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Retraction notice to: Clinical Importance of Evaluation of Iron Profile Parameters in Hypothyroid Patients

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This article (Accepted on 24 December 2017; Published 31 January 2018) in the Volume 4 Issue 1 January 2018 issue of the Journal by Dr. Neeraj Singla and Dr. Heena Singla, has been retracted with the agreement of the authors. It was brought to the attention of the Editor-in-Chief regarding misconduct by authors. Subsequently after thorough investigation and discussion by editorial team it was decided to retract the article because of Scientific Misconduct that involves Data fabrication and falsification.

We publish this editorial comment not only to inform the medical community but also to prevent similar situations from arising in the future.

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Original Research Article.

Clinical Importance of Evaluation of Iron Profile Parameters in Hypothyroid Patients

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ABSTRACT

Introduction: The prevalence of iron deficiency anaemia has been found to further increase along with increase in the incidence of thyroid disorders. Low thyroid function has been one of the most overlooked causes of iron deficiency anaemia. Also, normal thyroid status requires adequate levels of many trace elements, which include iodine and iron. This study was carried out for estimation of the levels of serum iron, TIBC and serum ferritin in hypothyroid patients.

Methods: This case-control study was carried out at a tertiary care center. 100 cases of hypothyroidism and 100 apparently healthy euthyroid controls were enrolled for the study. Apart from routine laboratory investigations, measurement of serum ferritin, iron and TIBC was done. Diagnosis of hypothyroidism was confirmed by measurement of levels of free T3, free T4 and TSH.

Results: Patients of hypothyroidism had significantly lower levels of iron and ferritin, while TIBC was significantly higher in these patients in comparison with euthyroid healthy controls. (p = 0.00, p =0.00, p = 0.00). Strong positive correlation was established between the levels of free T3 and serum ferritin (r = + 0.63, p< 0.05) in these patients.

Conclusion: Hypothyroidism may cause bone marrow repression and/or decrease in production of erythropoietin. In our case-control study, a large number of hypothyroid patients had underlying iron deficiency anaemia as well. So screening for iron deficiency anaemia and its timely treatment should be regarded as important treatment in hypothyroid patients to achieve best results.

Keywords: Primary Hypothyroidism, Iron Deficiency Anaemia, Erythropoietin.

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INTRODUCTION

Thyroid dysfunction is a common endocrine disorder worldwide. In India too, there is a significant burden of thyroid diseases. According to recent surveys, about 11.5% of Indian population suffers from thyroid disease, while prevalence of undetected subclinical hypothyroidism is much higher.[1] Normal thyroid status is dependent on adequate levels of many trace elements for both synthesis and metabolism of thyroid hormones. The most important ones being iodine, iron, selenium and zinc.[2]

An epidemiological study by Alvarez-Uria G et al found that iron deficiency is the major cause of anaemia in developing countries.[3] A study by Pasricha et al illustrated that around 70 percent children suffered from anaemia in India.[4] Another study by Thankachan P et al has also shown high prevalence of iron deficiency anaemia in young women in India.[5] Though most readily available sign of iron deficiency anaemia is low concentration of haemoglobin, a significant fall in haemoglobin in circulation cannot be detected until the late stage of iron deficiency.[6]

So iron deficiency has been defined as occurring when body's iron stores become depleted, a restricted supply of iron to tissues become apparent.[7]

A study by Takamatsu J et al has established a very close inter-relation between low thyroid function and low iron or more specifically, low ferritin.[8] Several studies have shown that nutritional iron deficiency may cause significant reduction in the levels of T3 and T4 in circulation.[9] Iron deficiency has been reported to impair synthesis of thyroid hormones, which could increase the need for thyroid medication. One hypothesis is that iron is a component of thyroid peroxidase (TPO). This enzyme participates in the first two steps of thyroid hormone synthesis.[10] Thyroid peroxidase is a membrane bound glycosylated haemoprotein which plays a key role in synthesis of thyroid hormones. This enzyme promotes oxidation of iodine to iodide radicals (organification), and further binding of iodide to tyrosyl residues of thyroglobulin. Hence mono-iodotyrosine (MIT) and di-iodotyrosine (DIT) are produced.

Thyroid hormone T3 is produced by coupling of mono-iodotyrosine (MIT) and di-iodotyrosine (DIT), while thyroid hormone T4 is produced by coupling of two molecules of di-iodotyrosine (DIT). A separate coupling enzyme has not yet been identified. Since it is an oxidative process, it is assumed that the same thyroid peroxidase (TPO) enzyme which promotes oxidation of iodine to iodide radicals, catalyses the coupling reactions also. This hypothesis is supported by the observation that the same drug which inhibits iodine oxidation also inhibits coupling step of thyroid hormone synthesis.[11]

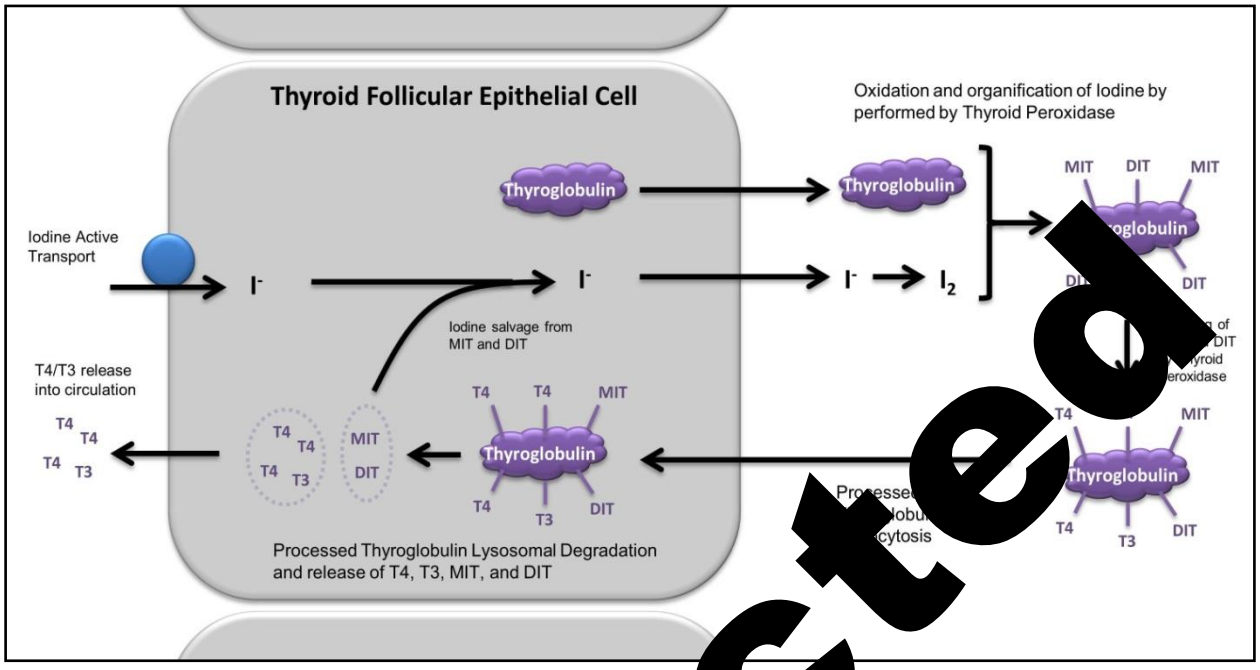

Fig 1: Role of Thyroid Peroxidase enzyme in t[illegible]id horm[illegible] synthesis.

Thyroid Peroxidase enzyme first generates I_2 by oxidizing I^- ions [illegible]60 years) and 100 age and sex matched euthyroid healthy present in the follicular lumen. Thyroid Peroxidase t[illegible] An informed consent was taken from all the study "organifies" the generated I_2 by covalently linking it with [illegible] su[illegible]s before enrolling them for the study. The diagnosis of tyrosine residues present in Thyroglobulin. This genera[illegible]either [illegible]othyroidism was made on the basis of clinical history, physical single or doubly-iodinated species of tyr[illegible]termed examination and measurement of thyroid profile parameters. A "Monoiodotyrosine (MIT)" and "Diiodotyro[illegible]e (DIT)", [illegible]ively. detailed clinical history of the subject was taken on a pre-designed Peroxidase then combines MIT and DIT [illegible]o gener[illegible]or proforma. Examination was done which included measurement of T_3 species within the thyroglobulin pr[illegible]ocess termed body weight, body mass index, pulse rate and palpation for "Coupling". Importantly, peroxidase is much [illegible]cient at enlarged thyroid gland. Then each patient was evaluated for combining of two DIT residues a[illegible]neration of T_4 occurs hypothyroidism or hyperthyroidism by separate questionnaires.[15,16] much more readily, explainin[illegible]hy t[illegible]thyroid gland primarily Summed scores of plus 20 or above in the hypothyroidism produces T_4 rather than T_3. questionnaire indicated a high probability of thyroid dysfunction.

Another reason[illegible]duced [illegible]conversion of T4 to T3 in iron defi[illegible]y. O[illegible]small fraction of T4 gets converted into T3, whi[illegible]er, [illegible]converted into rT3 which is a physiologic[illegible]e inert [illegible]e. A study has shown increased in vitro hepatic [illegible]dination in iron deficiency with decreased levels of T4-5' de[illegible]e in circulation.[12] Yet it is not clear how iron deficiency exerts its effect on activity of T4-5' deiodinase.

Hypothyroidism may itself lead to low iron levels due to poor gut absorption, which may be because of decreased levels of digestive acids, and/or presence of associated autoimmune diseases like celiac disease.[13] Iron deficiency in hypothyroidism may also be possibly due to heavy menstruation as seen in some female patients.[14] Therefore, this study was planned to estimate the levels of serum iron, ferritin and TIBC in hypothyroid patients.

MATERIALS AND METHODS

This case-control study was carried out in Department of Medicine, Govt. Medical College, Sector 32, Chandigarh. The study was conducted on 100 hypothyroid patients (age group

Zulewski's Hypothyroidism clinical score. [15]	
SYMPTOMS	
Diminished Sweating	12
Hoarseness	07
Paraesthesia	14
Dry skin	21
Constipation	14
Impairment of hearing	02
Weight increase	18
PHYSICAL SIGNS	
Slow movements	13
Delayed ankle reflex	16
Coarse skin	14
Periorbital puffiness	15
Cold skin	14
Women <55 years	10

After an informed consent, all the subjects were advised to visit Medicine OPD after 12 hours overnight fasting. Around six ml of peripheral venous blood was taken under all aseptic precautions. The investigations included CBC, PBF, Hb, FBS, lipid profile, liver function tests and renal function tests. Apart from these basic routine laboratory parameters, measurement of thyroid profile (free T3, free T4 and TSH) was done on Access-2 chemiluminescence machine.

Estimation of serum iron and TIBC was done on Siemens Dimension fully autoanalyser. Serum ferritin was measured on Immulite 1000 chemiluminescence machine for all the study subjects.

Reference ranges for the thyroid hormones are[17]:

Free T3 (2.5-3.9 pg/ml)

Free T4 (0.61-1.12 ng/dl)

TSH (0.35- 5.5 mIU/L)

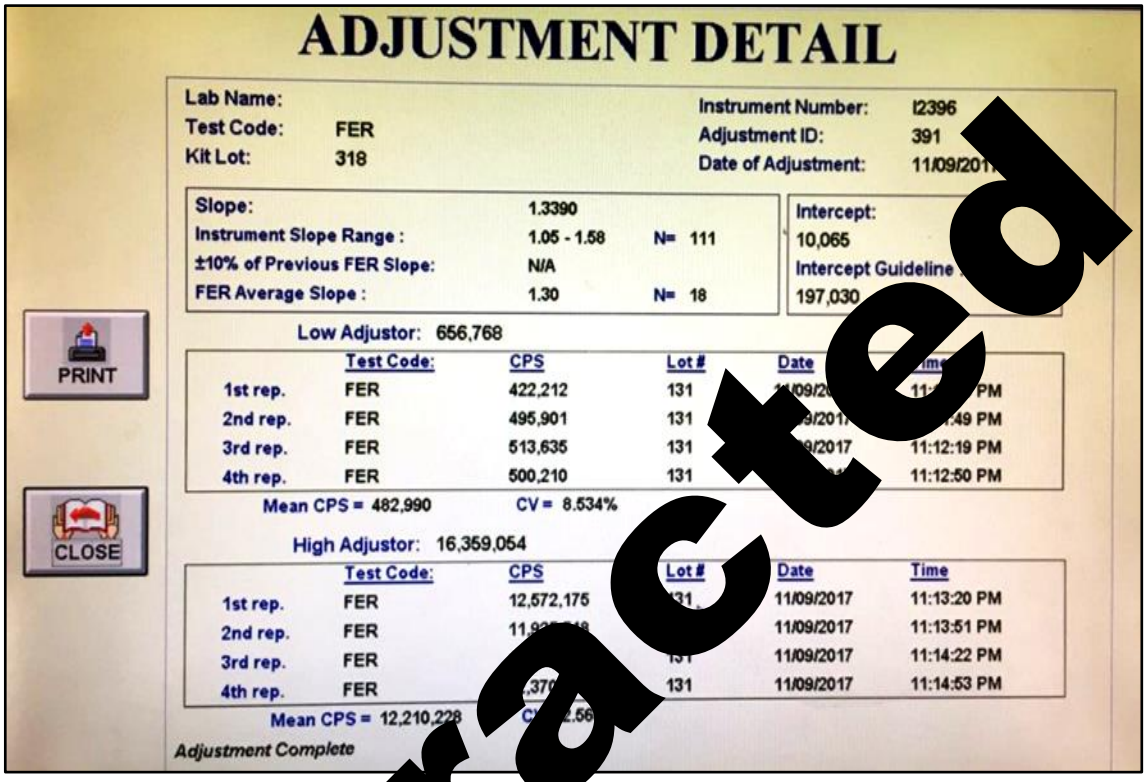

Fig 2: Adjustment details o in on Immulite 2000 chemiluminescence machine.

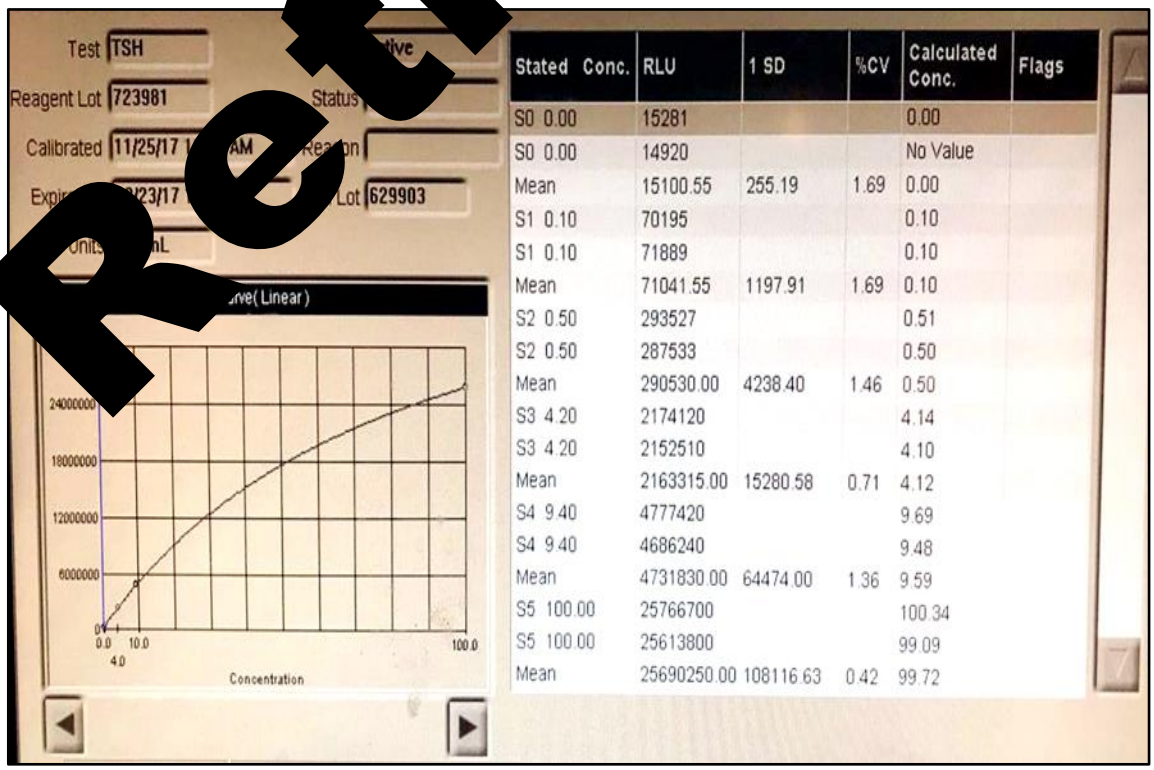

Fig 3: Calibration Curve of TSH on Access-2 chemiluminescence machine.

Following subjects were excluded from the study:

1. Patients with hepatic disorders and renal diseases since thyroid hormones metabolism is affected in these conditions.
2. Those on drugs which may affect thyroid hormone metabolism, including oral contraceptives since oestrogen has anti-thyroid action.
3. Pregnant and lactating females, and females with PCOD.
4. Those receiving iron supplements or taking treatment with thyroxine.

Statistical Analysis

Statistical analysis of the results was done using SPSS version 19 software. The p value was calculated to know the level of significance between the two groups. A p value < 0.001 was considered to be highly significant. Pearson's correlation coefficient (r value) was calculated to determine the level of correlation between the concerned parameters.

RESULTS

Haematological indices for iron status indicated that most of the cases of hypothyroidism were iron deficient. Peripheral blood smear of these patients showed microcytic hypochromic anaemia.

As shown in Table 1, we found significantly lower levels of iron and ferritin in most of the patients of hypothyroidism in our study. On other hand, TIBC was significantly higher in these patients. ($p < 0.001$, $p < 0.001$, $p < 0.001$) Iron and ferritin levels were significantly decreased in patients with deranged thyroid status.

As depicted in table 2, mean value of FT4 was much lower in hypothyroid cases in comparison with healthy controls, while mean value of TSH was much higher in hypothyroid cases in comparison with healthy controls ($p<0.01$, $p=0.00$ respectively).

There was a significant association of free T4 and TSH with only the serum ferritin ($r = +0.63$, $p< 0.001$, $r = -0.34$, $p< 0.05$ respectively). The statistical model show[illegible] that when serum ferritin was used as an independent variab[illegible]jects with lower ferritin had a significantly lower free T4 to fre[illegible] ($r = -0.51$, $p< 0.01$).

As shown in Table 3 and the above sca[illegible]t, the[illegible]as found strong positive correlation betwee[illegible] and free T4, while strong negative c[illegible]s fond between serum ferritin and TSH.

Table 1: Comparison of important iron profile parameters in hypo[illegible]ases [illegible]hy controls

Parameters	Cases (Hypothyroid subjects) (n = 100)	Healthy contro[illegible] (n = 100)	[illegible]alue	Level of significance
Haemoglobin(g/dl)	6.40 ± 1.13	12.60[illegible]	0.00	HS
Iron(µg/dl)	21.66 ± 7.93	79[illegible] 43.2	0.00	HS
TIBC(µg/dl)	445.57 ± 73.84	365[illegible] 77.97	0.00	HS
Ferritin(ng/ml)	11.09 ± 7.07	123.9[illegible]	0.00	HS
Age(years)	40 ± 20	[illegible]40 ± 20	>0.05	NS

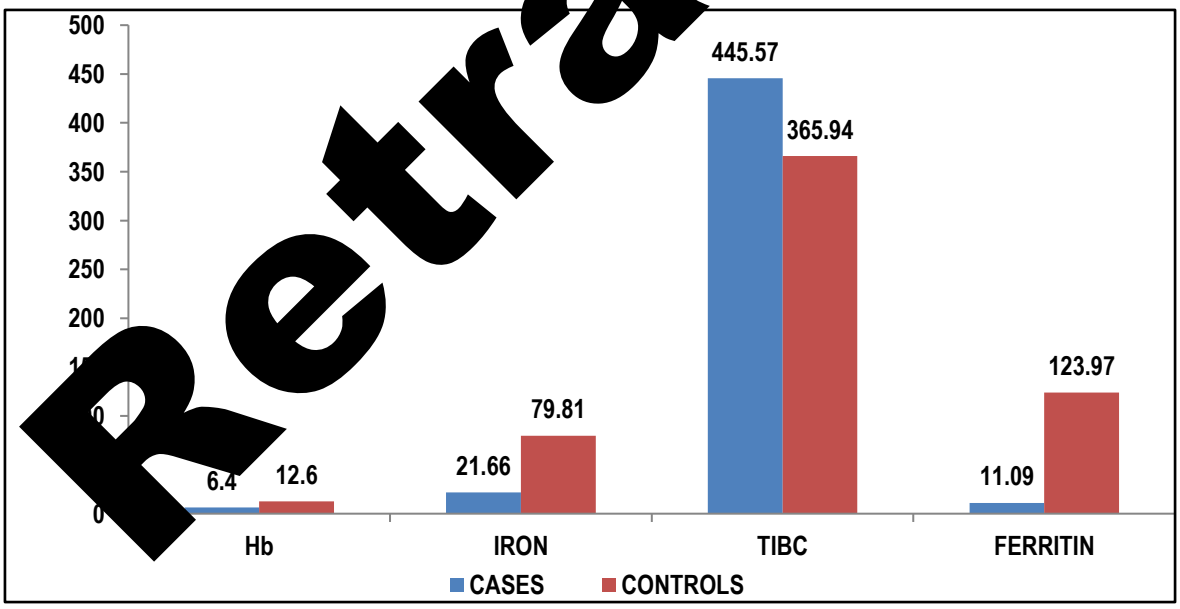

Fig 4: Comparison of important iron profile parameters in cases and healthy controls

Table 2: Mean value of thyroid profile parameters in cases and healthy controls

Parameters with range	Cases (Hypothyroid subjects) (n = 100)	Healthy controls (n = 100)	p value	Level of significance
FT3 (pg/ml) (Range)	2.73 ±0.82 (1.90 – 3.55)	2.85 ± 0.40 (2.12-3.8)	>0.05	NS
FT4 (ng/dl) (Range)	0.21 -1.06 (0.64 ±0.42)	0.90 ± 0.15 (0.63-1.2)	<0.01	HS
TSH (ulU/ml) (Range)	22.10 ±19.87 (12.12 – 51.87)	2.61 ± 1.12 (0.66-4.7)	0.00	HS

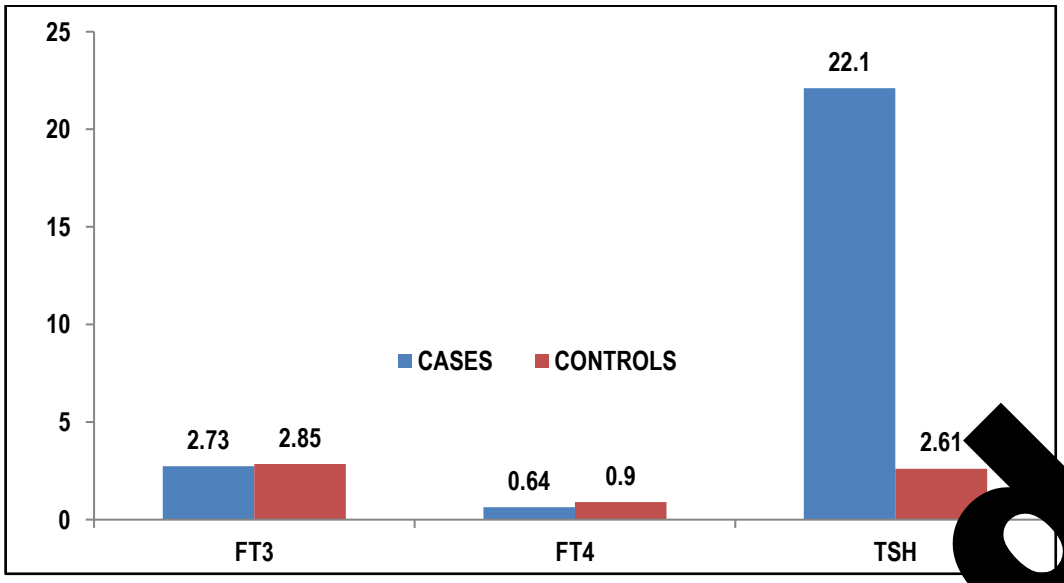

Fig 5: Comparison of thyroid profile parameters in cases and healthy controls

Table 3: Correlation between the levels of serum ferritin and thyroid profile parameters in hypothyroid subjects

Parameter	r value	p value	significance
Ferritin and free T4	0.63	<0.001	HS
Ferritin and TSH	-0.34	<0.001	HS
Ferritin and free T4 to free T3 ratio	-0.51	<0.01	HS

HS = Highly significant

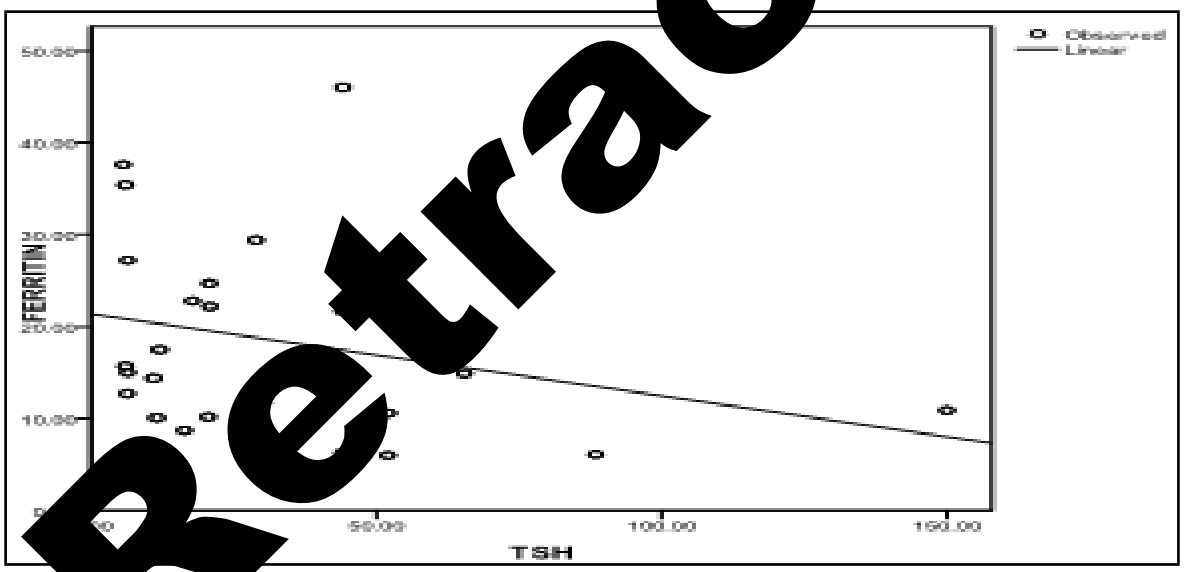

Fig 6: Scatter diagram showing correlation between Ferritin and TSH (r= - 0.34, p<0.001).

DISCUSSION

In our study, the cases of hypothyroidism had much lower serum ferritin, lower serum iron and higher TIBC. A larger fraction of hypothyroid subjects were deficient in iron. These results are in accordance with other studies which reported that iron deficiency anaemia is frequently associated with low levels of thyroid hormones.[9,12,14]

In our study, a significant negative correlation was observed between TSH and ferritin. Bremner AP et al found that serum iron levels were significantly lower in patients with subclinical hypothyroidism in comparison with euthyroid healthy controls. Their study also illustrated significant inverse relationship of TSH with serum iron and transferrin saturation.[18] Banday et al reported iron deficiency in a significant percentage of patients with primary hypothyroidism.[19] At same time, a study by Akhter S et al reported that deranged thyroid hormone status in iron deficient people could be a reflection of disturbed activities of iron dependent enzyme thyroperoxidase. This enzyme has an important role in synthesis of thyroid hormones.[20] A similar study by Hess Y et al mentioned the role of iron in transportation of thyroid hormone into the circulation. According to their study, lack of iron causes pooling of thyroid hormones leading to metabolically hypothyroid condition due to thyroid resistance.[21] Our study illustrated negative correlation of TSH with iron, while positive correlation was observed between TSH and TIBC, but these were not statistically significant.

Thyroid hormones have a well-known role in regulation of gene expression for transferrin. The expression of gene for ferritin has also been reported to be induced by T3 hormone.[22] These hormones also play an important role in erythropoiesis. They stimulate erythroid colony development. Hypothyroidism may cause bone marrow repression and/or decrease in production of erythropoietin due to decreased oxygen requirement.[23]

Thyroxine administration in these patients has been reported to increase erythropoietin levels and improve erythropoiesis. This leads to increased iron requirement and may culminate in manifestations of iron deficiency.[24] Already existing iron deficiency in these hypothyroid patients may make the clinical picture worse. On other hand, the key enzyme in thyroid hormone synthesis, thyroperoxidase is iron dependent. Hence iron deficiency may be the underlying cause in development of hypothyroidism. This fact is of great importance while treating these patients. The symptoms of sympathetic overstimulation due to anaemia may worsen on administration of thyroxine. Thus the condition becomes a vicious cycle since iron deficiency may both be a cause and/or effect of hypothyroidism. An important limitation of our study was that anti-TPO Antibodies (Anti-thyroperoxidase Antibodies) could not be assayed in the study subjects. We tried to exclude the patients on any kind of anti-oxidants supplements. But many patients are in habit of taking different herbs as a routine in our country, which may be missed even by a careful drug history.

CONCLUSIONS

Our study established a significant cause and effect relationship between iron deficiency and thyroid dysfunction. Hence it can be concluded that screening for iron deficiency anaemia is very important in patients with hypothyroidism since it may guide the treatment protocol in these patients.

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