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Fetuin-A and hs-CRP Levels in Subclinical Hypothyroidism

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ABSTRACT

Subclinical Hypothyroidism is a clinical condition in which levels of TSH increased with normal FT4 levels. It is asymptomatic in general may progress to overt hypothyroidism. Fetuin-A is liver derived glycoprotein which act as inhibitor of ectopic mineralization and can be contributing factor in insulin resistance or in metabolic syndrome. High-sensitivity C-reactive protein (hs-CRP) in inflammation is more sensitive non-specific marker of infection and tissue damage which help to quantify low grade of systemic inflammation in the absence of overt systemic inflammation disorder. The aim of study was to determine the levels of Fetuin-A and hs-CRP in SCH patients and compare it with healthy Euthyroid control. In this observational study 65 newly diagnosed Subclinical Hypothyroid Subjects and 130 age and gender matched euthyroid subjects acting as control were included. Serum concentrations of TSH, FT3, FT4, Fetuin-A and hs-CRP levels were assessed. The study showed that the mean serum Fetuin-A level in SCH subjects (293.4±76.5 µg/ml) is found statistically significantly lower than Euthyroid control (347.24±134.52µg/ml; P <0.0001). The mean hs-CRP level of SCH subjects (5.43 ±4.19mg/L) is found higher than Euthyroid controls (1.61 ± 1.3 mg/L; p<0.0001). Hence, it is concluded that in addition to levels of TSH, Fetuin-A together with hs-CRP can also be used as diagnostic measure and may be helpful in initiating treatment for SCH subjects.

Keywords: Fetuin-A, hs-CRP, SCH, TSH

INTRODUCTION

Subclinical hypothyroidism (SCH) can be defined as a state of high serum thyroid stimulating hormone (TSH) levels (less than 10µ IU/L) with normal serum free thyroxine (FT4) levels. Overall, the population prevalence of subclinical hypothyroidism is around 3% - 8%. Furthermore, SCH has been found to be significantly more frequent in the elderly population (Rosenthal et al.1987) especially in women and its incidence increases with age and is found to be higher in white than in black population. [(1)]

Subclinical hypothyroidism (SCH) is asymptomatic in general but it may progress to overt hypothyroidism. [(2)] It has also been reported that TSH level greater than 10 µIU/mL predicts a higher rate of progression to overt state than a level of less than 6 µIU/mL.[(3)] There may be symptoms like muscle cramps, constipation, puffy eyes, cold intolerance, hoarseness of voice, fatigue, depression, neuromuscular symptoms and menstrual abnormalities. [(4)] Subclinical Hypothyroidism may be associated with a modest increase in the risk of coronary heart disease and mortality, particularly in subjects with higher TSH levels. Dyslipidemia accelerates the atherogenicity and this is observed in the SCH. [(5)]

Fetuin-A is a liver derived carrier plasma glycoprotein and act as inhibitor of

ectopic mineralization. [6] By reacting with calcium and phosphate in serum to form calciprotein particle (CPP) and removes the calcium from the medium. It is internalized mainly by the Kupffer cells of the liver and macrophages in the splenic marginal zone and carries out the calcium clearance. [7] In addition, in humans, fetuin-A has been suggested to provide an important link between obesity, insulin resistance, type 2 diabetes mellitus and other condition associated with metabolic syndrome. [8,9]

High-sensitivity C-reactive protein (hs-CRP) in inflammation is more sensitive non-specific marker of infection and tissue damage than a standard test. hs-CRP assays help quantify low grade of systemic inflammation in the absence of overt systemic inflammatory or immunological disorders. Several signs and symptoms in patients with hypothyroidism suggest an abnormality of inflammation. These are thought to be the result of an interaction of IL-6 on TNF-α and IL-1. This interaction may result from the elevated CRP in hypothyroidism. Several studies have demonstrated significantly higher hs-CRP levels in patients with SCH. [10]

Therefore, the present study was aimed to determine the levels of Fetuin-A and hs-CRP in subclinical hypothyroid subjects and compare it with euthyroid subjects.

MATERIAL AND METHOD

In this observational study 65 newly diagnosed Subclinical Hypothyroid Subjects and 130 age and gender matched Euthyroid subjects acting as control were included. Diagnosis of thyroid disorder was made according to the criteria recommended by the European Thyroid Association Guidelines-2013.

Patients with diabetes, having history of rheumatoid arthritis, history of heart attack, thyroid supplementation and antithyroid agents and pregnant women were excluded. Persons using drugs that affect Serum High Sensitivity C-reactive protein level and Serum Fetuin-A level were also excluded. Detailed history of participants including age, history of any medications, addictions was taken. Written consent from all the subjects was obtained for the study.

Statistical Analysis

Data were recorded in a predesigned performa as mean±SD. Comparison of physical and biochemical parameters between SCH subjects and Euthyroid controls were performed using student t-test and statistical significance was seen by p value.

RESULT

The study was undertaken in two groups viz group-I and group-II i.e. 130 normal healthy controls and 65 subclinical hypothyroid subjects respectively. The anthropometric parameters viz, age in years was (38.47±10.8), (38.86±11.26) in group-I, group-II respectively, BMI mean ± SD in kg/m^2 in the group-I, group-II was (22.98 ± 5.03), (21.18 ± 4.6) respectively. The mean serum TSH level was found to be significantly high in group II (9.54±2.85 µIU/ml) as compared to group I (2.87±1.22 µIU/ml; P< 0.0001). The mean serum FT3 levels was found to be low in group II (3.09±0.47 pg/ml) as compared to group I (3.14±0.56 pg/ml; P > 0.05.The difference was statistically non significant (P>0.05). The mean serum FT4 levels was found to be low in group II (0.89±0.15 ng/dl) as compared to group I (0.97±0.18 ng/dl; P > 0.05).The difference in mean serum FT4 levels was statistically non significant (P>0.05) (Fig.1). The mean serum Fetuin-A level in SCH subjects (293.4±76.5 µg/ml) is found to be lower than Euthyroid control (347.24±134.52 µg/ml; P < 0.0001).This difference was observed statistically significant (P<0.0001). The mean hs-CRP level of subclinical Hypothyroid Subjects (5.43 ±4.19mg/L) is found higher than Euthyroid controls (1.61 ± 1.3 mg/L; p<0.0001).

Table 1: Anthropometric parameters of Euthyroid subjects and Subclinical Hypothyroid subjects

Parameters	GROUP I Euthyroid Subjects Mean ±SD (n=130)	GROUP II Subclinical Hypothyroid Subjects Mean ± SD (n=65)
AGE (Years)	38.47±10.8	38.86±11.26
WEIGHT(Kg)	51.58±4.9	60.32±4.6
HEIGHT(cm)	155.52±4.4	155.91±4.8
BMI (Kg/m^2)	22.98±5.03	21.18±4.6

Table 2: Biochemical parameters of Euthyroid subjects and Subclinical Hypothyroid subjects

Parameter	GROUP I Euthyroid Subjects Mean ± SD (n=130)	GROUP II SCH subjects Mean ± SD (n=65)	't' value	'p' value*
TSH (µIU/ml)	2.87±1.22	9.54±2.85	22.86	<0.0001(HS)
FT3(pg/ml)	3.14±0.56	3.09±0.47	0.39	0.69(NS)
FT4(ng/dl)	0.93±0.18	0.89±0.15	1.54	0.12(NS)
Fetuin A(µg/ml)	347.24±134.52	293.4±76.5	2.99	<0.0001(HS)
Hs-CRP(mg/L)	1.61±1.3	5.43±4.19	9.53	0.0001(HS)

DISCUSSION

Several studies have concluded the association between Fetuin-A, hs-CRP and Subclinical Hypothyroidism. Our study is in agreement with previous studies by Muratli S et al. (2015), [(11)] Bakiner et al. (2014) [(12)] who reported decreased Fetuin-A level in Subclinical Hypothyroid subjects as they also observed negative correlation between TSH and Fetuin-A level. Gromakova et al. (2001) have explained the mechanism of change in protein synthesis in liver by altering the RNA polymerase activity by thyroid hormone and that protein synthesis is increased in hyperthyroidism and decreased in hypothyroidism. Lin et al. (2003) reported in vitro experimental study and demonstrated that protein synthesis is increased in response to direct interaction with the promoter region of major proteins synthesized by the liver including Fetuin-A via the a-1 thyroid receptors with effects of FT3. The results of these studies may explain the low Fetuin-A levels in subjects with SCH along with increase in hs-CRP level which may be due to interaction between inflammatory mediator and Fetuin-A.

Our results of level hs-CRP in SCH subjects were in consistent with Sapna Vyakaranam et al 2018, [(13)] Devi Satya et al. (2018), Roy et al 2016., [(14)] Mhto et al 2012, [(15)] Sharma R et al 2011 [(16)] Tuzku et al. (2005) [(17)] who observed elevated levels of hs-CRP in Subclinical Hypothyroidism compared with Euthyroid subjects. Hence, we concluded that low-grade inflammation starts in the early stages of hypothyroidism, resulting in elevated hs-CRP.

Several signs and symptoms in patients with hypothyroidism suggest an abnormality of inflammation. These are thought to be the result of an interaction of IL-6 on TNF-α and IL-1. This interaction may result from the elevated CRP in hypothyroidism. Except for the above-mentioned cytokines, lack of thyroid hormones leads to slowing down the overall metabolic rate, so the decreased rate of CRP clearance may result in CRP serum level increase. Similarly, slow CRP uptake in target cells might also add to this phenomenon (Czarnywojtek et al. 2014). [(18)]

CONCLUSION

Serum Fetuin-A level is significantly lower and hs-CRP level is significantly higher in Subclinical Hypothyroid subjects. SCH, due to its asymptomatic nature usually goes undiagnosed. Therefore, confirmation of the level of Fetuin-A and hs-CRP in Subclinical hypothyroidism may be helpful in initiating treatment at an early stage. However, further studies are needed to illustrate the role of Fetuin-A and hs-CRP in Subclinical Hypothyroidism.

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