Evaluation of thyroid hormones and ferritin level in patients with β-thalassemia

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Abstract

Background and aims. Thalassemia is a condition that affects hemoglobin synthesis and is one of the most common hereditary illnesses in the world. Patients with thalassemia major require several blood transfusions. Multiple blood transfusions cause thyroid dysfunction, which leads to iron excess.

Methods. From August 2019 to January 2020, serum samples were obtained from 90 persons, 30 of whom were healthy, and 60 (46 male and 44 female) with β-thalassemia major, aged 5-20 years, who visited the thalassemia care center at Salah Aldeen General Hospital in Tikrit city.

Results. Patients had a significant increase (P≤0.01) in T4 and TSH hormones when compared to controls, whereas T3 was also significantly higher (P≤0.05) than in controls. Compared to controls, the level of ferritin had a very significant increase (P≤0.01) in all the study patients with beta-thalassemia, male and female.

Conclusions. Thyroid disorders are common in β-thalassemia patients who have been transfused multiple times.

Keywords: ferritin, β-thalassemia, triiodothyronine (T3), Ttyroxine (T4), thyroid-stimulating hormone (TSH)

Background and aims

Thalassemia, commonly known as Mediterranean anemia, is a hereditary condition characterized by a lack of hemoglobin synthesis. It can be classified based on the symptoms it causes or the genes that are impacted. People of various ancestries, especially those from the Mediterranean and Arabian Peninsula, are more likely to have beta-thalassemia.

In Iraq, thalassemia is a serious problem due to a lack of equipment and medications during various phases of the conflict, as well as a lack of security [1]. Thalassemia is categorized by an abnormal reduction of production in the formation rate of normal alpha-globin (α) or beta-globin (β) subunits of hemoglobin A. This hemoglobin A comprises 2 alpha and 2 beta-globin subunits (α1, α2; β1, β2). The alpha-globin genes are present on chromosome 16, while genes that are responsible for the formation of beta-globin are found on chromosome 11. β-thalassemia major (β-TM), or β-thalassemia requiring transfusion, is regarded as the most severe β-thalassemia, recognized by inefficient erythropoiesis, insufficient synthesis of hemoglobin A (HbA), disturbed red blood cell formation, anemia with hemolysis of the red blood cell [2,3]. A lifelong regimen of regular blood transfusions is the preferred management of β-thalassemia major patients [4].

Multiple blood transfusions are the only way to treat anemia in beta-thalassemia, which causes iron excess [5] and heart, liver, and bone damage [6]. Chelation treatment should reduce the amount of iron in the body, preventing fast clinical deterioration or possibly
death [7]. After absorbing iron from various regions of the small intestine, iron transporters bond with transferrin, which is subsequently stored in the reticuloendothelial cells of the spleen, liver, and bone marrow, where it binds with hemosiderin and ferritin [8]. Iron is a conundrum in human health since it is required for many critical biological functions while also having the potential to be damaging in others. Iron is a metal cofactor for several enzymes (ribonucleotide reductase, mitochondrial aconitase, oxidases, peroxidases, catalases, etc.) and is a component of hemoproteins (cytochromes, hemoglobin). The chemical characteristics of iron may harm biological systems [7]. At oxygen tension and physiological pH, Fe(II) is oxidized to Fe(III), which soon forms practically insoluble Fe(OH)3 polymers and is involved in the production of toxic oxygen radicals that induce peroxidative damage of key cellular structures. Thus, keeping an iron level within the useful and safe range is critical since a low amount can cause anemia, while a high level can cause tissue damage [9]. In eukaryotes and prokaryotes, ferritin is an internal iron storage protein that stores iron in a non-toxic and soluble state. It is a 450 kDa global protein complex made up of twenty-four protein components. The iron burden on the body is calculated using serum iron, TIBC, and ferritin levels. The estimate of serum ferritin is a critical test for assessing iron overload in β-thalassemia major patients [10,11].

Endocrine diseases currently represent one of the most well-known thalassemia consequences while determining the exact incidence is challenging due to variances in the age of initial chelation therapy exposure and the ongoing improvement in the longevity of well-chelated individuals. The incidence of thyroid dysfunction in β-thalassemia major patients is low and is dependent on the adherence to appropriate therapy. In thalassemia major patients, endocrine diseases induced by frequent blood transfusions are more prevalent. They are the second principal cause of death in this group, behind heart disease [6,12]. Hypogonadism is the commonest endocrine issue in thalassemia major individuals, and it is linked to pituitary iron sediment [13].

The most common causes of thyroid dysfunction include gland leakage, free radical damage, organ siderosis, and chronic tissue hypoxia. The thyroid gland is harmed long before the thyroid-pituitary axis, which is less impacted by iron damage than the gonadal axis [14]. FSH, LH, and TRH regulating secretions can be disrupted by a damaged anterior pituitary gland. With the introduction of iron chelators, survival rates increase noticeably, although endocrine problems appear to be recurring and have an impact on individual quality of life [15].

For more than four decades, dexeroxamine (marketed as Desferal) has been utilized all over the world. In iron-overloaded patients, deferroxamine can be given intravenously as an infusion in the hospital or, more often, subcutaneously at home. They generally describe a little battery-powered customized pump that administers IV infusions every eight to twelve hours. Deferasirox is the most often used iron chelator in the United States, and it is particularly efficient in removing iron from the heart and liver (these two organs are the most likely structures with significant iron overload). Deferasirox is available in two medication formulations: „Exjade”, a dispersible tablet that dissolves in fluids, and „Jadenu,” a swallowed tablet. Deferiprone „Ferriprox”, oral medicine that can be taken three times a day, is the most recent iron chelator agent to be licensed. Deferiprone, on the other hand, may be provided as a liquid or a tablet, and it may be the most effective treatment for eliminating excess iron from the patient’s heart. Although most people tolerated this medicine without any adverse effects, the most noticeable possible side effect was agranulocytosis, which can raise the risk of infection. As a result, when a person takes this medication, a full blood count must be performed every week to monitor the neutrophil count [16].

Growth abnormalities, diabetes mellitus, sexual development, fertility, hypothyroidism, hypoadrenalism, and improper bone mineralization are the most common endocrine issues in thalassemia patients. Thyroid problems are prevalent in β-thalassemia major’s endocrine consequences; however, their severity and incidence vary, and their history is hazy. Autoimmunity plays a detrimental role or function in the pathophysiology of thalassemia-linked hypothyroidism. Instead of the 5% of thalassemia patients who develop evident clinical hypothyroidism that requires treatment, a bigger number of them develop subclinical compensated hypothyroidism with normal T3 and T4 levels but high TSH serum levels. They frequently link it to severe anemia and/or iron overload thalassemia, although it is unusual in individuals who are normally treated [17].

Iron chelation is the most common medical treatment for beta-thalassemia. The elemental iron content of transfused red blood cells is approximately 200 mg per unit. Hepcidin production is suppressed by anemia and inefficient erythropoiesis. Iron chelation seeks to prevent iron excess consequences such as cardiac and hepatic dysfunction [3].

Materials and methods

From August 2019 to January 2020, serum samples were collected from thalassemia major patients who visited the thalassemia care center at Salah Aldeen General Hospital in Tikrit city. Several lab tests, including (T3, T4, and TSH) and ferritin, were performed on both groups, patients and controls (by Minividas). Serum samples were taken from 90 people, 30 of whom were healthy, and 60 (46 male and 44 female) β-thalassemia major patients ranging in age from 5 to 20 years. There was no personal history of hypertension, thyroid illness, or diabetes mellitus in any of
the patients. Patients with β-thalassemia were identified by specialists based on clinical signs and symptoms, followed by a laboratory and clinical evaluation. Patients who are treated with blood transfusions or dysferral injections should begin chelation therapy after roughly a year of chronic transfusions when serum ferritin levels are around 1000 ng/dL.

The Salah Aldeen Health Directorate’s Medical Ethics Committee gave its approval to this study (Code IQ.SAHD.REC.19.8628). Ethical permission statements from all participants were obtained based on the World Medical Association’s Helsinki Declaration, which was last revised in Edinburgh in 2000.

Using the Minitab statistics application, statistical analysis of the findings was performed using the (t) test. Duncan’s Multiple Range Test was utilized to compare averages to characteristic calculations with a probability threshold of \( P \leq 0.05 \).

### Results

In thyroid hormone levels, \( T_3 = (1.596\pm0.28, 1.63\pm0.28, 1.55\pm0.28) \) ng/ml in β-thalassemia patients were higher than in controls \( T_3 = (1.50\pm0.28, 1.46\pm0.30, 1.54\pm0.25) \) ng/ml in total subjects, male and female, respectively. \( T_4 = (10.43\pm2.17, 10.46\pm2.38, 10.41\pm1.97) \) ug/dl in β-thalassemia patients were higher than in controls \( T_4 = (9.37\pm1.49, 8.97\pm1.46, 9.77\pm1.43) \) ug/dl in total subjects, male and female, respectively. \( TSH = (5.53\pm3.29, 5.38\pm3.34, 5.66\pm3.28) \) IU/ml in β-thalassemia patients were higher than control \( TSH = (2.11\pm0.58, 2.13\pm0.47, 2.09\pm0.68) \) IU/ml in total subjects, male and female respectively, as shown in table I and figure 1. The level of ferritin increased in β-thalassemia patients in all subjects, male and female (1394±1522, 1458±1449 and 1583±1351) respectively; rather than control (183±84.8, 190.8±82.3, and 175.2±87.9) respectively; as shown in table I and figure 2.

When computing the correlation coefficient (r) as given in table I and utilizing regression plots in figures (3, 4, and 5) accordingly, there was a negative association between serum ferritin and \( T_3 \), \( T_4 \), and \( TSH \).

### Table 1.

| Test      | β-thalassemia patients (mean±SD) | Controls (mean±SD) |
|-----------|----------------------------------|--------------------|
|           | Total, Male, Female              | Total, Male, Female |
| Numbers   | 90, 44, 46                       | 60, 30, 30         |
| T3 ng/ml  | 1.59±0.28, 1.63±0.28, 1.55±0.28   | 1.50±0.28, 1.46±0.30, 1.54±0.25 |
| P value   | \( P\leq0.05^* \), \( P>0.05^{***} \), \( P\leq0.01^* \) | \( P\leq0.05^{***} \), \( P\leq0.01^* \) |
| T4 ug/dl  | 10.43±2.17, 10.46±2.38, 10.41±1.97 | 9.37±1.49, 8.97±1.46, 9.77±1.43 |
| P value   | \( P\leq0.01^* \)                 | \( P\leq0.05^{***} \), \( P\leq0.01^* \) |
| TSH IU/ml | 5.53±3.29, 5.38±3.34, 5.66±3.28   | 2.11±0.58, 2.13±0.47, 2.09±0.68 |
| P value   | \( P\leq0.01^* \)                 | \( P\leq0.01^* \) |
| Ferritin ng/dl | 1394±1522, 1458±1449, 1583±1351 | 183±84.8, 190.8±82.3, 175.2±87.9 |
| P value   | \( P\leq0.01^* \)                 | \( P\leq0.01^* \), \( P\leq0.01^* \) |
| r value   | -0.033                           | -0.046, -0.155     |

*Highly significant, ** significant, *** no significant
Discussion

The thyroid hormones of individuals with beta-thalassemia changed in both genders in the current research. T4 and TSH hormones showed a very significant rise (P≤0.01) in study patients compared to controls, whereas T3 showed a somewhat significant increase (P≤0.05) in patients compared to controls. Males and females had different hormonal shifts. As a result, thyroid hormones increased significantly (P≤0.01) in female patients compared to controls, but not in male patients. T3 and T4 hormones revealed no significant difference (P≥0.05) when compared to controls; however, TSH in patients showed a very significant rise (P≤0.01) when compared to controls. These findings corroborated in other studies as well: De Sanctis 2008 [18], Parijat De 2014 [19] and Zekavat OR 2014 [20], Karunaratna 2020 [16], Singhal A 2020 [21].

The current study discovered a high level of TSH in beta-thalassemia patients, along with a modest rise in thyroid hormones, compared to healthy levels. It is caused by an increase in iron synthesis, which causes the hypothalamus to generate a lot of thyrotrophic-releasing hormone (TRH). It causes a rise in the pituitary gland’s release of the hormone TSH, which aids in the reduction of thyroid hormones or survival at normal levels [18].

Hypothyroidism may be caused in part by the accumulation of iron in the thyroid gland as a result of excessive blood transfusion, resulting in gland malfunction. Despite claims linking thyroid dysfunction to iron excess, research has shown that iron overload, as measured by serum ferritin levels, is not linked to thyroid issues [21]. Because of hypothyroidism, the TSH level was higher than in controls, while T3 and T4 levels were somewhat higher than in controls, but still within Elisa Kit’s reference range. These findings might be the result of the disease extended duration, chelating medication, and frequent blood transfusions.

The level of ferritin in beta-thalassemia patients showed there was a highly significant increase (P≤0.01) in all the subjects, male and female, compared to controls (20% of serum ferritin in β-thalassemia patients were > 2000 ng/dl. These results agree with Ikram N 2004 [11], De Domnico I 2008 [18], Prabhu R 2009 [17], Zekavat OR 2014 [20], Koreti S 2018 [22]).

The results of this investigation revealed that individuals with beta-thalassemia have a higher amount of ferritin than healthy people. This discovery might be attributed to illness factors such as a genetic cause, which happens when a mutation or deficiency in the gene responsible for hemoglobin manufacturing arises, especially in infants. Then it causes difficulty with hemoglobin production and red blood cell disintegration, resulting in severe anemia, which allows iron to collect in numerous tissues, glands, and organs. It enhances the toxicity of iron and can be removed by treating the patient with desferrioxamine, which is connected with excess iron.

Figure 3. Correlation coefficient between serum ferritin and T3 in β-thalassemia patients.

Figure 4. Correlation coefficient between serum ferritin and T4 in β-thalassemia patients.

Figure 5. Correlation coefficient between serum ferritin and TSH in β-thalassemia patients.
and excreted from the body through the kidney when severe anemia occurs. As a result, blood must be transferred to the patient on a regular and continuous basis to compensate for the deficiency in red blood cells required for cell activity. This results in an increase in iron in the body due to increased ferritin, and the diagnosis of this increase is an indicator of disease [23].

Iron binds to transferrin, a carrier protein that helps deliver iron into tissues during normal physiological processes. Transferrin is generally saturated in excess iron circumstances, resulting in an excess of free iron in the circulation. Because free iron is typically highly reactive, it produces reactive oxygen species, which has harmful effects on the cells [24]. This results in organ destruction, which is the leading cause of morbidity and death in people with β-thalassemia [25].

Subclinical hypothyroidism, which is caused by anomalies in the thyroid gland and results in reduced thyroid hormone production, is the most prevalent kind of thyroid abnormality identified in thalassemia [26].

Finally, all nations with a high prevalence of thalassemia should fund preventive programs that include minor thalassemia diagnosis, genetic counseling, and bone marrow transplantation for children with significant beta-thalassemia [27]. As a result, using informatics methodologies, worldwide thalassemia education may be realized. With its ever-increasing cost, DNA analysis may be used more easily in screening as a first step. The use of microchip technology for the identification of α- and β-thalassemia patients, as well as DNA polymorphism, is highly beneficial in predicting the phenotype, and therefore preliminary hematological testing might be avoided. New technological advancements in fetal cell analysis or fetal DNA in maternal blood may enable these extraordinary noninvasive procedures to be used in clinical practice in the future.

Conclusions

Multiply transfused β-thalassemia patients are prone to metabolic and thyroid problems. The findings of this study demonstrated the need for thyroid hormonal assessment in people with β-thalassemia major. Thyroid dysfunction and iron overload, as well as a high ferritin level, may result from regular and frequent blood transfusions without appropriate chelation.

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