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Original Research Article

Study of impact of subclinical hypothyroidism on iron status and hematological profile

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ABSTRACT

Background: Thyroid hormones play an important physiological role to maintain balance of metabolism of entire human body. Erythrocyte abnormalities are frequently associated with thyroid disorder. Subclinical hypothyroidism, often a hidden entity, is associated with iron-deficiency anemia along with other hematological disorders. Thyroid hormones have a crucial role in metabolism and proliferation of blood cells. Thyroid dysfunction has profound effects on blood cells such as anemia, alters RBC indices including MCV, MCHC as well as iron stores. Present study was carried out to investigate and explore subclinical hypothyroid patients, to know the effect of subclinical hypothyroidism on hematological parameters and body iron store.
Methods: This retrospective study included 200 newly diagnosed, untreated subclinical hypothyroid, and 200 healthy euthyroid individuals. The hematological parameters and thyroid profile of the subjects were assessed by the mean, standard deviation (SD). Student's t-test was used to report our results, with p-value <0.05 considered as statistically significant.
Results: In this study we have compared hemoglobin level, red cell indices, serum Ferritin among study group and euthyroid healthy group and found that mean hemoglobin, serum ferritin and RBC indices were significantly depleted in subclinical hypothyroid patient in comparison to euthyroid group. 37 of total 200 [18.22%] newly diagnosed subclinical hypothyroid patients was suffering from Iron deficiency anemia with significant number of patients having hemoglobin level less than 10 gm%.
Conclusions: Iron deficiency anemia is quite common in Subclinical hypothyroidism and is often associated with depleted body iron store and complication of getting converted into primary hypothyroidism. As there is no significant clinical manifestation of SCH at earlier stages with anemia it is advisable to routinely investigate it for early detection allowing its early management.

Keywords: Anemia, Hypothyroidism, Iron, Subclinical

INTRODUCTION

Subclinical hypothyroidism, also called mild hypothyroidism, early thyroid failure, preclinical hypothy-roidism or decreased thyroid reserve is a condition with elevated serum thyroid-stimulating hormone in the setting of normal total or free thyroxine (T4) concentration in serum.[1] Most Patients have vague, nonspecific symptoms of subclinical hypothyroidism or are asymptomatic and identified during routine blood tests. The prevalence of subclinical hypothyroidism has been reported to be approximately 4% to 10% in different geographic populations but some reports have suggested the presence of subclinical hypothyroidism to be much

higher than previously reported. Subclinical hypothyroidism has been long associated with hypercholesterolemia, atherosclerosis, cardiovascular mortality, infertility, poor obstetric outcome, neuropsychiatric symptoms, unprovoked deep vein thrombosis, and common bile duct stones.[1-5]

Hematopoietic system is one of the primary systems affected by hypothyroidism and anemia is the most common manifestation. Hypothyroidism can cause a wide variety of anemic disorders. Numerous mechanisms are involved in the pathogenesis of this anaemia that can be microcytic, macrocytic and normocytic.[6] The most frequently encountered type of anemia is normochromic normocytic anemia. The most frequent reason of this is the bone marrow repression due to thyroid hormone deficiency which also causes defective erythropoietin production. Macrocytic anaemia is caused by malabsorption of vitamin B12, folic acid, pernicious anaemia and inadequate nutrition.

Microcytic anemia in hypothyroidism is due to iron deficiency and is largely due to malabsorption observed in hypothyroidism and menorrhagia occurring as a result of various hormonal instability. Low ferritin levels have been observed in hypothyroid patients.[7] Iron is a component of many enzymes including thyroid peroxidase (TPO) which takes part in the initial two steps in thyroid hormone biosynthesis.[8] Several studies in animals and humans have shown that nutritional iron deficiency may significantly lower the circulating levels of both thyroxine and triiodothyronine and may also reduce conversion of T4 to T3.[9,10]

Iron deficiency in turn decreases plasma concentrations of T3 and T4 and increase in vitro hepatic rT3 deiodination, suggesting 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.[6] Thus, the condition becomes a vicious cycle as iron deficiency may both be a cause and an effect of subclinical hypothyroidism. Thus, the relationship between subclinical hypothyroidism and iron deficiency is very complex and intriguing. 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 association of subclinical hypothyroidism and iron deficiency anemia, but due to limited number of large cohort studies, a definitive status of this entity is still eluting the clinicians posing problems in management.

Present study was carried out to investigate and explore subclinical hypothyroid patients, to know prevalence and severity of iron deficiency anemia in them and to investigate the effects of subclinical hypothyroidism on body iron stores and hematopoiesis by evaluating hemoglobin level and red cell indices.

METHODS

The cases were selected randomly from subjects attending the out-patient's clinics of Medicine department of King George Medical University (KGMU), Lucknow and from subjects referred to the Central Laboratory from other specialties for investigations during the period of one year, from August 2016 to July 2017. Five hundred and seventy-two patients of subclinical hypothyroidism presenting were evaluated for possible inclusion in this study.

Exclusion criteria were pregnant women, patients with hemolytic anemia, gastrointestinal and genitourinary losses, comorbid conditions such as connective tissue disorders, haemoglobinopathies, bleeding disorders renal insufficiency/failure, Coronary heart disease, uncontrolled hypertension, diabetes mellitus, or any endocrine disease other than hypothyroidism. Patients previously treated for hypothyroidism or on anti-thyroid medication were excluded. Patients under the treatment that might affect blood parameters such as steroids or had received anemia treatment were also not included in the study.

Out of the five hundred and seventy-two patients of subclinical hypothyroidism, 200 participants were recruited for the study after fulfilling inclusion criteria along with 200 apparently healthy age and sex matched euthyroid controls.

Demographic characters such as age, sex, height, and weight of all participants were noted. Serum Free T3, Free T4 and TSH were measured by Electrochemiluminescence Immuno Assay method. Estimation of serum anti-TPO antibodies in addition to the thyroid function test (T3, T4, and TSH) was carried out. Serum Iron, Iron binding capacity, Ferritin, Vitamin B12 and Folic acid levels were measured by Immuno assay method using Cobas Analyzer. EDTA samples were used for Complete blood count using Sysmex Fully Automated Hematology Analyzer. Peripheral smears of anemic patients were examined to confirm the type of anemia due to erythrocyte morphology and to exclude other pathologies such as leukemia. Patients also underwent upper GI scopy, stool for occult blood and urine analysis for hematuria to rule out secondary losses.

Anemia was defined as hemoglobin levels lower than 12g/dL in women and 13gm/dL in men and was further classified as: Mild - Hb 10 to 12gm%, Moderate - Hb 8 to 10gm%, Severe-Hb <8gm%.[4] Iron deficiency anemia was defined as serum iron levels lower than 60µg/dL, iron binding capacity greater than 215µg/dL, ferritin levels lower than 10ng/dL and with microcytosis and hypochromia in peripheral blood smear.

Statistical analysis

The collected data was analyzed by applying appropriate statistical tests- chi square test, (with continuity correction for all tables (2 by 2) and fisher exact test (for all 2 by 2 tables where p-value of chi-square test is not valid due to small counts), unpaired t-test (if data passes normality test), Mann-Whitney test (if data fails normality tests).

RESULTS

Two hundred participants meeting our inclusion criteria were investigated for the presence of anemia and to determine the status of body iron and compared to the control group (Table 1).

Table 1: Distribution of overt and subclinical hypothyroid patients.

	Study population
Subclinical hypothyroidism	200
Controls (Euthyroid)	200
Total	400

The mean age was 33.59±11.23 years in the cases and 34.11±10.15 years in the control group. On comparing it was found that age of the two groups in the study was comparable with maximum number of patients within the age group 31-40 years (44%). Amongst the cases, males were 9.43% and females were 90.57%. Controls had 9.38% males and 90.62% females. Thus, both the groups were comparable regarding the sex distribution. The hemoglobin level (gm/dl) in the cases and controls was 9.81±2.01 and 12±2.17 respectively. On comparing it was observed that the hemoglobin was significantly lower in the cases as compared to the controls (P<0.05).

Table 2: Comparison of prevalence of anemia in patients with subclincal hypothyroidism and control group.

	Total % (N)	Subclinical % (N)	Control % (N)
Anemia[a]			
Yes	42.5 (170)	57 (114)	29 (56)
No	77.5 (230)	43 (86)	71 (144)

[a]Anemia (Hb level < 12.0 g/dl(F), <13 g/dl(M)); no anemia (Hb level ≥12.0 g/dl(F), ≥13 g/dl(M)

When all the participants were evaluated for anemia, we observed that anemia was present in 57% patients (114 out of 200) in the subclinical hypothyroid group and 29% patients in the control group (Table 2). Frequency of microcytic anemia in subclinical hypothyroid group and control group was 18% and 6% respectively.

Table 3: Demographic measures and biochemical values.

Characteristics	Subclinical Hypothyroidism	Control Group	P value
N	200	200	
Gender, Female	90.57%	90.62%	0.98
Age (years)	33.59±11.23	34.11±10.15	0.62
TSH (mIU/ml)	8.21±3.94	3.72±1.96	<0.0001
FT4 (ng/dl)	5.48±2.66	12.11±3.25	<0.0001
FT3 (pg/ml)	2.34±1.48	6.7±1.56	<0.0001
Hb (g/dl)	9.81±2.01	12±2.17	<0.0001
MCV (fL)	84.8±5.8	83.8±6.9	0.12
S.Iron (ug/dl)	70.78±40.57	78.26±25.33	0.02
S. Ferritin (ng/ml)	41.44±22.83	45.51±29.67	0.13
TIBC (ug/dl)	393.80±79.19	343.17±42.3	<0.0001

*The data is expressed as mean ± SD. P value was calculated at 95 % confidence interval

On analysing the iron profile, serum iron level (µg/dl) in the subclinical hypothyroid group and the control group was 70.78±40.57 and 78.26±25.33 respectively(p<0.05).

The total iron binding capacity (TIBC) (µg/dl) in subclinical hypothyroid group and control group was 393.80±79.19 and 343.17±42.3 respectively (p<0.05). Serum ferritin levels (µg/dl) in the subclinical hypothyroid group and the control group was 41.44±22.83 and 145.51±29.67 respectively(p<0.05). Values of TIBC, Fe, ferritin were significantly lower in hypothyroid cases as compared to control (p<0.05).

Ferritin was found to be negatively correlated (r=0.271, p<0.05), iron was also negatively correlated (r=-0.161, p=0.02) while TIBC was found to be positively correlated with TSH (r=0.174, p=0.013). On studying the co-relationship between TSH and hemoglobin levels, we found that there was a negative correlation between these two factors in cases. Pearson's correlation coefficient was

-0.32 (95% CI: -0.52 to -0.07). This was statistically significant with a P value of 0.0066 (Figure 2).

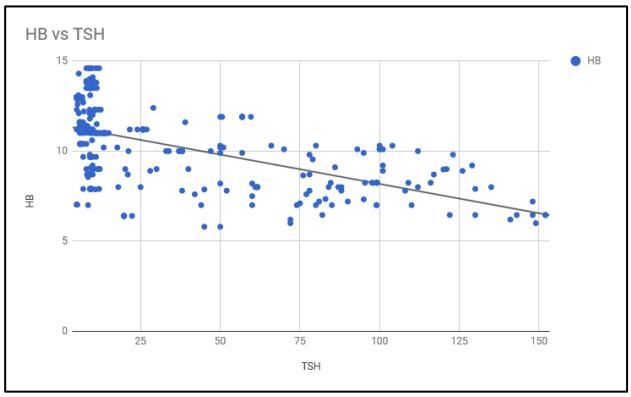

Figure 2: Scatter diagram showing correlation between hemoglobin and TSH.

DISCUSSION

Anemia is a severe public health problem in India, which may be precipitated by conditions such as hypothyroidism. Thyroid disorders arguably are among the commonest endocrine disorder worldwide with India as no exception. Recent population-based study in India for prevalence of hypothyroidism in adults shows it to be 3.9%. Prevalence of subclinical hypothyroidism is even higher at 9.4%.[11] The anemia of hypothyroidism has been ascribed to a physiological compensation for the diminished need of tissues for oxygen. The low plasma erythropoietin levels found in hypothyroid anemia is in accordance with this hypothesis.[12] Treatment of subclinical hypothyroidism with levothyroxine in patients with iron-deficiency anemia has beneficial blood count, white blood cell differential, reticulocyte effects on iron status and blood count indices.[13] Subclinical hypothyroidism is thus a hidden disorder which is detected during investigation of frequently encountered problems like anemia more precisely nutritional or Iron deficiency anemia should be investigated and corrected. Therefore, considering the prevalence of subclinical hypothyroidism to be much greater than overt hypothyroidism and the overt nature of the condition, magnitude of the problem has remained virtually unknown. Present study was carried out to investigate and explore subclinical hypothyroid patients, to know prevalence and severity of iron deficiency anemia in them and to investigate the effects of subclinical hypothyroidism on body iron stores.

In this study, while analyzing the study group author observed that eighty percent of total hypothyroid patients were females. Hypothyroidism is more prevalent in female population as estrogen has an anti-thyroid action. Thus, in reproductive age group, female propensity is seen in hypothyroid patients. Previous study has shown similar finding. Anemia was present in 57% patients in the subclinical hypothyroid group and 29% patients in the control group which was found to be clinically significant ($p<0.05$). This result gave rise to the thought that presence of subclinical hypothyroidism may be an important risk factor in anemia development considering its high prevalence. Frequency of microcytic anemia in subclinical hypothyroid group and control group was 18% and 6% respectively, which was statistically significant. Thus, subclinical hypothyroidism can be identified as a risk factor for development of microcytic hypochromic anemia and iron deficiency.

In the case control study, author found a significant low level of TIBC, iron and ferritin in subjects with altered thyroid profile indicated by decreased in blood levels of fT4 ($p<0.05$) and fT3 ($p=0.05$). Serum iron level (µg/dl) in the subclinical hypothyroid group and the control group was 70.78±40.57 and 78.26±25.33 respectively($p<0.05$). TIBC (µg/dl) in subclinical hypothyroid group and control group was 393.80±79.17 and 343.17±42.3 respectively. Serum ferritin levels (µg/dl) in the subclinical hypothyroid group and the control group was 41.44±22.83 and 145.51±26.67 respectively. Also, the levels of ferritin, iron were found to decrease while that of TIBC to increase in patients suffering from subclinical hypothyroidism as compared to healthy controls. These results are in accordance with other studies which reported that iron deficiency may be associated with low levels of thyroid hormones.[5,6,8]

In a study conducted by Das C et al, prevalence of anaemia in subclinical hypothyroid group was found to be 26.6%.[14] Similar to the pattern observed by us, normocytic, normochromic anemia was the most common type of anemia followed by microcytic anemia in 43.3% of all anemic patients. The observation made by us reported a higher proportion of anemics among patients with subclinical hypothyroidism with a major number of patients having microcytic hypochromic anemia.

Kulkarni et al observed the prevalence of anemia to be 75% in hypothyroid patients with normocytic normochromic (65.9%) as the most common type of anemia, they also reported a significant co-relation between TSH and hemoglobin similar to the co-relationship observed by us.[15] Previous study by Bremner et al. also reported significant relationships between free T3 and Hb, and inverse relationship of TSH with serum iron and transferrin saturation which was also observed by us.[16] Bivolarska et al. also found slight negative statistically significant correlative association between the levels of TSH and Hb ($r = 0.217$, $p = -0.033$) similar to our findings.[17]

In the study conducted by Larson et al, 52% (13 out of 25) of his patients of hypothyroidism had iron deficiency anaemia.[18] Mehmet et al reported the prevalence of microcytic anemia in overt hypothyroid patients, subclinical hypothyroid patients and normal subject to be 5%, 6%, 6% respectively($p=0.116$).[19] Kulkarni et al

observed microcytic hypochromic morphology in 22.72% patients similar to the observations made by us.

Some studies have also investigated the role of iron deficiency on thyroid function. Akhter S et al, reported that a significant difference in thyroid hormone status in iron deficient people could be a reflection of disturbed activities of iron depended enzyme such like TPO which disturb the overall metabolism of thyroid hormone.[20] A similar study was done by Hess SY et al, have found that thyroid peroxidase activity is significantly reduced in iron deficient rats they also mentioned the role of iron in transportation of thyroid hormone into the cells and lack of iron leads to pooling of thyroid hormone leading to metabolically hypothyroid condition.[21] Christ-Crain M et al, found that external intake of thyroxine increases the overall rate of erythropoiesis by increasing the level of erythropoietin, which leads to increased requirement of iron and dealt in manifestation of iron deficiency anemia.[22] Similar finding was observed by Erdogan M et al., which state the increased occurrence of microcytic hypochromic anemia in clinical and subclinical cases of hypothyroidism as compared to controls.[19] Eftekhari MS et al., have notice an increase in rT3 is related to change in iron status and that the increased level of rT3 is inversely correlated with changes in plasma ferritin concentration, they also consolidate the relation between iron deficiency and altered thyroid profile.[23] Some other studies have established the inverse correlation between Hb (Hemoglobin) and thyroid hormone staus, Bremmer AP et al., found the significant association between free T3 and Hb and inverse relationship of TSH with serum iron and transferrin saturation. Bivolarska A et al, reported the firm association between T4 level and Hb (r= 0.217, p=0.33), on the other hand some other study like Yavuz O et al., reported no association between thyroid hormone and iron deficiency.[24] Thus, subclinical hypothyroidism and iron deficiency anemia are interdependent entities who do not come to notice until the vicious cycle augments both the disease processes. Given the overt nature of subclinical hypothyroid state, all patients presenting with iron deficiency should be evaluated for thyroid dysfunction, and all subclinical hypothyroid patients should undergo evaluation for iron deficiency and treated accordingly to break the vicious cycle. Thus, it can be concluded that estimation of iron profile may be of significance in patients with subclinical hypothyroidism as it may affect the treatment protocol and also aid in monitoring the disease process.

CONCLUSION

Presence of anemia in subclinical hypothyroidism is also significantly high and since there is no significant clinical manifestation of subclinical hypothyroidism at initial stages it is advisable to routinely investigate it for early detection allowing its early management. Therefore, our study advocates that both overt and subclinical hypothyroidism should be considered a risk factor for development of iron deficiency anemia and should be treated adequately for optimal response to therapy.

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