Study of the function of Thyroid gland in β- thalassemia major male patients in Kirkuk city.

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Abstract

Thalassemia has been classified by the world health organization as a major public health problem. It occurs throughout the world and regarded as one of the major health problems in endemic regions as Middle East, Mediterranean countries, Asia and North Africa**.** Endocrine complications in Thalassaemia Major Patients with multitransfused Thalassaemia Major patients may develop severe endocrine complications. Due to multiple transfusions is the main cause of such complications, Iron accumulates in many tissues such as liver, heart and endocrine glands**.** The study aims to study the function of Thyroid gland in β- thalassemia Major male patients in Kirkuk city. The study was conducted β-thalassaemia major patients whom attended the thalassaemia center in Azadi Teaching hospital in Kirkuk Governorate from September 2015 to the end of January 2016. A total of 105 male subjects were participated in the study, (30 normal healthy subjects and 75 thalassaemic patients). Body weight height was measured. About, five ml of venous blood were obtained from all normal subjects and patients. One ml of blood sample was collected for measurement of packet cell volume (PCV) and heamoglobin (Hb). The remaining four ml of blood sample were used for serum separation. Serum used for measurement of serum thyroid stimulating hormones (TSH), T3 and T4. **Results of study showed** a high significant decrease in body weight and height of male thalassemic patients as compare with male counterpart of control subjects of same age**.** Also, there was a highly significant reduction in the concentration of heamoglobin and PCV value in thalassaemic male patients as compared with control male subjects. There is no significant increase in serum Thyroid stimulating hormone (TSH) concentration in male thalassemic patients as compare with male control subjects. However, there is highly significant reduction in serum T4 and T3 concentrations in male thalassemic patients as compare with male control subjects.

Key words: PCV, Hb, Weight, height, thyroid gland, T3, T4, male, Thalassemia, Kirkuk, Iraq.

دراسة وظيفة الغدة الدرقية لدى الذكور من مرضى الثلاسيميا الكبرى نوع بي في كركوك

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الخلاصة

تم تصنيف مرض فقر الدم الثلاسيميا من قبل منظمة الصحة العالمية كمشكلة صحية رئيسية عامة. ويوجد مرض الثلاسيميا في جميع أنحاء العالم، ويعتبر واحد من المشكلات الصحية الرئيسية في المناطق الموبوءة كالشرق الأوسط وشمال أفريقيا ودول البحر الأبيض المتوسط وآسيا.

ان مضاعفات الغدد الصم لدى مرضى الثلاسيميا المصاحب مع تعدد في نقل الدم في الثلاسيميا الكبرى مضاعفات شديدة و بسبب النقل المتعدد كونه السبب الرئيسي لمثل هذه المضاعفات، يتراكم الحديد الزائد في العديد من الأنسجة مثل الكبد والقلب والغدد الصماء الغدد. تهدف الدراسة الحالية دراسة وظيفة الغدة الدرقية لدى مرضى الثلاسيميا الكبرى في مدينة كركوك. **المرضى والطرق**: أجريت دراسة مقطعية على مرضى الثلاسيميا الكبرى-β الذين حضروا الى مركز الثلاسيميا في مستشفى آزادي التعليمي في محافظة كركوك من أيلول 2015 إلى نهاية كانون الثاني 2016. وشارك ما مجموعه 105 طفل من الذكور في هذه الدراسة، (30 طفل سليم و75 مريض). وقد تم قياس وزن و طول الجسم. تم الحصول على خمسة مل من الدم الوريدي من جميع المشاركين. وقد تم جمع واحد مل من عينة من الدم لقياس حجم الخلايا المتراصة و خضاب الدم (الهيموغلوبين). وقد تم جمع أربعة مل المتبقية من عينة الدم في أنبوب عادي، لفصل مصل الدم. استخدم المصل لقياس هرمون منشط الغدة الدرقية ((TSH، T3 و T4). **النتائج**: كان هناك انخفاض معنوي في وزن و طول الجسم لدى مرضى الثلاسيميا الذكور مقارنة مع نظيرهم من الذكور في مجموعة الضابطة من نفس الفئة العمرية. أيضا، كان هناك انخفاض كبير جدا في تركيز خضاب الدم وقيمة حجم الخلايا المتراصة في مرضى الثلاسيميا الذكور مقارنة مع نظيرهم من الذكور في مجموعة الضابطة من نفس الفئة العمرية. كذلك هناك زيادة غيرمعنوية في تركيزهرمون محفز الغدة الدرقية في مصل الدم (TSH) في مرضى الثلاسيميا الذكور مقارنة مع نظيرهم من الذكور في مجموعة الضابطة. ومع ذلك، هناك انخفاض معنوي في تركيز هرمون الثايروكسين (T4) في مصل الدم وتركيز ثلاثي ايوديد الثايرونين (T3) في مرضى الثلاسيميا الذكور مقارنة مع الاطفال في المجموعة الضابطة.

الكلمات المفتاحية:-

حجم الخلايا المتراصة، خضاب الدم ، وزن الجسم، هورمونات الغدة الدرقية، الأطفال الذكور، كركوك ، العراق.

Introduction

Thalassemias are a group of hereditary anemias which occur as a result of genetic disorders that affect the synthesis of normal hemoglobin (Hb), in which a reduced rate of synthesis of one or more of the globin chains leads to defective Hb production, and damage to the red cells [1,2]. Thalassemia occurs throughout the world and regarded as one of the major health problems in endemic regions as the, Middle East, Mediterranean countries, Asia and North Africa [3,4]. The two main types of thalassemia are called alpha and beta thalassemia, Individuals with alpha thalassemia do not produce enough alpha globin. Those with beta thalassemia do not produce enough beta globin. There are a number of different forms of alpha and beta thalassemias, with symptoms ranging from mild to severe [3,4].

Beta thalassemia in turn is classified into two categories: beta plus where the beta –chain production is reduced and beta zero, where there is no β-chain production found [5,6]. Beta-thalassemia probably is the most common single gene disorder causing a major genetic health problem in the world. There are at least two hundred and forty million carriers for hemoglobinopathies throughout the world [3]. Thalassemia is a congenital hemolytic anemia caused by partial or complete deficiency of globulin protein chain synthesis resulting in microlytic anemia of varying degrees [6]. Due to multiple blood transfusions is the main cause of such complications. Iron accumulates in many tissues such as liver, heart and endocrine glands [7-9]. Thyroid gland hormones are responsible for raising the level of activity in the systems essential for exercise performance [10-12].

The **aim** of study is determining the effect of iron overload in Thalassemic patients on thyroid gland function.

Patients and Methods

The study was conducted β-thalassaemia major patients whom attended the thalassaemia center in Azadi Teaching hospital in Kirkuk Governorate from September 2015 to the end of January 2016. One hundred and five male subjects were participated in the study. Seventy five β- thalassemia major male patients aged 8 to 16 years

and thirty male subjects apparently healthy, with no family history of hereditary blood diseases attendants to out-patient pediatric clinic, who were assessed by a pediatrician, all control healthy subjects aged 8 to 16 years. Body weight was measured and body height was measured in centimeter (cm).

Five ml of venous blood were obtained from all patients in this study by antecubital venipuncture, between 8.00 am and 10.00 am and distributed in the following manner; 1 ml of blood sample was collected into ethylene diaminotetracetic acid (EDTA) tube, with gentle shaking for proper mixing with anticoagulant, to be use for packet cell volume (PCV) and heamoglobin (Hb) measurements.

The remaining 4 ml of blood sample was collected into a plain tube, then incubate for 30 min and then centrifuged for serum separation so that the samples for males were subdivided and labeled for measurement serum Thyroid stimulating hormone (TSH), T3 and T4 for females were measured [13,14].

All data were presented as a mean and standard deviation (SD), unpaired student T test was used to compare between the mean of variables. Probability value less than $P \leq 0.05$ and 0.01 levels were considered to be a significant deference.

Results

There was a significant decrease ($p< 0.01$) in body weight of thalassaemic male patients (37.42 ± 7.34 kg) as compared with control male subjects (58.62 ± 9.32 kg) as shown in table (1). Also, there was significant reduction ($p< 0.01$) in body height of thalassaemic male patients (132.64 ± 7.4 cm) as compared with control male subjects (151.24 ± 9.5 cm) as shown in table (1).

Heamoglobin and PCV in male subjects:

There was a highly significant reduction ($p <0.01$) in the concentration of heamoglobin in thalassaemic patients (8.23 ± 0.276 gm/dl) as compared with control male subjects (13.965 ± 0.97 gm/dl) as shown in table 2. Also, there was a highly significant reduction ($p <0.01$) in the PCV value of thalassaemic male patients (29.98 ± 2.76 L/L) as compared with control subjects (40.32 ± 2.37 L/L) (table 2). There was a highly significant increase ($p <0.01$) in the serum ferritin concentration of thalassaemic male patients (3558.43 ±

298.4 ng/ml) as compared with control subjects (59.87 ± 8.13 ng/ml) (table 2).

Thyroid hormones

No significant increase in serum TSH concentration in male thalassemic patients (4.412 ± 0.21 **µIU/ml**) as compare with male control subjects (3.22 ± 1.23). There is highly significant reduction in serum T4 concentration (P≤0.01) in male thalassemic patients (0.683 ± 0.213 **µg/dl**) as compare with male control subjects (6.542 ± 0.62 **µg/dl**). Moreover, there is significant reduction in serum T3 concentration (P≤0.05) of male thalassemic patients (1.067 ± 0.273 **ng/ml**) as compare with male control subjects (1.994 ± 0.39 ng/ml).

Discussion

In present study, significant reduction in body weight and length of male body of thalassaemic patients as compared with control subjects. Possible reasons are persistent anaemia due to inadequate transfusion and complications of iron overload in addition to other factors [5,6]. Similar finding was reported by previous study [7]. In present study, there was a highly significant increase in the serum ferritin concentration of thalassaemic male patients as compared with control subjects. Similar results was reported in previous studies [11,12]. Key contributing factors to stunted growth in patients with thalassaemia major (TM) may include chronic anaemia, transfusional iron overload, hypersplenism, and chelation toxicity [4,12]. **Thyroid dysfunction** in β-thalassemic patients has been reported in various prevalence, ranging from a low prevalence of 0-12% [13,14]. The abnormal thyroid function found in the present patients was the slight elevation of TSH, which was consistent with the diagnosis of compensated hypothyroidism, the most common thyroid dysfunction in all previous reports [16]. Impaired thyroid function is frequent among present thalassaemia major patients and this necessitates regular follow up and early commencement of chelation therapy to prevent such complication [17].

In present study, there is significant reduction in serum T3 and T4 concentrations in thalassemic patients as compare with control subjects. Previous study was done in Irbil –Iraq, it was found that the mean levels of thyroid hormones; T3 and T4 were significantly lower (P<0.001) among

thalassaemia patients, while the mean TSH level was higher compared to the control group [18,19].

Other factors in addation to Iron overload, like hypoxia due to persistent anemia and perfusion defect, also contribute to the derangement. Hypothalamic pituitary axis, thyroid, para-thyroid, adrenal, pancreas, gonads, all showed hypoactivity [15,16].

Previous study found that the mean T4 of cases was significantly lower than that of controls. The mean TSH level was significantly higher ($p<0.01$) in cases as compared to controls [20]. 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 [21].

Thyroid dysfunction is known to occur frequently in thalassaemia major, but its prevalence and severity varies in different cohorts, and long-term natural history is poorly understood [20,22].

A wide spectrum of pathogenic mechanisms is involved. Tissue chronic hypoxia and iron overload have a direct toxic effect on the thyroid gland. High concentrations of labile plasma iron and labile cell iron which are considered responsible in the formation of free radicals and the production of reactive oxygen species (ROS) may lead to cell and organ damage [23,24]. From the present study and previous reinforce the importance of the regular follow up of patients with β -thalassaemia major and thalassaemia intermedia for early detection and management of associated complications. In this way, the future prevalence of endocrine abnormalities can be lessened [19,20].

Subclinical hypothyroidism may be associated with male and female gonad dysfunction and interferes with their reproductive ability. The awareness of the thyroid status in any infertile couple is crucial, because of its significant, frequent and often reversible or preventable effect on infertility [25,26]. Most complications are caused by increased iron sedimentation in tissues like heart, endocrine glands and these results in heart failure, arrhythmia, hypothyroidism and diabetes mellitus. Most of these complications occur slowly and appear in the second decade of a patient's life [27,28].

In the present study, It was found that highly significant reduction in the concentration of heamoglobin and packed cell volume (PCV) in thalassaemic male patients as compared with control male subjects. PCV values found in previous study that in Mosul city was the similar to the PCV result of the present study [29]. Also, it was found that Thalassaemic patients had a low PCV and low hemoglobin concentration as compared with their counterpart of same age and gender [30,32].

Present study **conclude** the Thalassemic male patients had a lower T3 and T4 as compare with normal healthy male control subjects of same age. However, there is a non significant increase in serum TSH concentration as compare with male control subjects. Present study **recommends** assessment of pituitary hormone especially growth hormone by carry out hormonal test for both genders as a routine follow up of thalassaemic patients.

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Table 1 The mean & standard deviation (SD) of age, body weight, and height of patients and controls.

Parameters	Control (30)	Patients (75)	P value
Age (years)	14.91 ± 2.11	13.84 ± 1.98	NS
Body weight (Kg)	58.62 ± 9.32	37.42 ± 7.34	0.001
Height (Cm)	151.24 ± 9.5	132.64 ± 7.4	0.001

Table 2 The mean and standard deviation of hemoglobin, PCV and serum ferritin of male thalassaemic patients and control male subjects:

Parameters	Thalassaemic males (n=75)	Control males (n=30	P. value
Hb (g/dl)	8.23 ± 0.276	13.965 ± 0.97	0.01
PCV (L/L)	29.98 ± 2.76	40.32 ± 2.37	0.01
Ferritin (ng/ml)	59.87 ± 8.13	3558.43 ± 298.4	0.01

Table 3 Show the mean & standard deviation (SD) of serum TSH, T3 & T4 hormones concentrations in patients and control subjects.

Parameters	Control	Patients	P value
TSH **(µIU/ml)**	3.22 ± 1.23	4.412 ± 0.21	NS
T4 **(µg/dl)**	6.542 ± 0.62	0.683 ± 0.213	0.01
T3 (**ng/ml)**	1.994 ± 0.39	1.067 ± 0.273	0.05