Can C - reactive protein As a Marker for Fasting Hyperinsulinemia in Subclinical Hypothyroidism

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Abstract: ***Objective: Subclinical hypothyroidism is a sub clinical entity with elevation of TSH and without elevation of T3 and T4. The purpose of this case – control study was to corelate C-reactive protein to Subclinical hypothyroidism with and without Fasting hyperinsulinemia. Method: This study was done at the Department of Medicine DR. PSIMS & RF, Chinaoutpally, A.P.India between Jan 2012 to Dec 2012. 100 patients (50 cases, 50 controls) above 18 years of age were included in the study. The TSH reference range was 0.4-4.5 µIU/ml and serum free thyroxine level between 5.13 – 14.06 µg/dl. Results: C-reactive protein levels were found to be significantly higher in Subclinical hypothyroidism patients with Fasting hyperinsulinemia than Subclinical hypothyroidism alone. Conclusions: Patients with Subclinical hypothyroidism with high fasting insulin levels have higher serum CRP, total and LDL-cholesterol levels than controls.***

Keywords: Subclinical hypothyroidism, C-reactive protein, Insulin

1. Introduction

Sub Clinical Hypothyroidism, in which minimal disturbance of thyroid function with either minimal symptoms or no symptoms of hypothyroidism, characterized by elevated serum thyrotropin (TSH) level, with normal serum free thyrosine (FT4) and tri iodo thyronine (FT_3) levels [1] Sub clinical hypothyroidism is a increased risk factor for coronary events, increased lipid levels, increased rates of congestive heart failure [2]. Sub-clinical hypothyroidism (SCH) is a derangement of all metabolisms leads to insulin resistance, elevated lipid levels, haemotological manifestations of increased clot formations and low grade inflammatory response [3]. Based on thyroid dysfunction, the involvement of cardio vascular events and lipid profile changes are proportional to the changes of carbohydrate metabolism, particularly development of insulin resistance [5]. Homeostatic model assessment (HOMA) is a method used for assessing beta-cell function and insulin resistance (IR) from fasting glucose in mg/dl and fasting insulin concentrations in uU/ml [5].The insulin resistance is measured from homeostasis model assessment (HOMA) as (HOMA-IR), calculated from estimations of fasting insulin (U/l) × fasting glucose(mg/dl)/405, as described by Matthews et al [5]. Positive Cut-off value >2.5 and negative <2.5 for assessment of insulin resistance in Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) [6]. Insulin resistance, intern causes changes in hepatic metabolism, particularly in lipid metabolism. The changes in lipid metabolism includes increased cholesterol and very low density lipoprotein (VLDL) synthesis [7] and increased clearance of high density lipoprotein (HDL) [8]. The changes of lipid profile patterns are triggered by insulin resistance in thyroid dysfunction individuals, particularly in hypothyroidism, as made out by Bakker et al [9].

On this background, our study aims at comparing the occurrence of C- Reactive protein in patients with Subclinical hypothyroidism group in relation to fasting hyperinsulinemia, thus, reflecting presence or absence of any additive effect of fasting hyperinsulinemia in Subclinical hypothyroidism in causing major cardiovascular or cerebro vascular complications and lipid abnormalities.

2. Material and Methods

A case – control study was undertaken in the Department of General Medicine, Dr.PSIMS&RF, Chinoutpally, Gannavaram, Krishna (Dt), Andhra Pradesh. 50 diagnosed Subclinical hypothyroidism cases, who attended to our hospital and 50 age, sex matched controls, were included in our study group. All patients survive till the end of study period of one year duration i.e., Jan 2012 to Dec 2012. Diagnosis of Subclinical hypothyroidism cases was done as per the biochemical parameters TSH reference range was 0.4 – 4.5 µIU/L and serum free thyroxine level between 5.13 – 14.06 µg/dl

Thyroid hormones in both cases and controls were estimated. Lipid profile, and C – reactive proteins were also estimated in both cases and controls as for supporting parameters in Subclinical hypothyroidism. The study was approved by the Ethics committee of our college. After fulfilling the inclusion and exclusion criteria, prior consent was obtained from the subjects.

3. Inclusion Criteria

Patients with TSH reference range was > 4.5 µIU/L in cases and < 4.5 µIU/L in controls

Age 18 or older.

4. Exclusion criteria

Patients with diabetes, hypertension, alcohol, heart failure, acute febrile illness, renal, hepatic, malignant disorders, chronic illnesses, asymptomatic infections and smokers

5. Sample collection and analysis

Both heparinised and plain blood samples were collected from each case and control. For analysis of FBS, lipid profile, CRP - serum was used. Serum glucose estimation was done by Trindler's GOD – POD method (commercial kit – ERBA – MANNHEIM), cholesterol estimation was done by CHOD – POD method (commercial kit – ERBA – MANNHEIM), Triglycerides estimation was done by GPO method (commercial kit – ERBA – MANNHEIM), HDL cholesterol estimation was done by APO protein precipitation or PTA method (ERBA – MANNHEIM), and HBA1c estimation was done by Ion exchange resin method (commercial kit – Randox Rx series). All these estimations were performed by Randox Daytona Autoanalyzer. VLDL-c or LDL-c levels of all cases and controls were calculated by using Friedwald's formula. CRP levels in all cases and controls were estimated by slide agglutination method in serial dilutions using serum.

Thyroid function tests were carried out by chemiluminiscence (CLIA) method and the reference values in our laboratory were TSH: 0.4 – 4.5 μIU/L, T_3 – 0.8-2.0 μg/ml T4 – 5.13 – 14.06 μg/dl.

Fasting Insulin levels and HOMA-IR index were also determined in cases and controls.

6. Results

The mean age in cases and controls was 40.26 ± 7.54, among in males was 41.00 ± 7.53 and in females was 39.81 ± 7.64, the percentage of females (62%) were higher than males (38%). The mean BMI in cases was 23.9 ± 1.1and in controls was 23.8 ± 1.09. The mean T_3 among cases was 1.0692 ±0.24 and in controls was 1.2212 ±0.36 (p = 0.0162), mean T_4 among cases was lower 7.6892 ±1.17than mean T_4 in controls 8.6148 ±0.93) with p = 0.05. The mean TSH was also compared among males (6.8079 ± 1.64) with females (8.8045 ± 3.14) p = 0.0139 which was significantly higher. Among cases had mean TSH 8.0858 ± 2.99 than controls mean TSH 2.0874 ± 1.01 (p = 0.05). The mean FBS levels in cases were 87.26 ± 9.62 statistically significant than controls 82.8 ± 8.5 (p: 0.0157). Mean FBS levels of sub clinical hypothyroid males were 87.89 ± 8.67 statistically not significant than controls 84.21 ± 8.57 (p 0.1962). Mean FBS levels of sub clinical hypothyroid females were 86.87 ± 10.27 statistically significant than controls 81.94 ± 8.47 (<0.0434). The mean fasting insulin levels in cases were 14.03460 ± 8.82127statistically significant than controls 5.85176 ± 3.56483 (p: 0.05). Mean fasting insulin levels of sub clinical hypothyroid males were 12.55105±7.30706 statistically significant than controls 4.61653± 3.87469 (p 0.0002). Mean fasting insulin levels of sub clinical hypothyroid females were 14.94387± 9.63397statistically significant than controls 6.60884± 3.1921 (<0.001).

The mean HOMA IR levels in cases were 14.03460 ± 8.82127statistically significant than controls 5.85176 ± 3.56483 (p: 0.05). Mean HOMA IR levels of sub clinical hypothyroid males were 12.55105±7.30706 statistically significant than controls 4.61653± 3.87469 (p 0.0002). Mean HOMA IR levels of sub clinical hypothyroid females were 14.94387± 9.63397statistically significant than controls 6.60884± 3.1921 (<0.001). The mean CRP levels in cases were 3.0906 ±1.87statistically significant than controls 0.7880 ±0.62 (p: 0.05). Mean CRP levels of sub clinical hypothyroid males were 2.7226 ±1.84statistically significant than controls 0.8547 ±0.77 (p 0.0002). Mean CRP levels of sub clinical hypothyroid females were 3.3161 ±1.88 statistically significant than controls 0.7471 ±0.52 (<0.001). The mean cholesterol in sub clinical Hypothyroidism cases was 197.06 ±42.83and in controls was 178.38 ±32.93 (p<0.05) which showed cholesterol is more significant elevation in sub clinical Hypothyroidism cases, The mean triglyceride level in cases was 196.90 ±87.89 and in controls was 138.72 ± 67.63 (p <0.05) which showed mean triglyceride level is more significant elevation in sub clinical Hypothyroidism cases, The mean LDL – cholesterol level in cases was 130.12 ± 46.91and in controls was 105.68 ± 34.63 (p <0.05) which showed mean LDL – cholesterol level is more significant elevation in Sub Clinical Hypothyroidism cases, The mean HDL – cholesterol level in cases was 34.22 ± 8.47and in controls was 37.76 ± 8.39 (p <0.05) which showed mean HDL – cholesterol level is more significant reduction in sub clinical Hypothyroidism cases.

Table 1: Age distribution

Variable	*Cases n 50*	*Controls n 50*	*P value*
Mean age	40.26 ± 7.54	40.26 ± 7.54	
Males	41.00 ± 7.53	41.00 ± 7.53	
Females	39.81 ± 7.64	39.81 ± 7.64	
BMI	23.9 ± 1.1	23.8 ± 1.09	
FBS	87.26 ± 9.62	82.8 ± 8.5	<0.0157
Males n 19	87.89 ± 8.67	84.21 ± 8.57	0.1962
Females n31	86.87 ± 10.27	81.94 ± 8.47	<0.0434

Table 2: Mean thyroid levels in cases and controls

Variable	*Cases*	*Controls*	*t value*	*P value*
TSH	8.0858 ± 2.99	2.0874 ± 1.01	13.4125	<0.05
T4	7.6892 ± 1.17	8.6148 ± 0.93	4.3668	<0.05
T3	1.0692 ± 0.24	1.2212 ± 0.36	2.4464	0.0162

Table 3: Mean fasting insulin levels in cases and controls

Variable	*Cases*	*Controls*	*t value*	*P value*
Total	14.03460 ± 8.82127	5.85176 ± 3.56483	6.0815	<0.001
Males n 19	12.55105± 7.30706	4.61653± 3.87469	4.1817	0.0002
Females n 31	14.94387± 9.63397	6.60884± 3.1921	4.5726	<0.001

Table 4: Mean HOMA IR levels in cases and controls

Variable	*Cases*	*Controls*	*t value*	*P value*
Total	3.0252 ± 1.9608	1.2146 ±0.7758	6.0715	0.0001
Males	2.6905 ±	0.9763 ±	4.1997	0.0002

n 19	1.54	0.88		
Females n 31	3.2303 ± 2.17	1.3606 ± 0.67	4.5690	0.0001

Table 5: Mean CRP levels in cases and controls

Variable	*Cases*	*Controls*	*t value*	*P value*
Total	3.0906 ± 1.87	0.7880 ± 0.62	8.2398	0.0001
Females n 3	3.3161 ± 1.88	0.7471 ± 0.52	7.3038	0.0001
Males n 19	2.7226 ± 1.84	0.8547 ± 0.77	4.0716	0.0002

Table 6: Mean lipid levels in cases and controls

Variable	Cases	Controls	t value	P value
Cholesterol	197.06 ± 42.83	178.38 ± 32.93	2.4449	0.0163
Triglyceride	196.90 ± 87.89	138.72 ± 67.63	3.7095	0.0003
LDL	130.12 ± 46.91	105.68 ± 34.63	2.9639	0.0038
HDL	34.22 ± 8.47	37.76 ± 8.39	2.0997	0.0383

7. Discussion

In this case control study of the association between markers of systemic inflammation and fasting insulin level among subclinical hypothyroid patients, we observed an association between elevated levels of CRP and fasting hyperinsulinemia in subclinical hypothyroid patients.

The mean age in sub clinical hypothyroid and control group was 40.26 ± 7.54, and 78% of these groups were noticed more between the age group of 21 – 40 years.This study shows the mean TSH levels of sub clinical hypothyroid group 8.0858 ± 2.99 was more than normal subjects. 2.0874 ±1.01 ,when compared with B.M.Singh et. al study,[11] the results were similar that is more in sub clinical hypothyroid group.Mean fasting insulin levels were more in sub clinical hypothyroid group (14.03460 ± 8.82127) compared to controls(5.85176 ±3.56483),statistically significant elevations are compared with B.M.Singh et. al study. Insulin resistance by HOMA-IR method was seen in 36% of sub clinical hypothyroid group when compared to controls 8%, statistically significant elevation in sub clinical hypothyroid group.Mean HOMA-IR levels in subclinical hypothyroid group was 3.0252 ± 1.9608 than compared to controls 1.2146 ±0.7758,statistically significant elevation in sub clinical hypothyroid group, when compared to B.M.Singh et. al study[11] our mean values are on higher side.The insulin resistance by HOMA-IR method in subclinical hypothyroid cases was 36 % when compared to controls was 8%, statistically significant was shown in subclinical hypothyroid group.The elevated CRP levels in HOMA-IR more than 2.5 in sub clinical hypo thyroid cases was 22% when compared to HOMA IR <2.5 in sub clinical hypothyroid cases was 6%, statistically significant elevation of CRP was observed in subclinical hypothyroidism with insulin resistance.This findings were contradictory to study by Al syed et. al[12] group, they studied HOMA IR levels in subclinical hypothyroidism in women only.Females showed increase in mean serum fasting insulin levels14.94387± 9.63397 in compared to males in subclinical hypothyroidism group. Serum total cholesterol, triglycerides and LDL were elevated in subclinical hypothyroid group compared to controls and HDL levels were decreased in subclinical hypothyroid group compared to controls, these findings are correalated with B.M.Singh study [11]. When compared to Andreas festa et al study,our study shows that CRP levels are significantly elevated in individuals having insulin resistance[13].The underlying mechanism responsible for elevated CRP levels might be increased stimulation of adipose tissue to release cytokines which triggers hemostatic, haemodynamic and metabolic changes ultimately causing insulin resistance.

8. Conclusions

CRP levels were found to be significantly higher in individuals with insulin resistance by 22% in subclinical hypothyroid patients. 78% of subclinical hypothyroid patients belong to 21 – 40 years age group. Female to male ratio were found to be 1.63: 1.In subclinical hypothyroid patients with elevated insulin resistance by HOMA IR method in 36% . Females with high mean fasting insulin levels with high mean CRP in subcinical hypothyroidism patients had developed significantly elevated lipid levels. Larger studies are required to clarify the significance of development of early insulin resistance before the development of diabetes and to consider the fasting insulin levels and serum CRP as regular and routine screening markers to identify sub clinical target organ damage in subclinical hypothyroidism patients.

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