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Original Article

Biochemistry Section

Iron Deficiency and Hypoferritinaemia in Patients with Subclinical Hypothyroidism: A Retrospective Observational Study

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ABSTRACT

Introduction: Iron acts as a cofactor in Thyroid Peroxidase (TPO) activity, and low iron levels can impact thyroid hormone metabolism. The function of ferritin and iron has been extensively documented in various studies in patients with Overt Hypothyroidism (OH), but their role in Subclinical Hypothyroidism (SH) remains largely unexplored.

Aim: To evaluate the serum ferritin and iron levels in patients who have SH.

Materials and Methods: A retrospective observational study was conducted between March 2018 and October 2018 at the Biochemistry Department of Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India. For the study, a total of 100 cases of SH were enrolled, and these patients were matched in terms of age and sex with 50 healthy controls. A fasting sample was obtained and analysed for serum ferritin, Total Iron Binding Capacity (TIBC), TT3, TT4, and Thyroid Stimulating Hormone (TSH). MedCalc software was used to perform statistical analysis.

Results: In the SH group, there were 32 males (32%) and 68 females (68%); in the control group, there were 21 males (42%) and 29 females (58%). The median values of TT3 (nmol/L), TT4 (µg/dL), and TSH (µIU/mL) were 1.55 (1.4-1.95), 7.8 (5.9-9.75), and 3 (1.9-3.75) for controls, and 1.4 (1.1-1.75), 6.85 (5.5-8.15), and 6.2 (4.8-8.05), respectively, for cases. In comparison to controls, the TSH level was significantly higher ($p<0.0001$) in cases. The median iron (µg/dL), ferritin (ng/mL), TIBC (µg/dL), and % saturation in cases were 56.5 (41.5-82), 110 (31.5-194.5), 329 (258-390), and 19 (11.25-26.75), respectively, while in controls they were 84 (68.5-96.5), 195 (121.5-338.5), 233 (188.5-294), and 25 (18-37.5). There was a significant decrease in iron level ($p<0.00001$), % saturation (<0.00001), and ferritin level ($p<0.00001$), and a significant increase in TIBC ($p<0.0001$) in cases when compared to controls.

Conclusion: In conclusion, the present study showed a significant negative correlation between SH and iron deficiency. Patients with this condition should be evaluated for ferritin and iron levels and treated appropriately to prevent hypothyroidism.

Keywords: Anaemia, Ferritin, Thyroid stimulating hormone, Total iron binding capacity, Transferrin

INTRODUCTION

The SH is defined as an increase in TSH level associated with a normal level of free T3 (fT3) and free thyroxine (fT4). An fT3 assay is of limited value as many extra-thyroidal factors also trigger a reduction of this hormone. It is widely accepted that a TSH value above 10 mU/L indicates hypothyroidism [1]. The frequency of SH varies from 5 to 10% and rises with age, depending on the patient population [2].

Patients with thyroid autoantibodies or other thyroid history are at an elevated risk of developing OH. SH is intriguing due to its nosological and physiopathological aspects. Confirming thyroid insufficiency based solely on a single criterion, a TSH value between 4 and 10 mU/L, is not possible [3,4]. Approximately one-third of SH cases are not asymptomatic, but their TSH levels rise with a significant titer of thyroid autoantibodies [5].

The metabolism of iron is intricate and interconnected with thyroid hormone metabolism. Iron acts as a cofactor in TPO, which catalyses the initial two reactions of thyroid hormone biosynthesis. Low iron levels can impact overall thyroid hormone metabolism by reducing TPO's effectiveness [6]. An indicator of the body's iron reserves is ferritin, which may be altered in subclinical and OH [7]. Estimating anaemia markers such as serum iron, ferritin, TIBC, and % saturation will be highly useful in hypothyroidism and SH. Anaemia has a detrimental impact on thyroid hormone status, whereas thyroid hormones actively stimulate the proliferation of Red Blood Cell (RBC) precursors both directly and through the enhancement of erythropoietin production [8]. Consequently, certain types of anaemia, such as macrocytic, microcytic, and normocytic anaemia, stem from decreased erythropoietin production, bone marrow suppression, and simultaneous deficiencies in iron, vitamin B12, or folate that can result from thyroid dysfunction [9]. Hence, for many patients, anaemia is the initial indication of hypothyroidism.

In SH, an increase in Low-density Lipoprotein (LDL) cholesterol correlates with an increase in TSH levels. A cross-sectional study has demonstrated an increased prevalence of aortic atheromatosis and myocardial infarction in women affected by SH [10]. Before definitively diagnosing SH, several other causes of elevated TSH must be ruled out, including thyroid hormone resistance syndrome, TSH-receptor mutations, thyrotropic adenoma, chronic kidney failure, and drug interference [11].

A Haemoglobin (Hb) value below 13.0 g/dL for adult males and postmenopausal women, and below 12.0 g/dL for premenopausal women, is considered anaemia according to the World Health Organisation (WHO). Low Hb concentration can result from a reduced number of RBC/ml or reduced haemoglobin content of RBCs. Thyroid dysfunction and anaemia both worsen with age and frequently coexist [12].

Based on a study conducted in India, a notable segment of individuals with type 2 diabetes experience either subclinical or clinical hypothyroidism [13]. Additionally, anaemia directly exacerbates cardiovascular conditions such as coronary artery disease, stroke, left ventricular hypertrophy, and left ventricular systolic dysfunction. These factors increase the risk of death, reduced quality of life, longer hospital stays, and hospitalisations for patients with anaemia from Chronic Kidney Disease (CKD) [14]. While the association between thyroid dysfunction and anaemia is established, the link between SH and anaemia remains largely unexplored.

Hence, the present study was conducted to evaluate biochemical indicators of ferritin and iron status in SH patients.

MATERIALS AND METHODS

This retrospective observational study was conducted in the Department of Biochemistry at Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India. Data were collected between March 2018 and October 2018, and the analysis was carried out between November 2018 and December 2018. The Institutional Ethical Committee at Nizam's Institute of Medical Sciences in Hyderabad, India, approved the study protocol (EC/NIMS/2164/2018), and all research subjects provided written informed consent.

Inclusion criteria: Cases with normal serum TT3 (1.1-3.1 nmol/L), TT4 (4.5-11.7 nmol/µg/dL), and high serum TSH (4.0-10.0 µIU/mL) were recruited for the study [15].

Exclusion criteria: Patients with well-established hypothyroidism, a previous history of clinical hypothyroidism, and a history of intake of thyroid drugs, steroids, and iron supplements were excluded from the study. Proven hepatic illnesses, cardiovascular diseases, renal disorders, and diabetes mellitus were additional exclusion factors.

Sample size: A total of 100 cases of recently diagnosed SH were included in this retrospective analysis. This cohort consisted of 32 men and 68 women. A total of 50 healthy controls matched for age and sex were compared to these cases.

Study Procedure

A 5 mL fasting blood samples were collected in plain vacutainers for TT3, TT4, and TSH, as well as markers of anaemia such as iron, TIBC, and ferritin. The serum samples were obtained for analysis using centrifugation at 2000×g for 10 minutes at room temperature.

Biochemical Measurements: The FerroZine method was used to evaluate serum iron levels (10-1000 µg/dL). Ascorbate converts the liberated Fe^{3+} ions to Fe^{2+} ions in an acidic environment, and these ions combine with FerroZine to produce a coloured complex. The Unsaturated Iron-binding Capacity (UIBC) of serum was quantitatively determined through direct measurement using FerroZine. The colour intensity is inversely correlated with the UIBC and directly correlated with the unbound excess iron concentration. The increase in absorbance at 552 nm is used for calculation. Serum iron and serum UIBC are measured, and the values are combined to determine TIBC. The serum iron concentration is divided by the TIBC and multiplied by 100 to determine the percentage saturation of transferrin with iron. Serum ferritin levels (8-450 ng/mL) were estimated using the turbidimetric immunoassay [16].

Using a fully automated Advia Centaur XP chemiluminescence analyser (Siemens Healthcare Diagnostics Inc., NY, USA), the total T3 (0.1-8 ng/mL), T4 (0.3-30 µg/dL), and TSH (0.010-150 µIU/mL) levels were estimated [17]. The TSH3-Ultra assay is based on a two-site sandwich immunoassay principle, while the T3 and T4 assays are competitive immunoassays that use direct chemiluminescent technology.

STATISTICAL ANALYSIS

MedCalc software version 22.021 was used to perform statistical analysis. The Mann-Whitney U test was used to compare nonparametric variables, which are expressed as medians (interquartile range). Pearson's formula was used to obtain the coefficient of correlation.

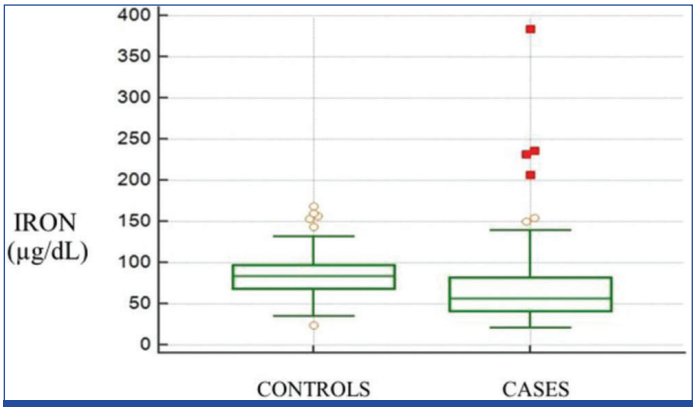
RESULTS

In the SH group, there were 32 males (32%) and 68 females (68%); in the control group, there were 21 males (42%) and 29 females (58%). No significant difference was found regarding the mean age among the groups. The median values of TT3 (nmol/L), TT4 (µg/dL), and TSH (µIU/mL) were 1.55 (1.4-1.95), 7.8 (5.9-9.75), and 3 (1.9-3.75) for controls, and 1.4 (1.1-1.75), 6.85 (5.5-8.15), and 6.2 (4.8-8.05) for patients. There was no significant difference in TT3 and TT4 levels between the SH and control groups. However, a statistically significant difference (p<0.0001) was observed in the mean TSH values between the SH group and the control group [Table/Fig-1].

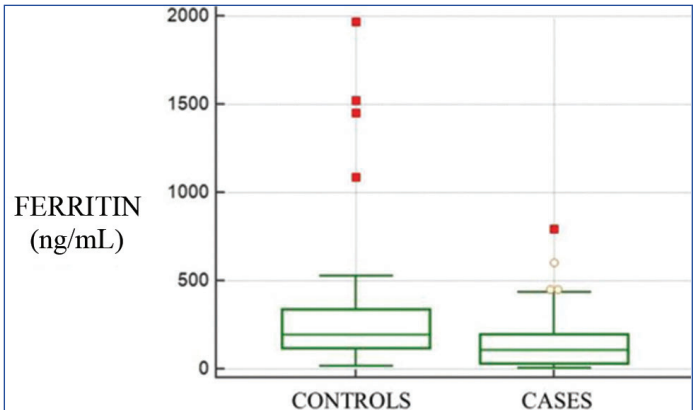
Variables	Controls (n=50)	Cases (n=100)	p-value
Age (years)	46.3±3.61	48.0±3.97	0.453
Gender	M-21 F-29	M-38 F-62	0.099
Total T3 (nmol/L)	1.55 (1.4-1.95)	1.4 (1.1-1.75)	0.723
Total T4 (µg/dL)	7.8 (5.9-9.75)	6.85 (5.5-8.15)	0.089
TSH (µIU/mL)	3.0 (1.9-3.75)	6.2 (4.8-8.05)	0.0001*

[Table/Fig-1]: Demographic data and thyroid hormone levels in controls and Subclinical Hypothyroidism (SH) cases.
Data is expressed as median and interquartile range. *p<0.05 compared to controls.
*p<0.0001 as compared to controls.

In cases, the median iron (µg/dL), ferritin (ng/mL), TIBC (µg/dL), and saturation percentage were 56.5 (41.5-82), 110 (31.5-194.5), 329 (258-390), and 19 (11.25-26.75), respectively. In controls, the corresponding values were 84 (68.5-96.5), 195 (121.5-338.5), 233 (188.5-294), and 25 (18-37.5). Compared to controls, there was a significant decrease in iron (p<0.00001), % saturation (<0.00001), and ferritin (<0.00001), but a significant increase in TIBC (<0.0001) in cases [Table/Fig-2-5].



[Table/Fig-2]: Comparison of serum iron in controls and SH cases (controls 84±15 µg/dL, cases 62±18 µg/dL).
p<0.00001 as compared to controls

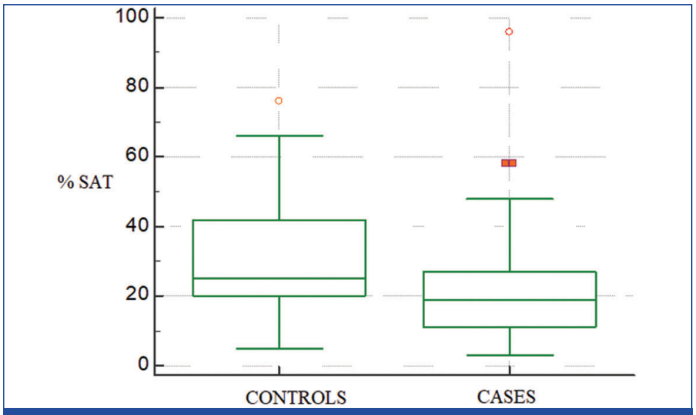


[Table/Fig-3]: Serum ferritin levels in controls and SH cases (controls 185±45 ng/mL, cases 120±35 ng/mL).
p<0.00001 as compared to controls

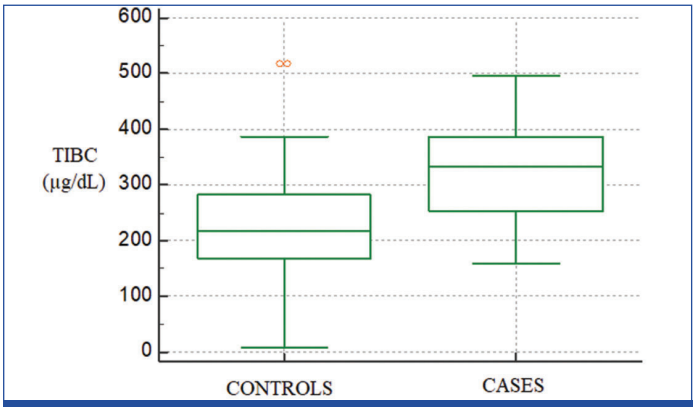
As shown in [Table/Fig-6,7], there was a negative correlation between TSH and iron, and ferritin (r=-0.063, p=0.438 and -0.21, p=0.04, respectively). However, there was a positive correlation between TSH and % saturation.

DISCUSSION

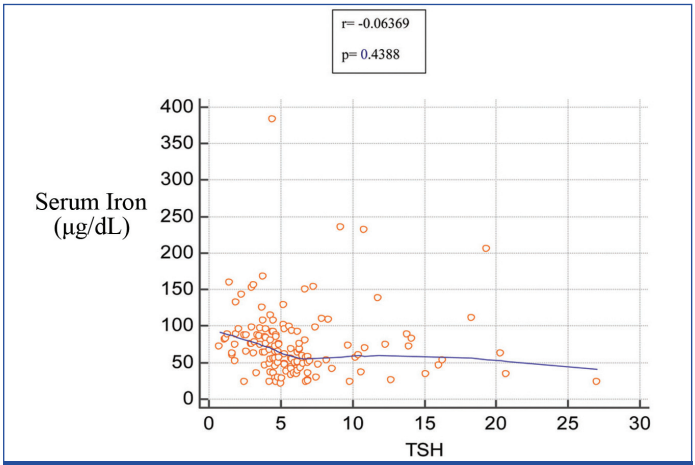
In the current study, patients with SH had lower levels of iron, ferritin, TIBC, and saturation percentage than the control group. There are



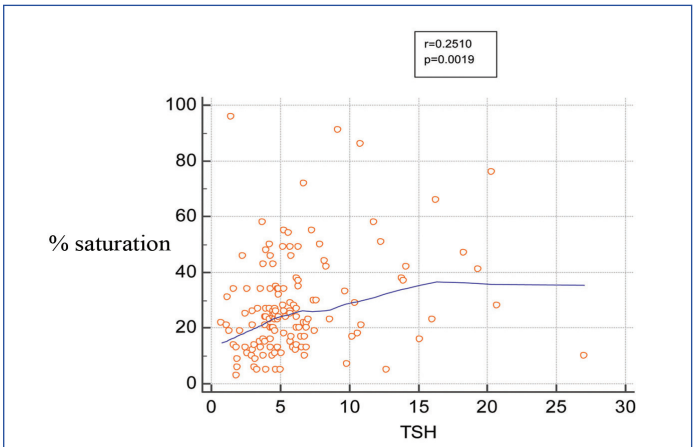
[Table/Fig-4]: Comparison of % saturation of transferrin with iron in controls and SH cases (controls 28±8%, cases 20±7%).
p<0.00001 as compared to controls



[Table/Fig-5]: Comparison of TIBC in controls and SH cases (controls 228±20, cases 333±36 µg/dL).
p<0.0001 as compared to controls



[Table/Fig-6]: Scatter diagram showing the correlation between serum iron and TSH in SH cases.



[Table/Fig-7]: Scatter diagram showing the correlation between % saturation and TSH in SH cases.

not many studies in the literature that address the iron profile status of patients with SH. According to a recent study by Soe YN et al., patients with SH had lower mean total T3, total T4, iron, TIBC, transferrin, and ferritin values than the control group [18]. SH and iron deficiency anaemia are important clinical disorders that are related to each other. The literature on iron markers in patients with SH is scarce [19].

One of the most crucial nutrients for thyroid function is iron. It is crucial for thyroid hormone synthesis and metabolism. Iron is necessary to produce the thyroid hormone T4, which is then converted to T3 [20]. According to Hess SY et al., there is a significant reduction in TPO activity in iron deficiency, and this reduction in TPO activity may be one of the factors contributing to the negative effects of iron deficiency anaemia on thyroid metabolism. Iron deficiency may inhibit iodine incorporation into thyroglobulin and the coupling of iodothyronine to form thyroid hormone by decreasing TPO activity [21]. Changes in thyroid function impact the haematological index and serum iron metabolism. Reduced iron levels in the body can lead to the development of SH into OH. Depleted bodily iron reserves and anaemia are frequently associated with hypothyroidism [22].

Ferritin is an intracellular protein responsible for storing iron and regulating its release. Ferritin is produced in every living organism. It possesses antioxidant properties and helps in the sequestration of iron. In subclinical hypothyroidism, elevated TSH levels might trigger inflammatory cytokines and reduce the body's antioxidant ability [23]. The ferritin mean concentration in SH patients was shown to be decreased in this study compared to the control group. The antioxidant property of ferritin through iron sequestration was decreased in SH. This study found that the mean ferritin and iron levels in SH patients were lower than those in the control group. These findings are consistent with previous research suggesting that hypothyroidism may be linked to a lower iron profile [24,25]. The present study results are also in agreement with the study conducted by Mishra AK et al., where they demonstrated that serum ferritin is significantly depleted in SH patients compared to the euthyroid group [19]. A total of 68 percent of the subclinical hypothyroid patients in this study were female. Women are more likely than men to suffer from SH because oestrogen may have an antithyroid effect [26].

Potentially active oxygen-derived free radicals are created during the redox cycling of catecholestrogen metabolites between quinone and catechol [27]. Iron is required for the generation of reactive oxygen species, predominantly superoxide radicals. In this study, the mean iron content of the control group was higher than that of the SH group. The primary enzyme in the manufacture of thyroid hormones, TPO, is primarily iron-dependent. Therefore, the development of SH into OH may be caused by an iron deficiency. Reduced oxygen delivery to different tissues occurs in patients with iron deficiency SH because thyroid hormones do not stimulate the establishment of erythroid colonies. Anaemia is caused by a decrease in erythropoietin levels, which also impacts iron metabolism [28]. An essential component of the system that delivers thyroid hormone into cells is serum iron. Even in the case of normal FT3 and FT4 levels, an iron deficit can cause the thyroid hormone to pool, resulting in a biologically hypothyroid state that mimics thyroxine resistance [12]. Thyroid hormones and iron metabolism were found to be negatively correlated with TSH and positively correlated with ferritin, but some authors have reported a strong positive link between TSH and ferritin. The findings of the present study are consistent with a study by Akhter S et al., which found that individuals with low iron levels had significantly different thyroid hormone statuses. This difference may be due to the iron-dependent enzyme (TPO) being less active, which disrupts the overall metabolism of thyroid hormones [29].

Hypothyroidism is the most common thyroid dysfunction in Indian patients with metabolic syndrome [30]. In older women, subclinical hypothyroidism (SH) is an independent risk factor for myocardial infarction and atherosclerosis [31]. Anaemia

and hypothyroidism are common conditions among pregnant women. According to one Indian study, 35 (31.81%) cases had elevated serum TSH (>2.5 mIU/L). TSH levels of more than 2.5 mIU/L were present in 42.86% of anaemia patients [32]. A large proportion of thyroid cases diagnosed during one Indian study highlighted hypothyroidism as the most common thyroid dysfunction in Indian patients with metabolic syndrome [30]. Pregnancy is frequently accompanied by anaemia and hypothyroidism. Diagnosing and treating hypothyroidism during pregnancy can help reduce anaemia and negative outcomes for both the mother and the foetus [32]. SH is more likely to develop in people with metabolic syndrome, and atherosclerotic heart disease morbidity and mortality are markedly elevated in SH patients [33]. Patients with untreated hypothyroidism have a significant chance of experiencing severe side effects. Mendes D et al., demonstrated that a significant section of the European population suffers from undetected hypothyroidism, specifically SH [34]. The challenging diagnosis and treatment of SH have long been linked to unwarranted deep vein thrombosis, common bile duct stones, and infertility [35-37]. Hence, it is important to screen for iron deficiency anaemia in all patients with SH since the two conditions are interdependent. The authors concluded that measuring iron and ferritin levels in patients with SH may be important, as it could enhance treatment outcomes and help track the progression of the condition from SH to OH.

Limitation(s)

The sample size was small, and there was no racial or geographical diversity in the study population. Therefore, the results may not be representative of the population at large. The data were obtained from a single centre without randomisation and further follow-up of patients.

CONCLUSION(S)

The current study concluded by showing a significant association between subclinical hypothyroidism (SH), hypoferritinaemia, and iron deficiency. Before progressing to OH, it is crucial to assess the ferritin and iron status of patients with SH. Compared to those with normal thyroid function, patients with abnormal thyroid status were more likely to develop anaemia. Because SH does not present with substantial clinical manifestations in its early stages, routine testing of ferritin and iron status is recommended for the early detection and prevention of anaemia.

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