Original Article

Impact of subclinical hypothyroidism on iron status and hematological parameters

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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 condition, is associated with iron-deficiency anemia along with other disorders. Thyroid hormones have a crucial role in metabolism and proliferation of blood cells. Thyroid dysfunction induces different effects on blood cells such as anemia, alters RBC indices including MCV and MCHC. In this study it was attempted to evaluate effect of subclinical hypothyroidism on hematological parameters and body iron store

Methods: This retrospective study included 158 subjects, among which 118 were newly diagnosed, untreated subclinical hypothyroid [n=118], and 40 healthy euthyroid [n=40] 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. 21 of total 118 [17.8%] newly diagnosed subclinical hypothyroid patients was suffering from Iron deficiency anemia with hemoglobin level less than 10 g%.

Conclusion: Subclinical hypothyroidism is often associated with anemia, 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.

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Introduction

Thyroid hormones are required for normal differentiation and development of fetus. It is a global need of our body to maintain physiological function and metabolic balance. Disorders of thyroid function are the most common endocrinal disorder. [1] Subclinical hypothyroidism (SCH), also called mild hypothyroidism, early thyroid failure, preclinical hypothyroidism or decreased thyroid reserve is a term used for a condition in which there are small elevations in thyroid-stimulating hormone [TSH], yet normal circulating levels of thyroid hormones. [2] In SCH serum TSH level > 5mIU/L with normal T4 is often taken as a cut-off though TSH level may be > 10mIU/L with normal T4 level which should be treated accordingly. Some patients may present with vague and nonspecific symptoms of subclinical hypothyroidism, but most affected individuals are asymptomatic and identified during routine blood investigations. The prevalence of subclinical hypothyroidism has been reported to be approximately 4% to 10% in different geographic populations. [3] The presence of subclinical hypothyroidism is far higher, and reported to be about 4-10% in multiple populations and as high as 18% in the elderly. [4-7] It is reported that subclinical hypothyroidism is much more common than hyperthyroidism.[8] The prevalence of SCH increases with age, more commonly in females; but it approaches male after 6th decade of life. Nonetheless, early detection and treatment of sub-clinical thyroid dysfunction is potentially beneficial. Significant proportion of hypothyroid patients suffers from anemia. [9] Thyroid hormone plays a role in hemoglobin synthesis in adults and maturation of hemoglobin in fetus and by affecting hematopoietic process, hypothyroidism results in anemia through slowing the oxygenation process. [10-12] It is thought that thyroid hormones affect hematopoiesis through an increase in erythropoietin production or hematopoietic factors by nonerythroid cells. [13] Iron deficiency anemia which is quite common in Indian subcontinent should be clarified with specific clinical condition that results in iron deficiency. Hypothyroidism has also been associated with low serum iron, folic acid and vitamin B12. In subclinical hypothyroidism iron deficiency anemia has been particularly reported.[3,14]Iron deficiency impairs thyroid hormone synthesis by reducing activities of heme-dependent thyroid peroxidase. Iron deficiency anemia blunts and iron supplementation improves the efficacy of iodine supplementation. [15] Generally it seems that hypothyroidism causes hypoplasia in all myeloid cell lineages and hyperthyroidism result in hyperplasia. With regard to lymphocytes, T3 is as a precursor substance for normal B cell formation in bone marrow through its mediation of pro-B cell proliferation. Therefore, thyroid disorders can induce different effects on various blood cell lineages. [16-18] Hypothyroidism can cause various forms of anemia [normochromic-normocytic, hypochromic- microcytic or macrocytic] through reducing the oxygen metabolism. Microcytic anemia generally attribute to malabsorption of Iron and loss of Iron by menorrhagia, whereas, macrocytic anemia causes or induces malabsorption of vitamin B12, folate, pernicious anemia and insufficient nutrition. [18]This study was taken to find out effect of hypothyroidism in body iron store in the form of Ferritin as well as effect on hematopoiesis by evaluating hemoglobin level and red cell indices.

Materials and Methods

Subjects and recruitment process: This retrospective-hospital based study was conducted at the Department of Biochemistry from November 2013 to July 2014. Pregnant females within the age group of twenty to forty year (both year inclusive) were taken into consideration in this study. All patients were referred from out-patient [OPD] and In-patient Department [IPD] to the central clinical laboratory for evaluation of thyroid function, complete blood count [CBC] along with other investigations. This study included 158 subjects, among which 118 were newly diagnosed untreated subclinical hypothyroid [n=118], and 40 randomly selected euthyroid and normal CBC count [n=40] individual.

Exclusion criteria: Patients with cardiovascular, cerebrovascular and neurological diseases, uncontrolled hypertension, Diabetes mellitus, chronic renal failure, previous history of any type thyroid disorder with thyroxine or antithyroid medication and pregnant females were excluded from the study.

Sample collection: About 5-6 ml of fasting venous blood was collected in EDTA and plain Vacutainer [BD Biosciences]. Plain tubes were kept in room temperature for half an hour for clot formation. Then plain tubes were centrifuged at 2500 RPM for 10 minutes to separate the serum. EDTA anticoagulated blood samples were processed in Abacus [Diatron, USA] five part cell analyzer for various hematological indices mainly hemoglobin [Hb], mean corpus-

cular value [MCV], mean corpuscular hemoglobin con- centration [MCHC].

Measurement of thyroid hormone profile and serum Ferritin: Serum aliquots of 500 µL were stored at 4°C in freezer to be run in batches. The samples were allowed to thaw prior to assay, mixed thoroughly. Hemolysed and lipemic samples were rejected. Bi level i.e. high and low control was run with each batch .Thyroid function test [TFT] comprising of total T3, T4 and TSH levels and serum ferritin measurement were carried out by chemiluminiscent Immunoassay[CLIA] method using Immulite 1000 [Siemens Inc, Germany] automated analyzer. Patients with thyroid hormone status of elevated serum TSH levels [>4.3 to <10 mIU/L] with normal levels of serum thyroxine [T4] and triiodothyronine [T3] were categorized as subclinical hypothyroidism. None of the patients had any indication [e.g., signs and symptoms of hypothyroidism, fatigue, constipation, depression, hyperlipidemia, goiter, infertility or menstrual irregularities]. All female patients were asked about their menstrual period duration, frequency, and amount of bleeding. Patients with a menstrual period lasting more than 5 days or more than usual amount of bleeding were excluded from study.

Statistical Analysis: Prior power analysis was not done to calculate the sample size in this study. The data of each group were checked for normality and found to have almost Gaussian distribution. The data of each group was expressed as mean ± standard deviation [SD]. Student t-test was carried out to compare with euthyroid healthy group. A *p*-value of <0.05 was considered as statistically significant. Data analysis, graph generation and statistical analysis were carried out by GraphPad Prism 5.0 software.

Result

In our study total 118 newly diagnosed subclinical hypothyroidism patients were recruited as cases [SCH] and 40 subjects were randomly selected as control [HC] that have normal thyroid profile and hematological parameters during investigation. Age and sex wise distribution and mean age of both the sexes among two groups have been shown in Table no 1.

21 out of total 118 SCH cases [17.8%] showed hemoglobin level less than 10 g% with altered MCV and MCHC values and depleted serum ferritin level. They were considered frank cases of Iron deficiency anemia as other common causes of increased iron loss or demand were excluded during selection of cases. Thyroid profiles of both the groups are shown in Table no 2. Notably high TSH [mean of 8.6 ± 10.6 mIU/L] values were observed in SCH when compared with HC with almost similar distribution of total T3 and T4 level. Distribution of Hemoglobin, MCV, MCHC and serum ferritin level in the groups are shown in Table no 3. All the four parameters in SCH were significantly depleted [*p*-value <0.001] when compared with HC group.

Table 1: Distribution of Age and sex

Groups	HC		SCH	
Sex	Male	Female	Male	Female
Number (n)	5	35	14	104
Mean age (Yr)	34.2	39.4	37	37.1
SD (Yr)	8.4	16.1	14.1	14.1

Table 2: Thyroid Profile of two study groups

Parameter	Mean (SD)	
	HC	SCH
TSH (mIU/L)	1.8 (1.1)	8.6 (1.6)
Total T3 (ng/dL)	119.1 (30.1)	119.2 (22.5)
Total T4 (µg/dL)	9.2 (3.3)	8.1 (1.8)

Table 3: Statistical result of parameters

Parameters	Mean (SD)		p-value
	HC	SCH	
Hemoglobin (g%)	13.67 (1.41)	11.14 (1.95)	<0.001
MCV (fL)	106.9 (7.13)	83.14 (10.57)	<0.001
MCHC (g/L)	25.85 (2.02)	22.35 (3.46)	<0.001
Ferritin (µg/L)	104.1 (43.5)	42.5 (22.6)	<0.001

Discussion

This retrospective hospital based study at Grant govt. Medical college & Sir JJ group of hospitals was carried out which is a major referral hospital of Mumbai city and its suburban areas. The National Family Health Survey-3 [NFHS-3] data suggests that nutritional anemia is a major public health issue in India and is primarily due to iron deficiency. [19]On the other hand thyroid disorders arguably are among

the commonest endocrine disorder worldwide with India as no exception. [20] 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%. [21]Thyroid hormones have crucial effect on erythropoiesis by induction of erythropoietin secretion and also proliferation of erythroid progenitors. [17,22] Subclinical hypothyroidism [SCH] is associated with serious complications. Substantial number of patients has risk of SCH getting converted into primary hypothyroidism and psychological disturbances. [23]There is increasing prevalence of subclinical hypothyroidism and primary hypothyroidism, especially in women. TSH measurement is well recognized sensitive test for detecting both subclinical hypothyroidism and primary hypothyroidism. It is the first recommended investigation for detection of thyroid disorder. [12] In our study major population with subclinical hypothyroidism was observed in females. Previous study has shown similar finding. [24] Thyroid diseases are frequently associated with erythrocyte abnormalities. [20] 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. [25] 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.[3] Subclinical hypothyroidism is a hidden disorder which is detected during investigation of some other causes. Frequently encountered problems like anemia more precisely nutritional or Iron deficiency anemia should be investigated and corrected. Their presence could steer towards thyroid dysfunction allowing its early detection and management. Subclinical hypothyroidism is known for its association with iron-deficiency anemia,[3,14] and all patients with iron-deficiency anemia who have no definite cause of blood loss or increased Iron demand or Iron malabsorption need to be examined for subclinical hypothyroidism. It may cause iron malabsorption or a decrease in iron incorporation and as a result an increase in iron loss. This may be reflected as depleted serum ferritin level. Hypothyroidism may have some effects on iron absorption by a decrease in acid secretion. Gastric acid degrades the organic iron complex [vegetable protein], reduces the trivalent ferric iron [Fe^{3+}] to ferrous iron [Fe^{2+}] which is physiologically active form, and improves proximal small bowel absorption of iron. Therefore levothyroxine prescription in such cases reverses the deleterious effect of hypothyroidism in iron deficiency. [3, 26, 27]The study results demonstrated that treatment of patients with subclinical hypothyroidism and iron-deficiency anemia with a combination of iron &levothyroxine resulted in a favorable outcome compared with treatment of patients with monotherapy of iron or levothyroxine alone. Hemoglobin as the leading indicator for improvement in anemia and thyroid stimulating hormone as an indicator for subclinical hypothyroidism both improved significantly in patients treated with the combination therapy compared with monotherapy. [28] We suggest those people with thyroid disorder should have routine screening of haematological, biochemical and hormonal profile assay and simultaneously proper management of this metabolic disease.

Conclusion

Hypothyroidism is the most common endocrinal disorder with variety of presentations. It has a detrimental effect on erythropoiesis which leads to depleted body iron store and anemia. As women are most common sufferer of hypothyroidism even with adequate iodine intake there should be mass screening for thyroid function along with hematological parameters for early detection and intervention. Subclinical hypothyroidism, which is detected by chance, will be detected earlier by screening and its consequences can be averted by proper intervention and follow up. India, where anemia is a burning health issue with most vulnerability to women of child bearing age, adolescent girls and young children, it is very important to investigate the root cause of anemia of one individual. In view of this study it is suggested that abnormal thyroid profile substantially influence the iron store and hematological indices leading to anemia. It was a hospital based retrospective study with limitation of small sample size and insufficient data. Further elaborate study is required to investigate the major endocrinal disorder of vulnerable population with its role in iron homeostasis of body and all types of anemia.

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Competing Interests
None declared

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