ASSESSMENT OF THYROID FUNCTION IN BETA THALASSEMIA MAJOR PATIENTS WITH MULTIPLE BLOOD TRANSFUSIONS: A CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Its well known that thalassemia is the most prevalent genetic disorder worldwide. β thalassemia major is the basic form of thalassemia major that requires lifelong blood transfusions. one of the most prevalent endocrine issues in beta-thalassemia major is hypothyroidism. The current study was aimed to assess the thyroid function status in chronically transfused Beta thalassemia major patients.

Methods: A cross-sectional study included 278 patients diagnosed with beta thalassemia major. The study lasted for 12 months interval, from January 2021 to January 2022. Serum free thyroxine, thyroid stimulating hormone and Ferritin levels were measured for all patients using Roche Cobas 6000 analyzer.

Results: The study observed a high prevalence rate of subclinical hypothyroidism (41.2%) and as well as, (2.9%) had overt hypothyroidism. There was insignificant high level of serum ferritin among hypothyroid patients. Nineteen of the subclinical hypothyroid patients (16.5%) had splenectomy, whereas, no one with clinical hypothyroidism had splenectomy.

Conclusion: The study conclude that near half of beta thalassemia major patients were had overt hypothyroidism and subclinical hypothyroidism.

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Keywords: *Beta thalassemia major, Hypothyroidism, ferritin, Thyroid function.*

Thalassemia is most prevalent inherited disorder (autosomal recessive inheritance pattern) in all over the world that characterized by deficiency in beta globin chains production with increasing level of hemoglobin F leading to ineffective erythropoiesis and decrease affinity of this hemoglobin to[2],[3] diphosphoglycerate[1-3]. β-thalassemia major (Transfusion dependent Thalassemia) is the classical type of thalassemia major that require lifelong blood transfusions in a regular duration for survival, starting in the first 2 years of life[4-6].

Hypothyroidism is one of the common endocrine diseases worldwide with the frequency of up to 5% of the population[7],[8]. Majority of them are primary hypothyroidism due to autoimmune thyroiditis or dietary iodin deficiency[9],[10]. Biochemically characterized by abnormal thyroid hormones concentration such as high TSH with low free thyroxine[11]. Whereas clinically characterized by non-specific symptoms, including weight gain, depression, menstrual irregularities, and constipation[12]. Moreover, it complicated with cardiovascular diseases development and infertility[11].

Patients with β-thalassemia major frequently have endocrine abnormalities despite receiving parenteral and oral iron chelation treatment[13],[14]. The prevalence and causes of the presence of hypothyroidism in patients with β-thalassemia major are differ from that of general population that was up to 30% in studies across the world[15-17]. This high prevalence is mostly related to iron overload and toxicity with free iron in blood

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(free radical formation) due to repeatedly transfusing blood and improve gastrointestinal iron absorption due to ineffective erythropoiesis[18]. Subclinical hypothyroidism is most communal type of thyroid disorder and the second most prevalent endocrine disorder found in patients with β thalassemia major with the 18.1% prevalence after hypogonadotropic hypogonadism[19-22].

The current study was aimed to assess the thyroid function status in chronically transfused patients with beta thalassemia major, in the first and second decade of life and to ascertain the impact of factors like serum ferritin level, and iron chelation therapy on thyroid function.

MATERIALS AND METHODS

A cross-sectional study was carried out at the Jeen center for blood disorders in Duhok province, Kurdistan region, Iraq. The study included 279 patients identified with β thalassemia major with the ages between 3 year and 25-year-old who were receiving regular blood transfusions (10-15 ml/kg every 2-6 weeks). The study lasted for 12 months' interval, from January 2021 to January 2022.

The study excluded patients with alpha thalassemia, sickle cell disease, β thalassemia intermedia, beta thalassemia minor, β. thalassemia major children known with thyroid disorders or receiving antithyroid supplements, other hemolytic diseases and those suffering from other acute illnesses. Following approval from the directorate of health ethics committee, Participants who matched the inclusion criteria were accepted into the study. All patients gave their informed consent after which a proforma was created to capture all the information.

Prior to the blood transfusion, beta thalassemia major patients were not taking any medications other than iron chelators, 3 ml of random Samples of venous blood were taken from each subject on the day of meeting, putted in a plain vacutainer (gel separator tube) for the measurement of serum free thyroxine, thyroid stimulating hormone and serum ferritin levels. The sample analysis was done in the clinical biochemistry department of Vin Private Laboratories using a Roche Cobas 6000 analyzer depending on principle of electrochemiluminescence immunoassay for all parameters.

According to the following criteria, thyroid dysfunction exists when as follows: clinical hypothyroidism with FT4 less than 12 pmol/l and TSH more than 4.2 mIU/L), subclinical hypothyroidism with normal FT4 and TSH more than 4.2 mIU/L).[23],[24].

Statistical Analyses

Statistical analyses were done using the SPSS Version 26.0 program (IBM). The basic information of study participants was shown in mean (SD) or number (%). The frequency of abnormal thyroid cases was presented as number (%). ANOVA one-way was used for evaluate the relationship between serum ferritin levels and abnormal thyroid cases. Pearson chi-square was performed to evaluate the association between the general characteristics and abnormal thyroid cases. A p-value of less than 0.05 was used to assess the difference's significant level.

RESULTS

The general characteristics of studied participants were shown in table 1. The mean ±SD of age was 12.29±6.64 years with approximate equal percent of both male (51.1%) and female (48.9%). Although, 248 (89.2%) of participants were taking Deferasirox (Exjade) iron chelation, the mean serum ferritin was 2275 ± 1186.7 ug/l.

Table 1. General characteristics of participants

Characters	Mean ± SD, No%
Age (years)	12.29±6.64
Gender	
Male	142 (51.1%)
Female	135 (48.9%)
Consanguinity	141 (50.7%)
Yes	137 (49.3%)

Characters	Mean ± SD, No%
No	
Iron chelator	
Desferal	9 (3.2%)
Exjade	248 (89.2%)
Both	21 (7.6%)
Frequency of transfusion	
<30	69 (24.8%)
≥30	209 (75.2%)
Splenectomy	
Yes	57 (20.5%)
No	221 (79.5%)
TSH mIU/L	4.47±2.80
FT4 pmol/l	16.52±2.48
Ferritin ug/l	2275.42±1186.79

The prevalence of thyroid abnormalities was shown in table 2. The study observed a high prevalence rate of subclinical hypothyroidism (41.2%), as well as, (2.9%) had over hypothyroidism (2.9%).

Table 2. Prevalence of hypothyroidism among beta-thalassemia major patients

Cases	No%, N=278
Clinical hypothyroidism	8 (2.9%)
Sub clinical hypothyroidism	115 (41.2%)
Euthyroid	155 (55.6%)

Table 3 shown the correlation between different parameters and abnormal thyroid function. There was insignificant higher level of serum ferritin among hypothyroid patients compared to euthyroid patients. Nineteen of subclinical hypothyroid patients (16.5%) had splenectomy, whereas, no one with clinical hypothyroidism had a splenectomy.

Table 3. correlation between different parameters and abnormal thyroid function

Characters	Clinical Hypothyroidism N=8	Sub clinical Hypothyroidism N=115	Euthyroid N=155	p value
Ferritin (ug/l)	2644.0±411.32	2266.59±962.64	2262.95±1353.7	0.068a
Age	9.87±8.40	12.47±6.63	12.25±6.58	0.062a
Gender				
Male	6 (75%)	56 (48.7%)	80 (51.6%)	0.348b
Female	2 (25%)	59 (41.3%)	75 (48.4%)	
Iron chelator				
Desferal	0	3 (2.6%)	6 (3.9%)	0.679b
Exjade	8 (100%)	105 (91.3%)	135 (87.1%)	
Both	0	7 (6.1%)	14 (9%)	
Frequency of transfusion				
<30	0	28 (24.3%)	41 (26.5%)	0.237b
≥30	8 (100%)	87 (75.7%)	114 (73.5%)	
Splenectomy				
Yes	0	19 (16.5%)	38 (24.5%)	0.095b
No	8 (100%)	96 (83.5%)	117 (75.5%)	

a ANOVA one-way and b Pearson chi-squared tests were performed for statistical analyses.

DISCUSSION

Hypothyroidism (overt or subclinical) is described as the thyroid gland's inability to produce enough thyroid hormone to meet the body's metabolic demands. It is a common clinical disorder seen in beta thalassemia major patients who have received multiple blood transfusions, resulting in iron overload[25].

Although its well know that thalassemia was shown to be the most common among specific family (relatives in the first degree), the present study found that approximately half of beta thalassemia major Patients had a history of marriages to each other, which is a substantial contributing factor in illness pathogenesis. This was consistent with a previous study shown that thalassemia was found most prevalent among relatives in the first degree[26].

The current study showed a high serum ferritin level among β-thalassemia major patients. This was mostly explained by the presence of hemosiderosis that is due to repeated blood transfusion with excessive iron accumulation in the body, as well as, it regarded as main cause of late morbidity and mortality in those patients[27]. This was matching with a study done by Bandyopadhyay et al. that showed a high level of serum ferritin in thalassemic patients in different age group including children and young age group[28].

The current study observed that near half of beta thalassemia major patients were had decreased thyroid function in the form of overt hypothyroidism (2.9%) and subclinical hypothyroidism (41.2%). This result was consistent with a prior study done in India by Singhal, A. and Goyal, H., as well as inconsistent with study done in Italy by Gamberini MR which shown a lower prevalence of hypothyroidism in patients with β thalassemia major 29. This is mostly contributed to regular blood transfusion (iron overload) and less commonly contribute to other factors such as ethnic groupings, disparities in transfusion and chelation therapy methods with notable variations in compliance and efficiency. Moreover; Higher ferritin levels were directly related to iron buildup in tissue, which typically impacts the heart, liver, lungs, and endocrine glands. De *et al*. noticed that the degree of iron excess that was observed is closely correlated with the prevalence of hypothyroidism with high serum iron storage protein level (ferritin)[30].

Despite the presence of high mean serum ferritin among β-thalassemia major patients in the current study, there was insignificant difference statistically between serum ferritin level and abnormal thyroid function disorders with that of euthyroid patients. This was in accordance with other study done by Deepmala A Budhrani et al., in India. Iron overload is the serious reason of endocrinopathy in beta thalassemia major patients, moreover, there are several plausible reasons for thyroid dysfunction than iron overload, including iron-free radical-mediated thyroid gland injury, persistent anemia, and dietary inadequacy[31].

Although, most of beta thalassemia major patients in our study were treated by Deferasirox (Exjade) as an iron chelator, the present results showed that almost all clinical hypothyroid patients as well as majority of subclinical hypothyroid patients were treated by deferasirox (Exjade) as an iron chelator as it considered a more effective than deferoxamine (Desferal) regarding treating the iron overload. Moreover, couple of research showed that the serum ferritin level was low among beta thalassemic patients treated with deferasirox (higher efficacy and compliance) compared to deferoxamine (poor compliance and efficacy). This was contrary to our results that showed an insignificant higher serum ferritin level among subclinical hypothyroid patients and clinical hypothyroid patients[32,33].

Its worthy to mention that in the present study, all subclinical hypothyroid patients and most clinical hypothyroid patients have

no history of splenectomy. This may be regarded as a reason of higher hypothyroid prevalence among beta thalassemia major patients as splenectomy has an important role in influencing the thyroid function[34]. The main pathophysiology in beta thalassemia major patients is the reticuloendothelial system's accelerated destruction of red blood cells, especially by the spleen, which causes it to expand. In contrary to our results, that showed little percent of patients had done splenectomy, many patients with beta thalassemia major require splenectomy, mostly in transfusion-dependent resulting in decreasing blood consumption and transfusion leading to reducing iron overload and subsequently decrease abnormality in thyroid function[35]. Conclusion: we found a higher serum ferritin level among beta thalassemia major patients and near half of beta thalassemia major patients were had decreased thyroid function in the form of overt hypothyroidism and subclinical hypothyroidism. all subclinical hypothyroid patients and most clinical hypothyroid patients have no history of splenectomy.

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پوختە

هەڵسەنگاندنی کارکردنی تایرۆید لە نەخۆشە سەرەکییەکانی بێتا تالاسیمیا کە چەندین جار خوێنیان وەرگرتووە: لێکۆڵینەوەیەکی بڕبڕەیی

پوختەیەک

پێشینە: زانراوە کە تالاسیمیا باوترین نەخۆشی بۆماوەییە لە جیهاندا. بێتا تالاسیمیا مەیجر فۆرمی سەرەکی تالاسیمیا مەیجەرە کە پێویستی بە گواستنەوەی خوێن هەیە بۆ ماوەی تەمەن. یەکێک لە باوترین کێشەکانی ناوپۆشی لەش لە بێتا تالاسیمیا مەیجردا کەمبوونەوەی غودەی دەرەقییە. ئامانجی ئەم توێژینەوەیەی ئێستا هەڵسەنگاندنی دۆخی کارکردنی غودەی دەرەقی لە نەخۆشانی تووشبوو بە تالاسیمیا درێژخایەنەکانی بێتا.

شێوازەکان: توێژینەوەیەکی بڕبڕەیی کە ٢٧٨ نەخۆش لەخۆدەگرێت کە تووشی بێتا تالاسیمیا سەرەکی بوون. توێژینەوەکە بۆ ماوەی 12 مانگ بەردەوام بوو، لە مانگی یەکی ساڵی 2021 تا مانگی یەکی ساڵی 2022. هۆرمۆنی غودەی دەرەقی بێ سیرۆم و هۆرمۆنی هاندەری غودەی دەرەقی و ئاستی فێریتین بۆ هەموو نەخۆشەکان بە بەکارهێنانی شیکارکەری ڕۆش کۆباس 6000 پێوانە کرا.

دەرەنجامەکان: توێژینەوەکە ئاماژەی بە بڵاوبوونەوەی بەرزی کەمی غودەی دەرەقی ژێر کلینیکی کردووە (41.2%) هەروەها کەمی غودەی دەرەقی ئاشکرا (2.9%). زیادبوونی نابەرچاو لە ئاستی فێریتین لە سیرۆم لە نێوان نەخۆشانی کەمکاری غودەی دەرەقیدا هەبوو. نۆزدە لەو نەخۆشانەی کە کەمکاری غودەی دەرەقی ژێر کلینیکییان هەبوو (16.5%)، نەشتەرگەری لابردنی سپڵیان بۆ کراوە، لە کاتێکدا هیچیان کە کەمی غودەی دەرەقی کلینیکییان هەبووە، سپڵیان لابرا.

دەرەنجام: توێژینەوەکە گەیشتە ئەو ئەنجامەی کە نزیکەی نیوەی ئەو نەخۆشانەی کە تووشی بێتا تالاسیمیا سەرەکی بوون، کەمبوونەوەی ئاشکرای غودەی دەرەقی و کەمی غودەی دەرەقی ژێر کلینیکییان هەبووە.

خلاصة

تقييم وظيفة الغدة الدرقية لدى مرضى الثلاسيميا بيتا الرئيسيين الذين أجريت لهم عمليات نقل دم متعددة: دراسة مقطعية

الخلفية: من المعروف أن م رض الثلاسيميا هو أكثر الأمراض الوراثية انتشاراً في العالم. بيتا الثلاسيميا الكبرى هو الشكل الأساسي للثلاسيميا الكبرى الذي يتطلب نقل الدم مدى الحياة. واحدة من أكثر مشاكل الغدد الصماء انتشارًا في بيتا ثلاسيميا الكبرى هي قصور الغدة الدرقية. تهدف الدراسة الحالية إلى تقييم حالة وظيفة الغدة الدرقية لدى المرضى المصابين بالثلاسيميا بيتا بشكل مزمن.

الطرق: دراسة مقطعية شملت 278 مريضاً تم تشخيص إصابتهم بالثلاسيميا بيتا الكبرى. استمرت الدراسة لمدة 12 شهرًا، من يناير 2021 إلى يناير 2022. وتم قياس مستويات هرمون الغدة الدرقية الحر في الدم والهرمون المحفز للغدة الدرقية والفيريتين لجميع المرضى الذين يستخدمون محلل روش كوباس 6000.

النتائج: لاحظت الدراسة ارتفاع معدل انتشار قصور الغدة الدرقية تحت السريري (41.2%) وكذلك (2.9%) قصور الغدة الدرقية العلني. كان هناك ارتفاع غير ملحوظ في مستوى الفيريتين في الدم بين مرضى قصور الغدة الدرقية. تسعة عشر من مرضى قصور الغدة الدرقية تحت السريري (16.5٪) خضعوا لاستئصال الطحال، في حين لم يتم استئصال الطحال لأي شخص مصاب بقصور الغدة الدرقية السريري.

الاستنتاج: خلصت الدراسة إلى أن ما يقرب من نصف مرضى الثلاسيميا بيتا الكبرى كانوا يعانون من قصور الغدة الدرقية الصريح وقصور الغدة الدرقية تحت السريري.