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ASSOCIATION OF SUBCLINICAL HYPOTHYROIDISM WITH HSCRP, SERUM INSULIN AND INSULIN RESISTANCE : A HOSPITAL BASED STUDY.

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ABSTRACT

Background: Thyroid disorders are one of the most prevalent endocrinopathies across the world. Overt hypothyroidism has been associated with cardiovascular disease, but the association of subclinical hypothyroidism with cardiovascular disease is unclear and controversial. Therefore, the present study was aimed to determine the level of HsCRP and insulin resistance in subclinical hypothyroid subjects and compare it with healthy controls.

Materials and Methods: An observational cross-sectional study was conducted involving 70 Subclinical hypothyroid patients (SCH) and 100 healthy controls. Newly diagnosed cases of subclinical hypothyroidism not taking any treatment, in the age group of 20 – 60 years were included in the study. 100 healthy cases of same age group were taken as control

Fasting blood sample from both the groups of patient was collected for estimation of T3, T4, TSH, total cholesterol (TC), triglycerides, high density lipoprotein (HDL), high sensitive C reactive protein (HsCRP), lipoprotein A , fasting blood glucose and insulin.

Results: The mean value of serum TSH are significantly higher in subclinical hypothyroid (SCH) patients (TSH 7.90 ± 1.25 µIU/ml) compared to that of control participants (TSH 2.70 ± 0.77 µIU/ml).The serum level of T3 and T4 of the two groups were within the normal reference range. The mean serum HsCRP level of patients with SCH was higher than those of control (4.19 ± 0.68 mg/L and 1.71 ± 0.41 mg/L respectively $p<0.0001$) The mean insulin level of subject with SCH were also higher than that of control subjects (7.91 ± 1.79 µu/l and 5.55 ± 1.70 µu/l respectively, $p<0.0001$). HOMA-IR in the SCH group was significantly higher than the control group (1.78 ± 0.47 and 1.24 ± 0.39 respectively, $p<0.0001$). Pearson correlation test was performed among TSH, insulin, HOMA-IR, HsCRP in the subclinical group. We found positively correlation of TSH with serum insulin, HOMA-IR and HsCRP .The correlation of TSH with insulin level and HOMA-IR was statistically significant whereas with HsCRP the p value was 0.06.

Conclusions: we concluded that low-grade inflammation starts in the early stages of hypothyroidism, resulting in elevated HsCRP level which may result in the future development of atherosclerosis leading to cardiovascular morbidity.

Keywords:, Subclinical hypothyroidism, High sensitive C-reactive protein, Insulin resistance.

Introduction

Thyroid disorders are one of the most prevalent endocrinopathies across the world. Subclinical hypothyroidism (SCH) is defined as mildly elevated serum thyroid stimulating hormone (TSH) with normal level of serum thyroxine (T4) and triiodothyronine (T3). SCH is usually asymptomatic and is detected either on routine screening of thyroid stimulating hormone (TSH) or when non-specific symptoms are evaluated.(1) The continuing debatable aspects regarding SCH are the associated dyslipidaemic state, atherosclerosis and cardiovascular risk underlying the pro-inflammatory state in these patients. Inflammation is believed to play an integral part in the progression of atherosclerosis leading to the complications.(2)

High-sensitivity C-reactive protein (HsCRP) is more sensitive non-specific marker of inflammation and tissue damage than a standard CRP test.(3) Several studies have shown an association between insulin resistance and overt hypothyroidism, but there is controversy as to whether this association is also present in subclinical hypothyroidism. Therefore, the present study was aimed to determine the level of HsCRP and insulin resistance in subclinical hypothyroid subjects and compare it with healthy controls.

MATERIALS AND METHODS

A cross sectional observational study was conducted in the department of biochemistry and medicine of SGT medical college hospital and research institute, Gurugram. 70 subclinical hypothyroidism cases and 100 healthy controls were included in the study. The study was approved by the ethical committee. Informed consent was taken from all the participants.

Newly diagnosed cases of subclinical hypothyroidism not taking any treatment, in the age group of 20 – 60 years were included in the study. 100 healthy patient of same age group were taken as control. Patient on treatment for hypothyroidism, age less than 20 years and more than 60 years, patients with history of any systemic illness like diabetes mellitus, renal failure, liver disorders and other chronic illness, and patient on chronic medications like antiepileptic or anti TB drugs were excluded from the study..

Fasting blood sample from both the groups of patient was collected for estimation of T3, T4, TSH, total cholesterol (TC), triglycerides, high density lipoprotein (HDL), high sensitive C reactive protein (HsCRP), lipoprotein A, fasting blood glucose and insulin.

Estimation of biochemical parameter i.e T3, T4 & TSH and insulin by Chemiluminescence immunoassay , serum HsCRP by ELISA Kit (Calbiotech), blood glucose by GOD-POD method using autoanalyzer, total cholesterol, triglycerides and high density lipoprotein by enzymatic kit using autoanalyzer and lipoprotein A by Elisa kit.

Assessment of insulin-resistance i.e. Homeostasis model assessment (HOMA) index for insulin resistance (HOMA-IR) was calculated with the formula [HOMA-IR = fasting plasma insulin (μU/ml) x (fasting plasma glucose (mmol/L)/22.5]

Statistical analysis: Results were expressed as mean ± SD range values. Unpaired ‘t’ test was used to compare different biochemical parameters between subclinical patients and healthy controls. Pearson’s correlation coefficient was used to assess the relationship between different variables.

Statistical analysis was done using SPSS 21 software.

Result

The study included two groups i.e. subclinical hypothyroid cases and healthy controls. Out of 70 subclinical cases 16 were male and 54 female whereas out of 100 healthy controls 20 were male and 80 were female. The mean age of the subclinical cases was 33.61 ± 10.09 years whereas the age of controls was 32.54 ± 9.88 years

The mean value of serum TSH are significantly higher in subclinical hypothyroid (SCH) patients (TSH 7.90 ± 1.25 µIU/ml) compared to that of control participants (TSH 2.70 ± 0.77 µIU/ml).The serum level of T3 and T4 of the two groups were within the normal reference range.

The mean serum HsCRP level of patients with SCH was higher than those of control (4.19 ± 0.68 mg/L and 1.71 ± 0.41 mg/L respectively p<0.0001). The mean insulin level of subject with SCH were also higher than that of control subjects (7.91 ± 1.79 µu/l and 5.55 ± 1.70 µu/l respectively, p<0.0001). The mean value of fasting blood sugar was similar in the two groups. HOMA-IR in the SCH group was significantly higher than the control group (1.78 ± 0.47 and 1.24 ± 0.39 respectively, p<0.001). The mean values of total cholesterol, triglycerides and high density lipoprotein were significantly higher in subclinical hypothyroid group than in control group. Lipoprotein A levels in both the groups were statistically similar. (Table 1)

Parameters	Controls (n=30)	Subclinical (n=70)	p value
Age (yrs)	32.54±9.88	33.54±9.88	0.74
Sex	M:F=1:4	M:F=1:3.4	0.72
BMI (kg/m^2)	24.47±3.51	27.10±5.25	0.0001
T3 (ng/ml)	1.12± 0.16	1.38±0.25	<0.0001
T4 (µg/ml)	7.67±1.16	8.04±1.06	0.18
TSH (µIU/ml)	2.70±0.77	7.90±1.25	<0.0001
FBS (mmol/l)	5.0±0.19	5.01±0.22	0.92
Insulin(µu/l)	5.55±1.70	7.91±1.79	<0.0001
HOMA	1.24±0.39	1.78±0.47	<0.0001
HsCRP (mg/l)	1.71±0.41	4.19±0.68	<0.0001
TC (mg/dl)	145.85±17.79	170.97± 32.13	<0.0001
TG (mg/dl)	120.63±15.12	144.52±22.02	<0.0001
HDL (mg/dl)	45.82±3.20	43.52±4.23	0.0008
Lp(A) (mg/dl)	14.86±2.79	15.56±2.03	0.46

Table 1: Anthropometric and biochemical parameters of subclinical cases and controls

Pearson correlation test was performed among TSH, insulin, HOMA-IR, HsCRP in the subclinical group. We found positively correlation of TSH with serum insulin, HOMA-IR and HsCRP .The correlation of TSH with insulin level and HOMA-IR was statistically significant whereas with HsCRP the p value was 0.06. (Table 2) (Fig 1-3)

Parameters	Pearson r	95% CI	R^2	P value	Significance
Insulin	0.64	0.48 – 0.76	0.41	<0.0001	Yes
HOMA-IR	0.64	0.47 – 0.76	0.41	<0.0001	Yes
HsCRP	0.22	-0.014-0.43	0.049	0.06	No

TABLE 2: Serum TSH correlation with serum Insulin, HOMA, HsCRP in subclinical hypothyroid patient

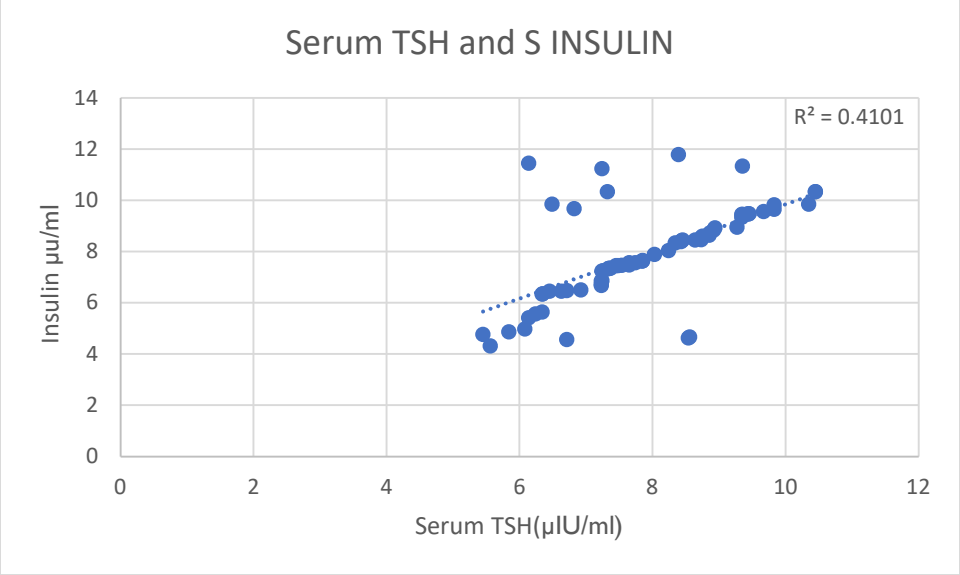

Fig 1: Pearson correlation of TSH with Insulin in subclinical hypothyroid cases

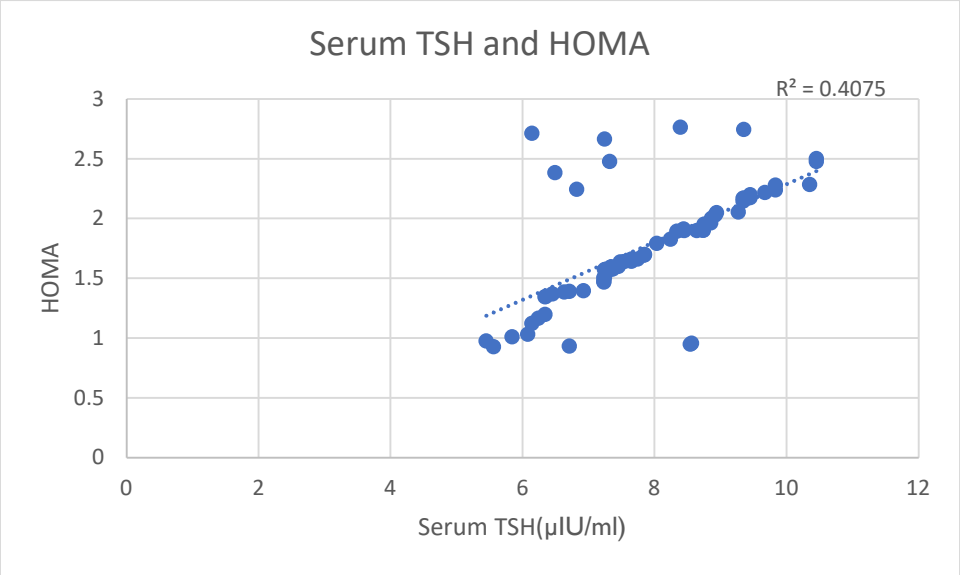

Fig 2: Pearson correlation of TSH with HOMA in subclinical hypothyroid cases.

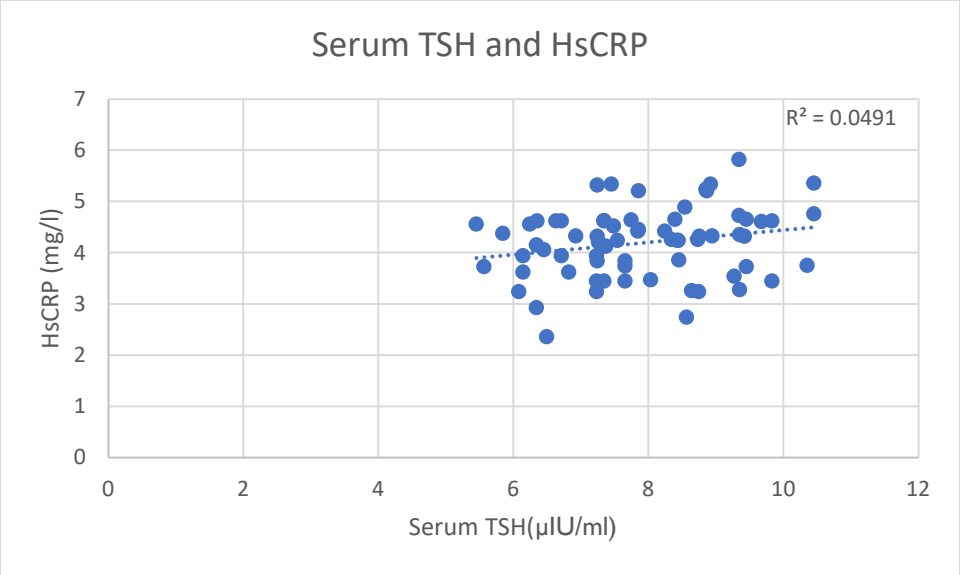

Fig 3: Pearson correlation of TSH with HsCRP in subclinical hypothyroid cases

Discussion

The incidence of subclinical hypothyroidism far exceeds the number of overt thyroid cases. In recent times, SCH is being diagnosed more frequently because of universal screening of the females during pregnancy. **T**hyroid disorder leads to dyslipidaemias and insulin resistance. The development of insulin resistance leads to many of the metabolic abnormalities. As the thyroid hormone dysfunction starts, the liver does not function properly and produces excess cholesterol, fatty acid and triglycerides which lead to the risk of heart disease.(4) Thyroid hormones exert profound effects in the regulation of glucose homeostasis. These effects include modifications of circulating insulin levels, counterregulatory hormones, intestinal absorption, hepatic production and uptake of glucose by peripheral tissue (fat and muscle). All these changes produce insulin resistance which is the culprit for many complications mainly cardiovascular.

In our study increased levels of TC and triglycerides, were seen in SCH cases in comparison to the control group, similar finding were also observed in the study done by Sridevi A et al and Kvetny l et al,(5)(6) In the Rotterdam study, TC was lower in SCH patients as compared to euthyroid patients.(7) Other studies done by Duntas et al (2002), Serter et al (2004) and A Squizzato et al (2005) found that there is hypercholesterolemia & dyslipidemia in hypothyroid patients .(8) (9) (10) HDL levels were lower in SCH group in comparison to control group in our study which was similar to the finding observed by Erdem et al. (11)

In the present study elevated level of HsCRP in SCH subjects were seen compared to the healthy controls which was consistent with Sapna Vyakaranam et al, Roy et al, Mahto et al and Tuzku et al. who also observed increased levels of HsCRP in subclinical hypothyroid subjects compared with euthyroid subjects. (12)(13) (14)(15)

In contrary , Perce et al and Hueston et al in their study found no difference in HsCRP level

between patients with SCH and euthyroid controls.(16)(17)).
In our study, the serum insulin level and subsequently HOMA-IR were significantly higher in the SCH group than the control group. Dessein PH et al, Annemieke et al, Owecki et al, Eirini Maratou et al, reported similar results which are in good agreement with our findings.(18)(19)(20)(21)
Our study showed that TSH levels positively correlated with insulin ($r=0.64$, $p<0.0001$), HsCRP ($r=0.22$, $p<0.06$) and HOMA-IR ($r= 0.64$, $p<0.0001$) in subclinical hypothyroid patients.
In the study done by Uppu SD et al and Sharma R et al it was found that the levels of HsCRP was significantly higher in SCH group than euthyroid group and it had positively correlation with TSH level in SCH group.(22) (23)

CONCLUSION

Subclinical hypothyroidism due to its asymptomatic nature usually goes undiagnosed. Therefore, universal screening over 40 years of age for hypothyroidism may help to pick up these subclinical cases and look for the inflammatory marker (HsCRP) which is the cause of our concern for cardiovascular complications. This may be helpful in initiating treatment at an early stage and therefore decreasing the morbidity and mortality caused by it. However, further studies are needed to illustrate the definite role of HsCRP leading to cardiovascular morbidity in patients with Subclinical Hypothyroidism.

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