with Various Inflammatory Markers

Subhashini Srinivas[1], Teena Eugene[2], Karkuzhali[3], Khowsalya Subrajaa[4]

[1]Assistant Professor Department of Pathology Sree Balaji Medical College

[2]Senior Resident Department of Pathology Sree Balaji Medical College

[3]Professor and Head of the Department of Pathology Sree Balaji Medical College

[4]Blood Bank Officer Kamakshi Memorial Hospital, Chennai

Abstract: ***Introduction: Subclinical hypothyroidism shows the mimic reaction more like to frank hypothyroidism which creates the dilemma. Inflammatory markers can be helpful in assessment of adverse effects of subclinical hypothyroidism, are not very well studied in the past. So the aim of this study was to investigate the role of inflammatory markers in Subclinical hypothyroidism patients. Materials and Methods: The study population consisted of 154 patients with recently diagnosed subclinical hypothyroidism and 100 healthy controls. TSH, FT4 & T3 were estimated by enzyme linked Immunosorbent assay (ELISA) for diagnosis of subclinical hypothyroidism. Total cholesterol, triglycerides, and HDL-C were estimated by spectrophotometric method. LDL – C was calculated by Friedewald formula. Inflammatory markers (ESR, C-reactive protein & Interleukin 6) were also estimated by enzyme linked Immunosorbent assay (ELISA). Results: In this study the level of TSH Mean ± SD (11.12±4.17 vs 2.73±0.80) and T3 Mean ± SD (0.96±0.17 vs 1.08±0.26) were significantly higher (<0.001) in subclinical hypothyroidism. Serum concentration of FT4 was not significantly different between the groups. Total cholesterol, triglycerides, and LDL-C were significantly higher in patients group. While the level of HDL-C was significantly lower in SCH patients compared to euthyroid group. TSH level was positively correlated with inflammatory markers in subclinical hypothyroidism, which were significantly different in subclinical hypothyroidism. Conclusion: This study suggests that subclinical hypo-thyroidism patients have increased inflammatory markers along with dyslipidemia and due to that future risk of further development of cardiovascular disorder can occur. Level of inflammatory markers increases in patients as disease progress.***

1. Introduction

Sub Clinical Hypothyroidism (SCH) is a clinical state defining the function of thyroid gland as mildly low with either minimal symptoms or no symptoms of hypothyroidism [1]. Declined thyroid function instigates the thyroid stimulating hormone (TSH) to increased because stimulation of pituitary gland. SCH is characterized by increased serum thyrotropin (TSH) level, while levels of serum free thyroxine (FT4) and tri iodothyronine (T3) remain normal [2]. SCH is common clinical disorder which is expressed by few to some symptomatic characteristics of hypothyroidism worldwide. Clinical Symptoms may or may not be present in SCH as in overt hypothyroidism [3]. India is not an exception as its prevalence varies from 9 to 11.4% in adult population [4]. It is more prominent in females rather than males [5]. SCH is confirmed by laboratory diagnosis of serum picture of elevated thyroid stimulating hormone (TSH) and normal serum concentration of free thyroxin (FT4) and total Triiodothyronine (T3) [6].

As the word suggests subclinical, thyroid symptoms are not well defined in SCH patients as present in overt hypothyroidism. Dyslipidemia has strong association with overt hypothyroidism due to reduced numbers of LDL receptors in the liver, by which fractional LDL-C is decreased, which is proved by previous study [7]. So it is still a topic of debate that SCH patients have abnormal serum concentration of lipid profile or not. Previous studies indicated that no disbalance occurs in normal serum concentration of lipid profile in patients of subclinical hypothyroidism [8,9]. While on contrary to it has been described that due to subclinical hypothyroidism alteration in lipid profile can present [10].

Due to presence of altered lipid profile, patients may also have further development of cardiac disease. Atherosclerosis being an inflammatory disorder, associated with accumulated cholesterol concentration might be developed in future in subclinical [11]. Some of the inflammatory markers are quite effective and well known future predictors of cardiovascular risk [12].

C-reactive protein CRP is an effective tool for diagnosis of cardiac risk [13]. Activity of CRP is induced by a specific cytokine; interleukin-6 (IL-6), important and well established marker for assessment of inflammation [14]. Studies in the past have created confusion with respect to such inflammatory markers in subclinical hypothyroidism from no risk to definite risk [15,16].

Therefore the aim of this study was to investigate the relationship between subclinical hypothyroidism and inflammatory markers (ESR, C-reactive protein and interleukin-6).

2. Materials and Methods

A cross-sectional study was carried out with 154 patients (91 females & 63 males), with newly diagnosed subclinical Hypothyroidism without having any previous medical history of any disease e.g. overt hypothyroidism, inflammatory disorder, diabetes, hypertension, cardiovascular risk factor, pregnancy, smoking etc. which

were compared with 100 healthy controls (62 females & 38 males) [17]. A group of 20-45 years of age of patients as well as euthyroid groups were enrolled for the study. This study was ethically approved by the institutional ethical committee. Age and Body mass index was quantified by bioelectrical impedance analysis. TSH, fT4, T3, total cholesterol (TC), triglycerides (TG), HDL-C, LDL-C, levels along with inflammatory markers mainly interleukin-6, C-reactive protein and ESR were estimated in all participants.

Every participant voluntarily participated in the research work. A written consent was taken from every patient. Fasting Serum sample from cases as well as control group was obtained to determine the following investigations. Thyroid function tests were measured by (Avantor Performance Materials, India) kit using enzyme linked Immunosorbent assay (ELISA). Normal range of thyroid tests was TSH – 0.39–6.16 (µIU/ml), free T4 – 0.8-2.0 (ng/dl) and T3 – 0.52-1.85 (ng/ml). Patients with TSH levels > 6.2 (µIU /ml) with normal FT4 & T3 values were accepted to have SCH [18]. Total cholesterol, triglycerides, HDL-cholesterol was investigated by CHOD/POD method, GPO-PAP method and CHOD-POD/ Phosphotungstate method respectively. (Erba Mannheim) kits were used for the investigation. LDL-C was calculated by means of Friedewald formula [19]. An inflammatory marker such as interleukin-6 and C-reactive protein were estimated by enzyme linked Immunosorbent assay Kits were used respectively for investigation in aforesaid population [20,21]. Erythrocyte sedimentation rate (ESR) was estimated by westergren's tube method [22].

3. Statistical Analysis

All the baseline characteristics (age, body mass index, TSH, FT4, T3, total cholesterol, triglycerides, HDL-C, LDL-C, ESR, C reactive protein and interleukin-6) were expressed in Mean ± SD. To analyse the difference among different parameters of subclinical hypothyroidism patients group and control group Unpaired student's t-test was used. An association betwen TSH and inflammatory markers (C reactive protein, interleukin-6, and erythrocyte sedimentation rate) in the subclinical hypothyroidism group were analysed using pearson correlation coefficient test. A p-value <0.05 was considered statistically significant.

4. Results

Total 154 patients (91 females and 63 males) with subclinical hypothyroidism were enrolled for the study and compared with 100 euthyroid controls (62 females and 38 males). There were no significant differences in age, between groups. There was statistically significant difference in Body mass index between patients with subclinical hypothyroidism and healthy control group. The Mean±SD (27.76±3.17) was higher in SCH patients group compared to control group Mean±SD (22.91±1.71). The p-value was <0.05, which is significant. Subclinical hypothyroidism group defined by higher TSH concentration (>6.16) along with normal level of FT4 & T3. TSH level was significantly higher in SCH group compared with control group Mean ± SD (11.12±4.17 vs 2.73±0.80). FT4 level was not significantly different in SCH group Mean ± SD (1.16±0.25 vs 1.15±0.22) while T3 concentration was significantly different compared with control group Mean±SD (0.96±0.17 vs 1.08±0.26). [Table/Fig-1].

TC, Triglycerides, HDL-C, and LDL-C levels were significantly different in SCH patients compared to controls. Total cholesterol was significantly higher in SCH group compared with control group Mean ± SD (206.65±23 vs 186.56±16.57). Other parameters of lipid profile like triglycerides Mean±SD (126.65±26.42 vs 105.42±23.36), and LDL-C Mean ± SD (137.06±21.41 vs 113.70±18.59) were also significantly higher in SCH group. While serum concentration of HDL-C Mean ± SD (42.38±2.52 vs 47.10±4.7) was significantly lower in SCH group [Table/Fig-1].

Table 1: Baseline characteristic between subclinical hypothyroid & control group :

: Baseline cha	SCH Group (154)	Control (100)	p-Value
AGE (yrs)	35.98±3.47	35.32±3.98	NS
BMI (kg/m2)	27.76±3.17	22.91±1.71	<0.05
TSH (µIU/ml)	11.12±4.17	2.73±0.80	<0.05
FT4 (ng/dl)	1.16±0.25	1.15±0.22	NS
T3 (ng/ml)	0.96±0.17	1.08±0.26	<0.05
Total cholesterol (mg/dl)	206.65±23	186.56±16.57	<0.05
Triglycerides (mg/dl)	126.65±26.42	105.42±23.36	<0.05
HDL-C (mg/dl)	42.38±2.52	47.10±4.7	<0.05
LDL-C (mg/dl)	137.06±21.41	113.70±18.59	<0.05

Table 2: Makers of Inflammation

	SCH Group	Control	p-Value
Interleukin-6(pg/ml)	9.30±2.54	4.04±0.70	<0.05
C- RP (ng/ml)	5.2±1.78	2.45±0.69	<0.05
ESR(mm/hr)	20.81±3.02	8.81±3.53	<0.05

Table 3: Correlation between TSH and inflammatory markers in SCH

Inflammatory markers	R-value	p-value
Interleukin -6	0.66	<0.05
C- reactive protein	0.59	<0.05
ESR	0.19	<0.05

In case of inflammatory markers IL-6, C-RP and ESR also were significantly higher in SCH group when compared with control group. IL-6 Mean ± SD (9.30±2.54 vs 4.04±0.70) and C-reactive protein Mean ± SD (5.2±1.78 vs 2.45±0.69) was significantly higher in SCH group compared with control group. ESR Mean ± SD (20.81±3.02 vs 8.81±3.53) was also significantly higher in SCH group [Table/Fig-2]. Inflammatory markers were positively co related ESR (r=0.19), C-reactive protein (r=0.59), and IL-6 (r=0.66) with TSH in subclinical hypothyroidism [Table/Fig-3].

5. Discussion

This study supports the hypothesis that subclinical hypothyroidism is associated with relatively increased inflammatory markers levels along with dyslipidemia compared to control group and they can give rise to future development of cardiovascular risk in SCH. The level of inflammatory markers was found to be elevated in patients group as compared to control in this study. CRP is a very well established, strong predictor of cardiovascular events

[23]. Its levels rise rapidly in various pathological conditions and various inflammatory disorders e.g. overt hypothyroidism [24], myocardial infarction [25] and rheumatoid arthritis [26]. In this study both case and control group did not have any medical history of inflammatory disease. So the rise of inflammatory markers in SCH group was not due to result of any pathological situations.

Several studies done in the past, have produced varied results regarding the subclinical hypothyroidism and disturbed lipid parameters, which are still not clearly defined [27,28]. Higher concentration of total cholesterol, triglycerides and LDL cholesterol in SCH patients in this study were also observed by various studies [29,30]. Erdem et al., supported this study by observing the decreased concentration of HDL cholesterol [31]. C reactive protein an acute phase reactant is known to influenced by several factors e.g. body mass index [32] and cholesterol concentration [33], etc. which may be associated with subclinical hypothyroidism [34]. This study suggests that level of inflammatory markers was relatively higher in SCH patients than control group and they were positively correlated with TSH level in SCH group. Studies have described an elevated concentration of C reactive protein in SCH patients [35,36] which was positively correlated with TSH concentration [37].

Duntas et al., suggested that SCH has been strongly associated with dyslipidemia and cardiovascular risk along with abnormal C- reactive protein level [38]. Xiang et al., concluded that SCH patients have been presented increased symptoms of CVD as associated with altered lipid profile and hs-CRP [39]. Vaya et al., supported this study by reporting that CRP level was significantly higher in SCH [40]. IL-6, a pro inflammatory cytokine, indirectly promotes atherogenesis by increasing hepatic production of C-reactive protein [41]. Taddai S et al., concluded that subclinical hypothyroidism patients were characterized by higher C- reactive protein and interleukin 6 [42]. IL-6 release is stimulated by thyroid stimulating hormone in adipocytes [43]. Significantly higher concentration of interleukin 6 in SCH patients in this study was supported by Turemen et al., study [44].

6. Conclusion

On the basis of data, observed in this study, it can be suggested that SCH patients are associated with dyslipidemia and increased inflammatory markers. Future development of cardiovascular risk may occur due to that. By the outcomes of this study we can give torch to the clinicians working in their general practice that subclinical hypothyroidism should be treated in early detection to avoid the risk of cardiovascular diseases. Our findings contribute to the growing evidence about the adversity created due to impact of subclinical Hypothyroidism. Though, our findings require confirmation in additional cohorts. As this study has some limitations like sample size and few inflammatory markers, so the study with more establishing tool to assessment of cardiovascular risk should be tested to establish this fact. Further studies are also required for a general assumption on the aspects that correlation between obesity and variations of normal thyroid function, exist or not with more focus on mechanistic prospects.