ORIGINALARTICLE

Study of Serum Ferritin and Thyroid Dysfunction in known Beta-Thalassemia Patients

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Abstract:
Background: Iron overload is the common side effect in Beta-Thalassemia patients due to repeated blood transfusions. It may affect endocrine glands like thyroid gland leading to thyroid dysfunction. The aim of the study was to evaluate serum ferritin level and to check for any thyroid dysfunction in known Beta- Thalassemia patients on regular blood transfusion. The objectives were to measure serum ferritin, Thyroid Stimulating Hormone (TSH), Free Tri-iodothyronine (fT_3)and Free Thyroxine (fT_4) hormone levels, and to study association of serum ferritin and frequency of blood transfusion with these hormone levels. *Material & Methods:*In this hospital based cross sectional study, blood samples from consecutive cases admitted to the Thalassemia unit of the hospital were studied. Age, sex, anthropometric data like height, weight were measured and BMI was calculated. Case history about blood transfusion and chelation therapy and other related complications was taken from the patients' file. Blood samples were collected and serum was tested for Serum Ferritin and Thyroid Function Test including Thyroid Stimulating Hormone (TSH), Free Tri-iodothyronine (fT_3) and Free Thyroxine (fT_4) using chemiluminescence method. *Results:*Our study found that mean serum ferritin level (1848.9 ng/mL) was higher than the reference range. Mean TSH, fT3 and fT4 levels were normal. *Conclusion:*This study found that all the patients with Beta-thalassemia on regular blood transfusion had raised serum ferritin levels than the reference range, but they were euthyroid. This was due to regularly maintained serum ferritin levels by appropriate chelation therapy and regular follow up.The limitation of the study is its small sample size. A larger prospective study is needed to support the results of this study.

Keywords: Serum Ferritin, Thyroid Dysfunction, Beta-Thalassemia, Blood Transfusion.

Introduction:
Beta-Thalassemia is one of the most important genetic disorders which may be associated with repeated blood transfusions in Beta-Thalassemia intermedia and Beta-Thalassemia major patients [1]. Iron overload is a major concern in these patients because of repeated blood transfusion. There is possible link between iron overload and dysfunction of thyroid in Beta-Thalassemia patients [1,3]. Studies from last several years have shown correlation between repeated blood transfusion, overload of iron as well as endocrinopathies in Beta-Thalassemia patients [2,3]. Increased hemolysis of transfused erythrocytes results in excess of hemosiderin, the iron containing pigment from the breakdown of hemoglobin, and its deposition in various tissues. Primary thyroid damage (from iron infiltration) and or secondary problems (because of pituitary dysfunction) are reported in patients [2]. It was found that period of transfusion therapy is one of the decisive factors in the progression of hypothyroidism [3]. Although iron overload is found to be major reason for endocrinopathies, other factors like low oxygen supply, desferrioxamine toxicity, cardiac overload, nutritional deficiencies, impaired calcium homeostasis and liver and pancreas involvement are also responsible for endocrine dysfunction. Despite therapy with desferrioxamine to treat iron overload, the risk of secondary endocrine dysfunction remains high [4], [6]. Patients with Thalassemia Major frequently present endocrine complications mainly due to organ damage secondary to iron overload. But in patients with Thalassemia-Intermedia one would expect less severe

endocrine abnormalities in few patients [5]. Few studies have reported subclinical hypothyroidism, primary as well as secondary hypothyroidism in Thalassemic patients [7, 9].There is varied and contradictory data about thyroid dysfunction and its correlation with iron overload in patients [8, 9,11]. The mechanism behind high levels of body iron induced organ damage is not yet fully understood. Free iron circulating in blood or present in the cells is labile. It is able to cycle between ferrous (Fe^{2+}) and ferric ($Fe3^{+}$) states, thereby generating reactive oxygen species, leading to lipid peroxidation. This leads to generation of both unsaturated (malondialdehyde and hydroxynonenal) and saturated (hexanal) aldehydes. Both have been implicated in cellular dysfunction, cytotoxicity and cell death [11]. It is known that dysfunction of thyroid occurs frequently in patients with Thalassemia major, but its prevalence and severity vary in different cohorts [12]. The etiology of thyroid disorders in thalassemia patients is substantially different from that of the general population. Therefore, the knowledge of risk factors influencing the development of thyroid dysfunction is a critical component for long-term monitoring and treatment of Thalassemia major patients [14]. In this study we have assessed the thyroid dysfunction and correlated it with iron overload in patients diagnosed with Beta-Thalassemia. The aim of the study was to evaluate serum ferritin level and to check for any thyroid dysfunction in known Beta-Thalassemia patients on regular blood transfusion. The objectives were to measure serum ferritin, Thyroid Stimulating Hormone (TSH), Free Tri-iodothyronine (fT_3)and Free Thyroxin (fT_4) hormone levels, and to study association of serum ferritin and frequency of blood transfusion with these hormone levels.

Material and Methods:

This was a cross sectional study and was conducted at MIMER Medical College Hospital, TalegaonDabhadeafter getting approval from the Institutional Ethics Committee and after receiving signed informed consent from patients of Beta– Thalassemia admitted to the Thalassemia unit. All consecutive cases admitted to the Thalassemia unit of the institute during the study period were included in the study with their consent. The cases included both male and female participants above 18 years of age admitted and diagnosed as Beta-Thalassemia Major.

Pregnant women were excluded. The patients who had a family history of thyroid dysfunction were excluded from the study. Patients with any other acute and/or chronic illness were excluded. Anthropometric data (height, weight) was measured using measuring instruments during the time of sample collection. Body Mass Index (BMI) was calculated using this data, using the formula [weight (kg)] / [height (m)]^2. Case history including details of blood transfusion, chelation therapy and any related complications was collected from patients' files. Venous blood samples (3 ml) were collected in plain tubes from the subjects. Thyroid Function Test (TFT) including Thyroid Stimulating Hormone (TSH), Free Tri-iodothyronine (Free T3), Free Thyroxine (Free T4) and Serum Ferritin was performed on the blood sample by enhanced chemiluminescence immunoassay using VitrosECi Immunodiagnostic system of Ortho – Clinical Diagnostics (a Johnson and Johnson Company). Complete Blood Count (CBC) was measured using BC–6000 6-part differential Hematology analyser from Mindray.Facility for testing was available in Diagnostic laboratory of the institute.Statistical analysis included measurement variables. Correlation coefficient between serum ferritin and Free T3, Free T4 and TSH was studied. The same was studied between frequency of blood transfusion and these hormone levels. Data analysis was done using Microsoft excel and Graphpad statistical software on personal computer. P values <0.05 were considered statistically significant.

Results:

A total of 21 patients of β-thalassemia were studied. Out of these ten were male & eleven were female patients. The age of the patients ranged from 18 years to 48 years (Mean 29.2 $\pm$ 7.4). Frequency of blood transfusion ranged from 8 days to 22 days (14.9 $\pm$ 4.5 days). All the patients were on regular daily oral chelation therapy. The mean serum ferritin level was higher than the normal 1848.9 ($\pm$ 1721.7) ng/mL. Mean free T3 was 3.3 ($\pm$ 0.3) pg/mL, mean free T4 was 1.4 ($\pm$ 0.2) ng/dL, and mean TSH was 1.3($\pm$ 0.4)µIU/mL. All these hormone values were within normal range indicating that all patients were euthyroid. (Table 1)Mean body mass index (BMI) was normal. Four patients (20%) had BMI below 24.9 and two patients (10%) had BMI more than 29. Mean hemoglobin level was low in both male & female patients. Significantly high serum ferritin was found in all the patients with thalassemia irrespective of the regularchelation therapy. Serum free T3, free T4 & TSH were normal in all the patients (Table 1).When compared with the serum ferritin, no statistically significant

alteration was found in Free T3, Free T4 andTSH hormone levels. As per Lab results, all the patients were thyroid. No case of primary/ secondaryhypothyro-idismwas observed. Similarly, no statistically significant

Table 1 Demographic & biochemical characteristics of patients

association was found between frequency of blood transfusion and Free T3, Free T4 and TSH levels.

Parameter	Min.	Max.	Mean±SD	Reference range
Age (yrs.)	18	48	29.2±7.4	-
BMI	17.2	25.8	21.1±2.4	18.5 – 24.9
Frequency of blood transfu-sion (days)	8	22	14.9±4.5	-
Hemoglobin	8.3	10.8	9.4 ± 0.6	Female: 12.1 - 15.1g/dL Male:13.8 17.2 g/dL
Ferritin	342	5000	1848.9 ± 1721.7	Female:12-150 ng/mLMale: 12-300 ng/mL
Free T3	2.77	3.88	3.3 ± 0.3	1.4- 4.4 pg/mL
Free T4	1.03	1.87	1.4 ± 0.2	0.7-1.53 ng/dL
TSH	0.84	2.11	1.3 ± 0.4	0.45.5µIU/mL

Discussion:

Beta– Thalassemia is a group of inherited blood disorder characterized by reduced or absence of beta chain of haemoglobin. The body's inability to construct new beta-chains leads to the underproduction of HbA (adult haemoglobin). Reductions in HbA available in turn lead to microcytic anemia. Due to this factor, the patient may require blood transfusions to make up for the blockage in the beta-chains. Repeated blood transfusions cause severe problems associated with iron overload. Increased haemolysis due to repeated blood transfusions in thalassemia major patients causes iron overload and increase in serum ferritin levels. Deposition of hemosiderin in thyroid may cause thyroid dysfunction in these patients. Study by AysegulUgurKurtoglu et al suggested endocrinopathies in Beta-Thalassemia major patients which included glucose intolerance, diabetes mellitus, hypothyroidism (12.8%), hyperthyroidism (2.8%), hyperparathyroidism (2.8%) [3].The anterior pituitary gland is particularly sensitive to iron overload which disrupts hormonal secretion resulting in acquired hypothyroidism and hyperparathyroidism. Primary hypothyroidism and hyperparathyroidism, usually appear in the second decade of life; are related to iron overload and may be reversible at an early stage by intensive chelation [2]. In this study, mean serum ferritin level in known Beta– Thalassemia major patients who were undergoing regular blood transfusion was found to be increased above the reference range but the result of thyroid function tests including Thyroid Stimulating Hormone (TSH), Free T3, Free T4 were within normal limits indicating no apparent thyroid dysfunction. Reason for raised Serum ferritin levels being regular blood transfusion. However, Complete Blood Count (CBC), showed normal Red Blood Cell (RBC) count, normal White Blood Cell (WBC) count, Haemoglobin was lower than normal. Frequency of blood transfusion was ranging from every 8 days to every 22 days depending on the age of the patient and requirement. Most of the patients were undergoing regular chelation therapy with desferrioxamine which was taken orally on daily basis. Thyroid status is most likely due to the adherence to regular chelation therapy. Iron overload causes deposition of iron in the thyroid gland, with consequent fibrosis of the glandular parenchyma, and progressive thyroid dysfunction going through different degrees of severity up to overt hypothyroidism. Thyroid dysfunction is known to occur frequently in thalassemia major, but it's prevalence and severity varies and long term natural history is poorly understood [3]. Sara Ahmed Malik et al showed that primary hypothyroidism occurs significantly in beta thalassemia major patients in the absence of obvious clinical signs of hypothyroidism. A significant association was found between ferritin levels and thyroid functional status; the ferritin levels of hypothyroid patients being significantly higher than those of euthyroid patients. The precise mechanism by which iron overload causes tissue damage is not completely understood, though it is suggested that tissue iron deposits act at the cellular level causing damage via free radical formation and lipid peroxidation resulting in mitochondrial, lysosomal and sarcolemmal membrane damage. In the thyroid gland this affects the production of thyroid hormones and manifests as varying degrees of primary hypothyroidism. Hence, it was postulated that higher serum ferritin levels predispose to a greater risk of developing endocrinopathies like hypothyroidism and

conversely, hypothyroid patients are likely to have higher serum ferritin levels than euthyroidthalassemics[5].Our study findings suggested that even though there is increased serum ferritin level, thyroid dysfunction may not be developed. Similar findings were noted by some other studies. Hypothyroidism is thought to be a rare complication. Thyroid dysfunction has been reported but its variability differs. Presence of overt hypothyroidism is low, milder forms of thyroid dysfunction are more common, though again there are wide variations in reports. These discrepancies can be attributed to differences in patient ages and different treatment protocols, including different rates of transfusion and chelation. In past when chelating therapy was often not performed the thyroid dysfunction was and hypothyroidism was more common [6]. Study conducted by Yassouf MY et al demonstrated that non-compliance with chelation increases the thyroid dysfunction [7].As per study of Karamafir et al, there was no statistically significant difference in development of thyroid dysfunction and iron overload[8].Hashemi A et alalso in their study demonstrated that there was no correlation between hypothyroidism and serum ferritin level. They also concluded that regular follow up was a key to prevent complications [9].Soliman AT et al concluded that there was a significant negative correlation between serum ferritin and FT4, but no correlation was found between ferritin and TSH levels [11].The thyroid pituitary axis is less sensitive than the gonadal axis to iron-induced damage. Abnormal thyroid function may be reversible in the initial stages. Progression pattern is not fixed. Further, it may take years to progress from normal to uncompensated hypothyroidism [12]. In study conducted by Khandelwal R et al, there was a significant negative correlation between Ferritin and T3 levels and a positive correlation between Ferritin and T4, TSH levels. However, the correlation was significant with TSH [13]. Special attention has to be paid to patients with clinical features or laboratory findings of reduced growth velocity, short iron stature, delayed puberty, cardiac failure, arrhythmias, or stature, delayed puberty, cardiac failure, arrhythmias, or overload. A recovery of subclinical hypothyroidism has been observed in some iron overloaded Beta thalassemia major patients after intensive iron chelation therapy [14]. Farmaki K and BerdoukasVdemonstrated in their study that continuous monitoring of Beta Thalassemia patients for iron overload and endocrinopathies and administration of appropriate chelation led to the reversal of the endocrinopathies in early stages including that of thyroid dysfunction [16].

Conclusions:

This study found that all the patients with Beta-thalassemia on regular blood transfusion had raised serum ferritin levels than the reference range, but they were euthyroid. No case of primary/ secondary hypothyroidism was observed. This was due to adherence to the regular treatment including daily chelation therapy. Regular follow-up of patients with beta-thalassemia major is essential for early detection and management of associated complications. The limitation of the study is its small sample size. A larger prospective study is needed to support the results of this study. However, this study emphasizes on the importance of regular chelation and regular follow ups for keeping a check on thyroid dysfunction which may be associated with the repeated and frequent blood transfusion.

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Conflict of Interest-Nil

Sources of Support-Nil

References

1. D. Rund and E. Rachmilewitz. Beta-thalassemia. *The New England Journal of Medicine* 2005;353(11): 1135-1146.
2. Toumba M, Sergis A, Kanaris C, Skordis N. Endocrinecomplicationsin patients with Thalassaemia Major. *Pediatric Endocrinology Reviews* 2007;5:642-648.
3. Kurtoglu AU, Kurtoglu E, Temizkan AK. Effect of iron overload on endocrinopathies in patients with beta-thalassaemiamajor and intermedia. *EndokrynologiaPolska* 2012;63:260-263.
4. Shamshirsaz AA, Bekheirnia MR, Kamgar M, Pourzahedgilani N, Bouzari N, Habibzadeh M, et al.

Metabolic and endocrinologic complications in beta-thalassemia major: A multicenter study in Tehran.*BMC Endocrine Disorders* 2003;3:4.

5. Malik SA, Syed S, Ahmed N. Frequency of hypothyroidism in patients of beta-thalassaemia. The *Journal of The Pakistan Medical Association*2010;60:17-20.
6. Najafipour F, Aliasgarzadeh A, Aghamohamadzadeh N, Bahrami A, Mobasri M, Niafar M, et al. A cross-sectional study of metabolic and endocrine complications in beta-thalassemia major. *Annals of Saudi Medicine* 2008;28:361–366.
7. Yassouf MY, Alquobaili F, Kabalan Y, Mukhalalaty Y. Compliance with Desferrioxamine Therapy and Thyroid Dysfunction of Ptients with Beta – Thalassemia Major in Syria. *Hemoglobin* 2019;43(3):218-221.
8. Karamifar H, Karimi M, Amirhakimi GH, Badiei M. Endocrine function in thalassemia intermedia. *International Journalof Biomedical Science*2006;2:236–240.
9. Hashemi A, Ordooei M, Golestan M, AkhavanGhalibaf M, Mahmoudabadi F. Hypothyroidism and serum ferritin level in patients with major β thalassemia. *Iran Journal of Pediatric Hematology and Oncology* 2012;2:12-15.
10. Persani L. Clinical review: Central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges. *The Journal of Clinical Endocrinology and Metabolism* 2012;97:3068-3078.
11. Soliman AT, Al Yafei F, Al-Naimi L, Almarri N, Sabt A, Yassin M, De Sanctis V. Longitudinal study on thyroid function in patients with thalassemia major: High incidence of central hypothyroidism by 18 years. *Indian Journal of Endocrinology and Metabolism* 2013;17:1090-1095.
12. Landau H, Matoth I, Landau-Cordova Z, Goldfarb A, Rachmilewitz EA, Glaser B. Cross-sectional and longitudinal study of the pituitary thyroid axis in patients with thalassaemia major. *Clinical Endocrinology (Oxford)* 1993;38:55-61.
13. Khandelwal R, Gundluru M, Mehta KL. Thyroid profile in patients of thalassemia with multiple blood transfusions and high serum ferritin: a cross-sectional study. *Pediatric Review- International Journal of Pediatric Research* 2020;7(8):401-408.
14. De Sanctis V, Tanas R, Gamberini MR, Sprocati M, Govoni MR, Marsella M. Exaggerated TSH response to TRH ("sub-biochemical" hypothyroidism) in prepubertal and adolescent thalassaemic patients with iron overload: prevalence and 20-year natural history. *Pediatric Endocrinology Reviews* 2008;6(1):170-173.
15. Alexandrides T, Georgopoulos N, Yarmenitis S, Vagenakis AG. Increased sensitivity to the inhibitory effect of excess iodide on thyroid function in patients with beta-thalassemia major and iron overload and the subsequent development of hypothyroidism. *European Journal of Endocrinology* 2000;143:319-325.
16. Farmaki K, Berdoukas V. Reversal of endocrinopathies in transfusional iron overload patients- The next frontier in iron chelation. *European Journal of Clinical and Medical Oncology* 2010;2:59-66

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