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Research Article

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Association of thyroid stimulating hormone and iron profile among patients with subclinical primary hypothyroidism

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ABSTRACT

Introduction: Physiologically, thyroid hormones have a vital role in maintaining metabolic balance of the human body. Subclinical hypothyroidism is often associated with hematological disorders including iron-deficiency anemia. This study aims to correlate thyroid stimulating hormone and iron profile in patients with subclinical primary hypothyroidism.

Materials and methods: This is a cross-sectional study conducted in Nepal Medical College and Teaching Hospital, Kathmandu, Nepal among patients with subclinical primary hypothyroidism. The study was conducted from October 2018 to December 2019. Total of 60 patients above the age of 18 years were enrolled for the study. Thyroid function test was done by automated machine using electro chemiluminescent immunoassay technique and iron profile test was done by Immunoassay method using Vitros Analyzer. Pearson's correlation test was applied to find the correlation between thyroid stimulating hormone and iron profile.

Results: Among the 60 participants with subclinical hypothyroidism 23% were males and 77% were females with a mean age of 43 years. The mean serum iron (male =81.14 µg/dl female = 69.5 µg/dl), mean total iron binding capacity (male =470.35 µg/dl, female = 477.94 µg/dl) and mean ferritin level (male=91.15 µg/dl, female=95.51 µg/dl) were within reference value of our laboratory. A negative correlation was observed between thyroid stimulating hormone levels and serum iron (r=0.376, P=0.003), thyroid stimulating hormone and total iron binding capacity also showed a negative correlation (r=-0.083, P=0.27). Similarly thyroid stimulating hormone and transferrin saturation also showed a negative correlation (r=-0.098, P=0.455) whereas, a positive correlation was observed between thyroid stimulating hormone and ferritin (r=0.037, P=0.779).

Conclusions: This study concludes that thyroid stimulating hormone is negatively associated to serum iron, total iron binding capacity and transferrin saturation whereas, positively associated with ferritin among patients with subclinical hypothyroidism.

Keywords: Ferritin, iron, subclinical hypothyroidism, thyroid stimulating hormone, total iron binding capacity, transferrin saturation

INTRODUCTION

The thyroid gland secretes two major hormones thyroxine (T4) and triiodothyronine (T3), they have an important role in various physiologic processes which affects mostly every organ system in the body. The thyroid hormones are crucial for basal metabolism and functions of tissues in the body. [1] Subclinical hypothyroidism (SCH) is diagnosed on the basis laboratory results rather than signs and symptoms. The serum thyroid stimulating hormone (TSH) is more than the normal reference range and serum free thyroxine (T4) is within the reference range in SCH.[2]

SCH has been long known to be associated with obstetric complications, infertility, neurological and psychiatric symptoms, hypercholesterolemia, atherosclerosis, thrombosis, cardiovascular complications, cholelithiasis, iron-deficiency anemia and other hematological disorders.[3–6]

Thyroid hormones enhance erythropoiesis as they stimulate erythropoietin (EPO) via gene expression and increase proliferation of immature erythroid progenitors. They also stimulate expression of hypoxia inducible factor1 (HIF-1) which increase formation of erythroid colonies: Colony Forming Unit-Erythroid (CFU-E) and Erythroid Burst Forming Units (BFU-E). They also aggravate 2, 3 DPG (Diphosphoglycerate) density of red blood cells, which augment delivery of oxygen to tissues. They are also known to alter red blood cell indices including mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC) as well as iron stores.[7]

This study aims to correlate serum iron, total iron binding capacity, serum ferritin and transferrin saturation with TSH in subclinical hypothyroidism.

MATERIALS AND METHODS

A quantitative, cross sectional, observational study was conducted in Internal Medicine, Out Patient Department, Nepal Medical College Teaching Hospital. The study took place from October 2018 to September 2019. A total of 60 patients diagnosed with subclinical hypothyroidism were included by convenient sampling. Patients with increased TSH >4.68 micro -international units per milliliter (μIU/ml), but normal FT4 (within 0.7 – 2.1 nanogram per deciliter (ng/dl)) and FT3 (within 0.9– 2.4 picogram per milliliter (pg/ml)) were included. Patients under 18 years, pregnant females and patients under medication were excluded. Free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH), serum iron, serum ferritin, total iron binding capacity (TIBC) and percentage saturation of transferrin were included after consent was obtained from the participants. About 4 ml blood was withdrawn by standard venipuncture. On the same day of collection serum was separated by centrifugation at 2000-2500 rpm for 15 minutes at room temperature and stored at 2-4°C until analysis. The thyroid function test (TFT) was done by fully automated dry chemistry analyzer, Vitros-250 manufactured by Johnson and Johnson - Orthoclinical diagnostic using electro-chemiluminescent immunoassay (ECLIA) technique in the laboratory of NMCTH. The reference thyroid function test level was taken according to reference values used in laboratory of NMCTH. Parameters of iron profile (serum iron, serum ferritin, TIBC) was done by Immunoassay method using Vitros Analyzer in the laboratory of NMCTH. The reference ranges for iron profile were according to reference values used in laboratory of NMCTH. Statistical analysis was performed using the statistical package for social sciences (SPSS) version 25. Pearson's correlation test was applied to associate TSH with iron profile.

RESULTS

A total of 14 males and 46 females with subclinical hypothyroidism with a mean age of 43 years (18 years to 81 years) were enrolled in the study. TSH values more than 4.68 μIU/l was taken. Majority of the females and males had TSH > 10 μIU/l as shown in table 1.

Among all the cases of subclinical hypothyroidism, mean serum iron was within reference value of our laboratory (male =81.14 μg/dl female = 69.5 μg/dl), mean TIBC was also within reference value

Table 1: Distribution of TSH according to gender

TSH	Female	Male
4.69 - 10 μIU/l	8	6
> 10 μIU/l	38	8
Total	46	14

Table 2: Iron profile in accordance to gender among patients with subclinical hypothyroidism

Iron Profile	Sex	Minimum	Maximum	Mean	SD
Serum iron µg/dl	Male	47	115	81.14	21.8
	Female	6	115	69.5	25.39
TIBC µg/dl	Male	330	751	470.35	143.31
	Female	34.6	800	477.94	172.86
Transferrin Saturation µg/dl	Male	10.3	31	18.59	7.59
	Female	1.52	130	18.13	18.5
Ferritin µg/dl	Male	16	551	91.15	135.33
	Female	4.56	130	95.51	169.02

(male =470.35 µg/dl, female = 477.94 µg/dl). The mean ferritin level too was within normal range (male=91.15 µg/dl, female=95.51 µg/dl). However, percentage of transferrin saturation was on the lower side of normal range (male=18.59 µg/dl, female=18.13 µg/dl) as shown in table 2.

Serum iron, TIBC and transferrin saturation were negatively associated with TSH whereas, there was a positive correlation seen between ferritin and TSH. There was a significant negative correlation observed between serum iron and TSH as shown in table 3.

Table 3: Correlation of TSH with iron profile using Pearson Correlation

Iron Profile	Female	Male
Serum iron	-.376*	0.003
TIBC	-0.083	0.527
Ferritin	0.037	0.779
Transferrin saturation	-0.098	0.455

*p value < 0.05

DISCUSSION

In this cross-sectional, observational study, 60 patients with subclinical hypothyroidism were included by convenient sampling. Among the participants more females (n=46, 77%) had subclinical hypothyroidism than males (n=14, 23%). This study showed a significant negative association between TSH and serum iron (r-value = -3.76, p-value=0.003). TSH had a negative association with TIBC and transferrin saturation whereas a positive association was observed with ferritin. However, these associations were not significant.

Similar to this study various studies done in different parts of Asia on prevalence of SCH, showed higher prevalence among women than men. A study conducted by Aryal et al in Nepal showed that among the participants who had SCH, 47% were females and 19% were males.[3] A similar study conducted by Mishra et al. in India observed 90.57% who had SCH were females.[4] Similarly, a study conducted by Ashraf et al. in Iran showed 8.6% among 1248 women and 3.1% among 1275 men had SCH.[8] It has been speculated that estrogen may play a role in modulation of thyroid cell function and proliferation by estrogen receptor dependent mechanism which may explain the higher prevalence of SCH among the females.[9]

A study conducted by Khatiwada et al in Nepal among children observed 21 children with SCH were iron deficient from a total of 37 children. [10] Similarly, a study conducted by Duntas et al. showed lower serum iron among patients with

SCH 41.6±16 µg/dl compared to euthyroid group 61±21 µg/dl; however the TIBC levels (384±62 µg/dl vs 305±45 µg/dl) were more and ferritin levels (31±17 µg/dl vs 44±19 µg/dl) were lower than the control group.[11] A study conducted by Akhter et al. in Bangladesh also observed the mean TSH was higher in iron deficient participants (3.31±1.49 mIU/l) than iron sufficient participants (1.91±0.85 mIU/l).[12] Mehmet et al also observed similar results in Turkey, the mean iron was lower than the euthyroid group (73.8±33.8 µg/dl vs 75.5±58.8 µg/dl) however the mean ferritin in contrast to this study was lower in the SCH than the euthyroid group (42.1±47.4 µg/dl vs 48.1+58.8 µg/dl).[13] In contrast to this study Chandel et al. observed lower levels of serum ferritin among SCH patients (42.5±22.6 ng/ml) when compared to euthyroid controls (104.1±43.5 ng/ml).[14]

In similarity to our study Bremner et al. also observed that there was, a significant reduction in mean serum iron (15.9 µm vs 18.4 µm; p-value = 0.001) and transferrin saturation (24.5% vs 28.6%; p-value = 0.011) in participants with SCH compared with the euthyroid group. However, they found no significant relationship between thyroid function and iron stores, as measured by serum ferritin (126 µg/l vs 154.2 µg/l; p-value = 0.61).[15]

Similar to this study Mishra et al. also observed negative correlation between TSH and iron (r=-0.161, p=0.02) whereas in contrary to this study ferritin had a negative correlation with TSH (r=-0.271, p<0.05) and TIBC had a positive correlation with TSH (r=0.174, p=0.013).[4]

Similar to this study Khatiwada et al. also observed TSH had a significant negative correlation with transferrin saturation (r =−0.204, p=0.002). The mean serum iron in euthyroid and hypothyroid children were 74.0±36.7 µg/dl and 57.0±26.6 µg/dl respectively and the mean transferrin saturation in euthyroid and hypothyroid children were 21.5 ± 13.2 µg/dl and 14.6 ± 8.1 µg/dl respectively.[10]

A study conducted by Cinemre et al. indicated iron deficient anemia treated with iron in combination of levothyroxine had significant positive response on the hematological parameters.[16] Thyroxine and triiodothyronine cause stimulation of erythropoiesis. They increase 2,3 bisphosphoglyceric acid concentration in red blood cells. Deficiency of thyroid hormones may cause anemia.[17] The iron deficiency seen in this study may be caused by excessive blood loss during the menstrual cycle due hormonal imbalance and malabsorption seen in SCH patients.[18] It appears that anemia and hypoxia alters thyroid metabolism as there is decreased stimulation by TSH on thyroid cells.[18,19] The association of TSH with TIBC, transferrin saturation and ferritin which were not significant may be due to the inadequate sample size taken in this single centric study.

The findings of this study recommend assessment of iron profile among patients with SCH specially among female patients. Screening of iron deficiency anemia among SCH patients may help in early diagnosis, appropriate treatment and better prognosis of patients.

LIMITATIONS

The blood samples were not collected at the same time which could have caused diurnal variation of the blood samples. Other possible causes and risks of iron deficiency anemia were not considered in this study. Patients with SCH were not categorized according to age and gender which may have caused variations in the results.

CONCLUSION

This study concludes that there is a significant negative correlation between TSH and serum iron. TIBC and transferrin saturation also has a negative correlation with TSH whereas, Ferritin has a positive correlation with TSH though the association was not statistically significant. Consideration of a combined treatment of SCH and iron deficiency anemia may produce favorable outcome.

CONFLICT OF INTEREST

None.

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