

ALTERED IRON METABOLISM IN SUBCLINICAL HYPOTHYROIDISM: MYTH OR REALITY

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Abstract

Introduction: Subclinical hypothyroidism refers to thyroid hormone deficiency in patients who have no apparent clinical features. Both iron deficiency anemia and subclinical hypothyroidism, due to their high prevalence and close interrelation, are significant clinical problems.

Aims and Objectives: Association of subclinical hypothyroidism and disordered iron metabolism was studied so that better management of iron deficiency could be advised in these patients.

Materials and Methods: 150 newly diagnosed subclinical hypothyroid patients and 150 healthy euthyroid controls were included. Total T₃, total T₄, TSH, iron, TIBC, transferrin and ferritin were measured. Data was analysed by student 't' test and Person's formula.

Results: Mean total T₃, total T₄, iron, TIBC, transferrin and ferritin values of study group were lower than that of control group ($p < 0.05$). Mean TSH values of study group was higher than that of control group ($p < 0.05$). Total T₄ and T₃ were positively correlated with transferrin ($p < 0.05$). The patients of subclinical hypothyroidism had altered iron metabolism.

Conclusion: Decreased iron profile in subclinical hypothyroidism was significantly high. It was suggestive to regularly investigate iron profile for early detection and its early management in case of subclinical hypothyroidism.

Keywords: Subclinical Hypothyroidism, Serum Iron, TIBC, Ferritin, Transferrin

Introduction:

Thyroid hormones play a critical role in cell differentiation during development and help maintain thermogenic and metabolic homeostasis in the adult. Thyroid Stimulating Hormone (TSH), secreted by the thyrotrope of the anterior pituitary, plays a pivotal role in control of the thyroid axis and serves as the most useful physiologic marker of thyroid hormone action. Subclinical hypothyroidism refers to biochemical evidence of thyroid hormone deficiency in patients who have few or no apparent clinical features of hypothyroidism (1). It is also called as mild hypothyroidism; early thyroid failure, preclinical hypothyroidism or decreased thyroid reserve and is a condition characterized by elevated serum TSH in the setting of normal total or free thyroxine (T₄) concentration in serum (2). Most

patients have uncertain, nonspecific symptoms of subclinical hypothyroidism or are asymptomatic and identified only during routine blood tests (3).

Iodine deficiency is prevalent in many mountainous regions and in central Africa, central South America, and northern Asia. The World Health Organization (WHO) estimates that about 2 billion people are iodine-deficient based on urinary excretion data (4). Total goiter prevalence of South-East Asia region due to iodine deficiency was 15.4% in 2003 (4). In areas of relative iodine deficiency, there is an increased prevalence of goiter and, when deficiency is severe, hypothyroidism and cretinism (4).

Body iron is distributed into different compartments that include (i) hemoglobin (Hb), (ii) storage iron (ferritin and hemosiderin), (iii) myoglobin, (iv) a labile iron pool, (v) other tissue iron, and (vi) transport iron

(transferrin and apotransferrin). The body iron status can be assessed by measuring the hemoglobin, serum iron, total iron binding capacity (TIBC), transferrin and ferritin levels (3). Mild to moderate iron deficiency may be prevalent in up to 50% of the world, resulting from poor dietary diversity coupled with periodic blood loss and pregnancies (1). In India, the prevalence of iron deficiency anemia is the highest among the adolescents, 97.8%. Among them, 27.1% are severely anaemic (5).

Both iron deficiency anemia and subclinical hypothyroidism, due to their high prevalence and close interrelation, are significant clinical problems. Many studies have attempted to study the relationship between subclinical hypothyroidism and iron deficiency anemia, but due to limited number of large cohort studies, a definitive status of this entity is still eluding the clinicians posing problems in management. There are limited data related to iron profile in hypothyroid patients in the study area.

The association of subclinical hypothyroidism and disordered iron metabolism would be studied so that better management of iron deficiency can be advised in these patients.

MATERIALS AND METHODS

This cross-sectional and observational study was conducted in Biochemistry department in a tertiary care hospital. The cases were selected randomly from subjects who were attending the medical out-patient department of tertiary care hospital during the period of one year, from 01 January 2018 to 31 December 2018. 587 subclinical hypothyroid patients were registered in medical OPD during the study period.

The exclusion criteria were the following - pregnant women, patients with haemolytic anaemia, gastrointestinal and genitourinary losses, connective tissue disorders, haemoglobinopathies, bleeding disorders, renal insufficiency/failure, coronary heart disease, uncontrolled hypertension, diabetes mellitus, any endocrine disease other than hypothyroidism and all patients previously treated for hypothyroidism or on anti-thyroid medication. The inclusion criteria were all cases of Subclinical Hypothyroidism who had normal total T_3 and T_4 values and values of TSH between 4.05-10 μ U/mL who were symptomatic with features of tiredness, weakness, constipation, dyspnea, parenthesis, difficulty concentrating, poor appetite (1).

According to the exclusion and inclusion criteria, 150 out of 587 subclinical hypothyroid patients were selected. 150 apparently healthy age and sex matched euthyroid persons who were attending transfusion medicine for blood donation, were included as control in the study. The diagnosis was based on detailed history and thyroid profile analysis (1).

Six mL of venous sample was collected in plain vacutainer aseptically after getting informed consent and taking institutional ethical committee sanction. Serum was separated and stored at -20°C for estimation of iron, TIBC, ferritin and transferrin in batches. Total T_3 , T_4 and thyroid stimulating hormone (TSH) were analysed using standard radioimmunoassay (Beckman Coulter, USA). Iron and TIBC were analysed using end point colorimetric method; transferrin was analysed using turbidimetric assay endpoint detection and ferritin was analysed using one-step enzyme immunoassay method by Siemen Dimension EXL 200, USA.

The values for various statistical parameters like mean, standard deviation and coefficient of correlation 'r' were calculated using SPSS version 20.2 software. Analytical data was analysed using student 't' test for various parametric variables and coefficient of correlation was calculated by applying Person's formula.

RESULTS

There were 52 males (34.67%) and 98 female (65.33%) in subclinical hypothyroidism group and 71 males (47.33%) and 79 female (52.67%) in control group. In comparison the demographic measures and biochemical parameters of subclinical hypothyroidism group and control group, all values were statistically significant ($p < 0.05$) except age parameter (table 1).

The mean total T_3 , total T_4 , iron, TIBC, transferrin and ferritin values of subclinical hypothyroidism group were lower than that of control group and these differences were statistically significant ($p < 0.05$). The mean TSH values of subclinical hypothyroidism group were higher than that of control group and these differences were statistically significant ($p < 0.05$).

TSH had positive correlation with iron and TIBC but was not statistically significant (Iron: $r = 0.114$, $p = 0.166$, TIBC: $r = 0.081$, $p = 0.324$). TSH had negative correlation with transferrin but had no statistical

significance ($r = -0.055$, $p = 0.502$). TSH was no correlation with ferritin ($r = 0.005$, $p = 0.956$).

Total T_4 had positive correlation with TIBC and Transferrin that was statistically significant (TIBC: $r = 0.2$, $p = 0.014$, Transferrin: $r = 0.264$, $p = 0.001$) (Figure 1-A, B). Total T_4 had negative correlation with iron and ferritin but was no statistically significant (Iron: $r = -0.014$, $p = 0.863$, Ferritin: $r = -0.110$, $p = 0.179$).

Total T_3 was positively correlated with transferrin and was statistically significant ($r = 0.232$, $p = 0.004$) (Figure 2). Total T_3 was positively correlated with iron and TIBC but was no statistically significant (Iron: $r = 0.072$, $p = 0.384$, TIBC: $r = 0.144$, $p = 0.079$). Total T_3 was negatively correlated with ferritin and not statistically significant ($r = -0.128$, $p = 0.119$).

Table 1: Demographic measures and Biochemical values

Characteristics	Subclinical hypothyroidism		Control		p value
	Mean	SD	Mean	SD	
Number	150		150		
Age (years)	38.39	14.73	39.99	9.45	0.309
Total T_3 (nmol/L)	1.79	0.61	2.10	0.39	0.000
Total T_4 (nmol/L)	84.64	32.44	113.51	25.62	0.000
TSH (μ IU/mL)	11.82	14.39	1.79	0.81	0.000
Iron (μ g/dL)	74.61	34.07	84.05	25.26	0.007
TIBC (μ g/dL)	400.89	119.54	335.22	57.11	0.000
Transferrin (mg/dL)	317.62	72.82	280.65	30.16	0.000
Ferritin (ng/mL)	70.55	223.45	109.77	61.30	0.036

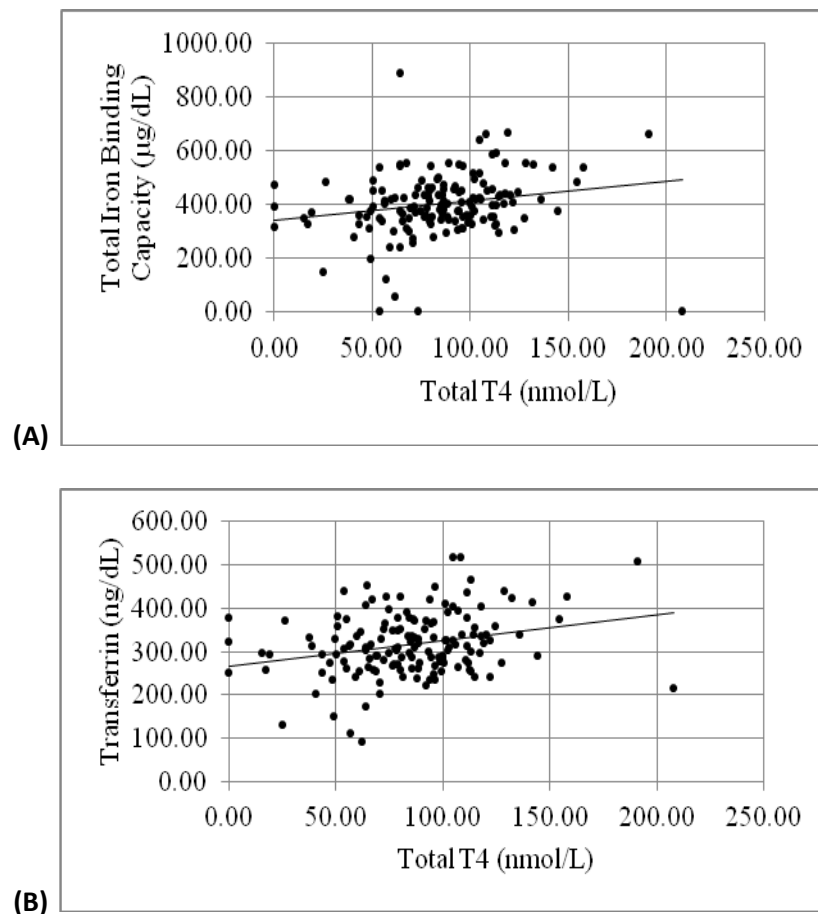


Figure 1: Scatter diagram showing correlation of total T_4 with (A) TIBC and (B) Transferrin

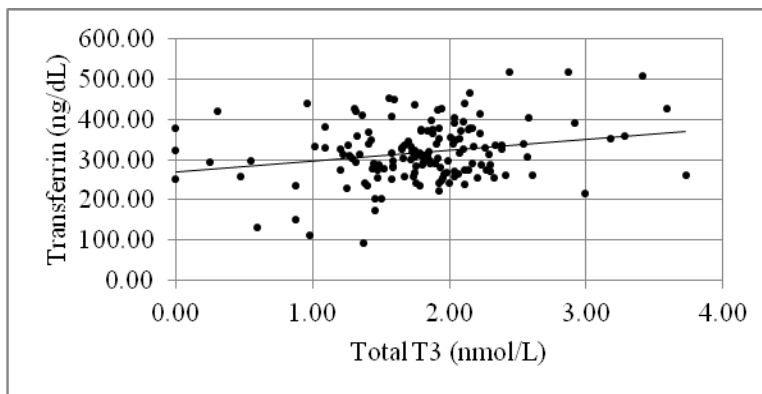


Figure 2: Scatter diagram showing correlation of total T₃ with Transferrin

DISCUSSION

Both iron deficiency anemia and subclinical hypothyroidism, due to their high prevalence and close interrelation, are significant clinical problems. Many studies have attempted to study the relationship between subclinical hypothyroidism and iron deficiency anemia, but due to limited number of large cohort studies, a definitive status of this entity is still eluding the clinicians posing problems in management. Not many reports are available in literature to report on iron profile in hypothyroid patients (6).

Ferritin is an iron storage protein found in all living organisms involved in iron sequestration with some antioxidant properties. High TSH, as observed in subclinical hypothyroidism, may prompt inflammatory cytokines and to decrease the concentration of antioxidants in the body (7). This may be a supplementary reason for decrease in ferritin levels, which exhibits antioxidant properties, in these patients. The expression of gene for ferritin has also been described to be induced by T₃ hormone (8). Mean Ferritin concentration of subclinical hypothyroidism group was lower than that of control group in this study. This result can be deduced that antioxidant property by ferritin was decrease in subclinical hypothyroidism.

Iron metabolism is very complexly connected to thyroid hormone metabolism. Normal thyroid status requires the presence of many trace elements e.g., iron, iodine, selenium, and zinc for both the synthesis and metabolism of thyroid hormones. Iron is a component of many enzymes including thyroid peroxidase (TPO) which takes part in the initial two steps in thyroid hormone biosynthesis (9). Iron deficiency has also been reported to decrease plasma concentrations of T₃ and T₄ and increase in vitro

hepatic rT₃ deiodination, proposing the thyroid hormone metabolism via a deactivating pathway in iron deficiency. It is possible that a small fraction of T₄ gets converted to T₃ and a larger proportion is metabolized to a physiologically inactive metabolite, rT₃. It is not yet clear how iron deficiency exerts its effects on deiodinase activity (10). According to this theory, subclinical hypothyroidism may lead to hypothyroidism via decrease iron concentration in the body.

In this study, the mean iron, transferrin and ferritin values of subclinical hypothyroidism group were found to decrease as compare to healthy control. These results are in agreement with other studies which reported that decrease iron profile may be associated with hypothyroidism (11-12).

In this study, sixty-five percent of subclinical hypothyroid patients were females. Subclinical hypothyroidism is more predominant in female population as estrogen has an anti-thyroid action. Redox cycling of catecholesterogen metabolites between quinone and catechol forms is a mechanism of generating potentially active oxygen radicals (13). Metal ions, especially iron, are necessary for the production of extremely reactive hydroxy radicals shifting the balance of body towards increased oxidative stress (14). Increased oxidative stress has been reported in hypothyroidism and iron is a key player in this mechanism (15-16). Metal ions, especially iron, are required for generation of reactive oxygen species. Mean iron concentration of subclinical hypothyroidism group was lower than that of control group in this study.

Thyropoxidase, the key enzyme in thyroid hormone biosynthesis, is iron-dependent. Thus, iron deficiency may be the underlying cause in the progress of hypothyroidism. This fact is of great significance while

treating these patients. The symptoms of sympathetic overstimulation due to iron deficiency may worsen on administration of thyroxine due to overstimulation. Thyroxine administration has been described to increase erythropoietin levels and develop erythropoiesis. This leads to increased requirement of iron and may occur in manifestations of iron deficiency (17). Already existing iron deficiency in these subjects may make the clinical picture poorer. In hypothyroid condition, lack of stimulation of erythroid colony development by thyroid hormones, reduction in oxygen distribution to tissues and reduction of erythropoietin level leads to anemia and the component effect on iron metabolism (18). Thus, the condition becomes a cycle as iron deficiency may both be a cause and an effect of hypothyroidism. Iron forms an important part of the mechanism that transports thyroid hormone into the cells and lack of it can lead to pooling of thyroid hormone leading to metabolically hypothyroid condition even in presence of normal FT₃ levels, producing a thyroxine resistance like situation (9). According to the result of this study, iron profile of patients should be mindful before treating the hypothyroid patient.

The limitations of this study were the small sample size, lack of follow-up of these patients with treatment and lack of the history of nutritional status especially iodine intake of the patients. This study did not explore hematological investigation for iron profile of the patients.

CONCLUSION

Decreased iron profile in subclinical hypothyroidism is significantly high and since there is no significant clinical manifestation of subclinical hypothyroidism at initial stages. It is suggestive to regularly investigate iron profile for early detection and its early management.

REFERENCES

1. Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J. Harrison's Principles of Internal Medicine. 19th ed. Vol. 16. McGraw Hill Education; 2015. 2283–2308 p.
2. Rugge B, Balshem H, Sehgal R. Screening and Treatment of Subclinical Hypothyroidism or Hyperthyroidism. :123.
3. Rifai N, Horvath AR, Wittwer C, editors. Tietz textbook of clinical chemistry and molecular diagnostics. St. Louis, Missouri: Elsevier; 2018. 1867 p.
4. World Health Organization. Iodine status worldwide: WHO global database on iodine deficiency. 2004;
5. Chellan R, Paul L. Prevalence of Iron-Deficiency Anaemia in India: Results from a Large Nationwide Survey. 2010;19(1):23.
6. Mishra AK, Anand R, Verma SP, Gupta KK. Study of impact of subclinical hypothyroidism on iron status and hematological profile. Int J Adv Med. 2018 Mar 21;5(2):446.
7. Yilmaz S, Ozan S, Benzer F, Canatan H. Oxidative damage and antioxidant enzyme activities in experimental hypothyroidism. Cell Biochem Funct Cell Biochem Its Modul Act Agents Dis. 2003;21(4):325–30.
8. Torti FM, Torti SV. Regulation of ferritin genes and protein. Blood. 2002;99(10):3505–16.
9. Hess SY, Zimmermann MB, Arnold M, Langhans W, Hurrell RF. Iron deficiency anemia reduces thyroid peroxidase activity in rats. J Nutr. 2002;132(7):1951–5.
10. Smith SM, Johnson PE, Lukaski HC. In vitro hepatic thyroid hormone deiodination in iron-deficient rats: effect of dietary fat. Life Sci. 1993;53(8):603–9.
11. Das C, Sahana PK, Sengupta N, Giri D, Roy M, Mukhopadhyay P. Etiology of anemia in primary hypothyroid subjects in a tertiary care center in Eastern India. Indian J Endocrinol Metab. 2012;16(Suppl 2):S361.
12. Beard JL, Borel M, Derr J. Impaired thermoregulation and thyroid function in iron-deficiency anemia. Am J Clin Nutr. 1990;52 (5): 813–9.
13. Santin AP, Furlanetto TW. Role of estrogen in thyroid function and growth regulation. J Thyroid Res. 2011;2011.
14. Lampka M, Junik R, Nowicka A, Kopczyńska E, Tyrakowski T, Odrowąż-Sypniewska G. Oxidative stress markers during a course of hyperthyroidism. Endokrynol Pol. 2006;57(3): 218–22.
15. Baskol G, Atmaca H, Tanriverdi F, Baskol M, Kocer D, Bayram F. Oxidative stress and enzymatic antioxidant status in patients with hypothyroidism before and after treatment. Exp Clin Endocrinol Diabetes. 2007;115(08):522–6.
16. Bhimte B, Agrawal B, Sharma V, Chauhan SS. Oxidative stress status in hypothyroid patients. Biomed Res. 2012;23(2):23.
17. Christ-Crain M, Meier C, Huber P, Zulewski H, Staub J-J, Muller B. Effect of restoration of euthyroidism on peripheral blood cells and erythropoietin in women with subclinical hypothyroidism. Horm-ATHENS. 2003;2:237–42.
18. Mehmet E, Aybike K, Ganidagli S, Mustafa K. Characteristics of anemia in subclinical and overt hypothyroid patients. Endocr J. 2012;59(3):213–20.