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A Study to Evaluate Effect of Levothyroxine Supplementation in Iron Deficiency Anemia Patients having Subclinical Hypothyroidism

KEYWORDS: Iron deficiency anemia, subclinical hypothyroidism, levothyroxin

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ABSTRACT *INTRODUCTION- Patients of iron deficiency anemia (IDA) with subclinical hypothyroidism are often resistant to iron therapy. This combo state requires combination therapy with both levothyroxine and iron to achieve maximal improvement. OBJECTIVE- To evaluate the effect of levothyroxine supplementation in IDA patients having subclinical hypothyroidism. MATERIAL AND METHODS- A case control study done at medical college hospital in North India among 50 female patients of SCH having IDA. Study participants were divided into two groups, 25 were taken as cases and other 25 as controls. Cases were given 300 mg of elemental iron in divided doses and 25ug of levothyroxine daily for 3 months. Controls were given 300 mg of iron only. Hematological parameters (Hb, Hct, serum Iron, TIBC, serum ferritin), FreeT4 and TSH were assessed in both the groups. RESULTS- On completion of therapy, increase in Hb, Hct, Serum Iron, Serum Ferritin and FreeT4 was significantly more in cases than controls ($p<0.001$ for each). Reduction in TSH and TIBC was significantly more in cases than controls ($p<0.001$).CONCLUSION -Treatment of SCH has significant beneficial effect on both hematological as well as iron indices in patients of IDA.*

INTRODUCTION

Deficiency of thyroid hormone affects almost all systems of body. Subclinical hypothyroidism(SCH) is although considered an asymptomatic state, but it is actually associated with multiple complains like lack of energy, menstrual irregularities, weight gain, mood swings, hair fall, dry skin and fertility issues. On investigating them we find some metabolic abnormalities also, in form of dyslipidemia, dilutional hyponatremia and anemia.

In our clinical practice, we see patients of iron deficiency anemia(IDA) who receive iron for long periods without significant improvement. Studies show a high incidence of subclinical hypothyroidism in these refractory patients.[1,2] Hypothyroidism is a common endocrine disorder and is frequently associated with IDA.[3] Subclinical hypothyroidism (SCH) is also a common problem with a prevalence of 4-10% in general population.[4] IDA in SCH is because of malabsorption of iron, loss of iron in menorrhagic state. Malabsorption of iron is attributed to achlorhydria of subclinical hypothyroidism. Iron deficiency state also impairs thyroid hormone synthesis by reducing activity of thyroid peroxidase.

We have very few studies in Indian context on SCH and it's relation with IDA. Anemia as a consequence of untreated subclinical hypothyroidism is however suggested by some studies. One study shows iron deficient state as a frequent finding in women with SCH.[5] This study advised routine evaluation of ferritin in such patients. However an another study showed no significant improvement in Hb and Hct level after achieving euthyroidism in women with subclinical hypothyroidism.[6] A previous study also emphasize relation between low levels of iron and hypothyroid state.[3] Many studies have shown direct relation of thyroid hormone in erythropoiesis.[7]

Since there had been very few studies on subclinical hypothyroidism in iron deficiency anemia, here we planned this study to evaluate the effect of levothyroxine supplementation in IDA patients having SCH.

MATERIAL AND METHOD-

This was a case control study done at medical college hospital in North India among 50 female patients of iron deficiency having subclinical hypothyroidism, after taking due informed consent from study participants and permission from Institutional Research Review Board / Institutional Ethics Committee. Study participants were divided in two groups, 25 patients taken as cases and other 25 (age matched) patients as controls. Subclinical hypothyroidism is defined as elevated serum TSH (Thyroid stimulating hormone) in the setting of normal total or free T3 and T4 levels.[8] Subclinical hypothyroidism was diagnosed when TSH was 4.5-10mIU/L.[9] IDA was diagnosed when Hb <11 gm/dL, low serum iron (<30 µg/dL) with low serum ferritin (<15 µg/dL) and raised iron binding capacity(>360 µg/dL) were present.[10]

Cases were given 300 mg of elemental iron in divided doses and 25 ug of levothyroxine daily for 3 months whereas controls were given 300 mg of elemental iron in divided doses daily for same period. Patients having anemia other than iron deficiency, taking drugs that interfere with iron metabolism (i.e. Proton pump inhibitor), associated comorbid conditions (i.e. renal failure, coronary artery disease, hypertension, diabetes mellitus) were excluded. Patients who had received blood transfusion in last 120 days were also excluded. Subjects with history of previous thyroid disease and treatment were also excluded. From each patient a complete history taking and thorough physical examination was performed. After an overnight fast, venous sample was taken from antecubital vein and sent for Hb, Hct, Serum Iron, TIBC, Serum Ferritin ,TSH, free T_4 .

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TSH was measured by immunoradiometricassay and FreeT_4 by radioimmunoassay.

STATISTICAL ANALYSIS-
Microsoft Excel and SPSS 17.0 for Windows were used for data storage and analysis._Continuous variables were expressed as mean ± standard deviation. Student's t test was used to determine statistical difference between variables. Statistical significance was set at P value ≤ 0.05.

RESULTS-
In our study 50 female patients with SCH and concomitant IDA were recruited. There was no significant difference in case and control for age. Also there was no significant difference in Hb, Hct, serum ferritin, serum iron, TIBC, free T_4 and TSH before the start of treatment. (P >0.05 for each). After treatment the difference in hematological parameters (Hb, Hct), iron indices (serum ferritin, serum iron, TIBC) and thyroid parameters (free T_4, TSH) was statistically significant among cases and controls (p <0.001 for each) (Table No. 1)

The mean change in Hb for cases (1.70±1.75 gm/dL) was significantly higher than controls (0.40±0.23 gm/dL) (p<0.001) and thus making the combined treatment highly effective. Similarly the mean change in Hct was also significantly higher in case group (6.70±2.88 %) compared to controls (1.40±1.11%) (p <0.001). Mean change in serum ferritin also followed the same trend with change of 12.40±2.15 µg/dL for cases and 3.80±2.21 µg/dL for controls (p <0.001). The mean increment in serum iron was significantly higher in cases group (53.00±7.47 µg/dL) compared to controls (10.00±4.71 µg/dL) (p <0.001). Mean reduction in TIBC was also greater for cases (30.00± 11.46 µg/dL) compared to controls (4.00±1.32 µg/dL) (p <0.001). Similarly mean reduction in TSH was significantly more in cases (4.00±1.35mIU/L) than controls (0.20±0.20 mIU/L)(p <0.001). Free T_4 improved significantly with a mean change of 1.50± 0.89ng/dL and 0.30±0.40ng/dL for cases and controls respectively.(p <0.001) (Table No.2)

DISCUSSION
In this study we have evaluated the effect of levothyroxine supplementation in IDA having SCH.

Many studies indicate that iron deficiency impairs thyroid metabolism[11]. Reduced levels of T3 and T4 and elevated levels of TSH are found in IDA.[12,13] This supports our clinical observation of high prevalence of SCH in IDA patients.

In our study, we found significant improvement in serum iron indices as well as in hematological indices in IDA patients having SCH after 12 weeks of levothyroxine with iron supplementation compared to iron supplementation alone. Consistent with our study Cinnemere et al[1] also found a statistically significant difference in patients treated with the above combination. These findings support that treating SCH in iron deficient state had utmost importance and patients having IDA resistant to iron alone might benefit from treating SCH. In a study done by Ravanbod et al[14] both Hb and TSH improved significantly in patients who were treated with combination of Levothyroxine and Iron than iron alone. It thus further supports our concept of correction of both the metabolic problems jointly.

One study by Christ crain et al[6] didn't show any change in Hb and Hct even after achieving euthyroid state. These results are contrary to our findings. Possible explanation of this might be recruitment of older and non-anemic subjects by Christ crain et al[6]. Another fact is that hemoglobin/HCT alone is not the reliable marker of RBC population. Hypothyroidism per se is a hypovolumic state and it may increase Hb/HCT falsely thus interfering with proper evaluation.[15] Our study population was euvolumic as they had SCH and the improvement in hematological parameters, including Hb/HCT, cannot be attributed to reduced plasma volume alone.

Our study shows significant mean change in both hematological and iron indices. Thus thyroid hormone had effect on both hematological variables and iron indices. It thus reflects that apart from stimulating erythropoiesis, iron metabolism is also significantly affected by thyroxine. This is also consistent with Cinemere et al[1]. Previous reports[16] also showed that other mechanisms are involved in IDA of SCH. No response of exogenous erythropoietin administration in anemia was observed in renal failure patients with SCH, concluding mechanisms other than erythropoietin also play their role in anemia with SCH. It suggests thyroid hormone helps erythropoiesis in multiple ways including incorporation of iron into erythrocytes[17], increasing iron absorption, helping proliferation and differentiation of erythroid progenitors.[18]

In summary our study highlights the importance of treating SCH in IDA. This study concluded that resistant IDA will get benefited by levothyroxine supplementation.

Our study also had some limitation including a smaller sample size and small follow up period. Also current study was done at a tertiary care center so the study population might not represent the whole population. We suggest further studies with a larger sample size and long follow up.

CONCLUSION:
Treatment of SCH had significant effect on both hematological as well as iron indices in patients of IDA. Subclinical hypothyroidism should be sought and treated in Iron deficiency anemia.

CONFLICT OF INTEREST: None
SOURCE OF SUPPORT: Nil

Table No. 1: Various parameters of study subjects before and after treatment

Parameter	Pre-treatment			Post-treatment		
	Case (n 25)	Control (n 25)	P	Case (n 25)	Control (n 25)	P
Hb (gm/dL)	9.30±0.78	9.40±0.79	>0.05	11.00±0.34	9.80±0.64	<0.001
Hct(%)	31.70±1.23	30.90±1.27	>0.05	38.40± 2.59	32.30±1.17	<0.001
Serum Ferritin (µg/dL)	10.60±1.18	11.00±1.25	>0.05	23.00±1.53	14.80±1.24	<0.001
Serum Iron(µg/dL)	22.00±3.44	18.00±3.53	>0.05	75.00±6.41	28.00±2.95	<0.001
TIBC(µg/dL)	375.0±0.72	380.0±11.86	>0.05	345.0±9.50	376.0±11.67	<0.001
Free T_4 (ng/dL)	13.50±0.72	12.30±0.79	>0.05	15.00±0.64	12.00±0.93	<0.001
TSH(mIU/L)	7.60±0.80	6.70± 0.54	>0.05	3.60±0.86	6.50±0.60	<0.001

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Table No. 2: Mean change in various parameters after treatment in study subjects

Parameter	Mean change		
	Case	Control	P
Hb (gm/dl)	1.70±1.75	0.40± 0.23	<0.001
Hct(%)	6.70±2.88	1.40± 1.11	<0.001
Serum Ferritin (µg/dL)	12.40±2.15	3.80± 2.21	<0.001
Serum Iron(mg/dl)	53.00±7.47	10.0±4.71	<0.001
TIBC(µg/dL)	30.0±11.46	4.00± 1.32	<0.001
Free T_4(ng/dl)	1.50± 0.89	0.30± 0.40	<0.001
TSH(mIU/L)	4.00±1.35	0.20± 0.24	<0.001

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