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The Variation in Levels of Some Male Pituitary and Gonadal Hormones in Beta-Thalassemia Major Patients in Iraq

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Abstract

This study was aimed to investigate the iron overload effect on the levels of ferritin, testosterone, follicle stimulating hormone (FSH), luteinizing hormone (LH) and prolactin (PRL) in male patients with β-thalassemia. Blood levels of sex hormones and ferritin were determined in (50 males) beta-thalassemia patients, aged (16-23) years and in (30) healthy males matched for age. They were recruited from the Abin Al-Balady Hospital in Baghdad. Ichroma™ kits were used to determine the blood levels of sex hormones and ferritin. The results showed that the level of testosterone, LH and FSH were significantly ($p\leq 0.05$) lower in β-thalassemia male patients compared to controls. Furthermore, the level of ferritin and prolactin in male patients were significantly ($p\leq 0.05$) higher than the values obtained in the controls. Significant positive correlations ($p\leq 0.05$), ($r= 0.3834$) were detected between level of LH and ferritin in male patients. Non-significant positive correlations ($p\geq 0.05$) in the level of testosterone and ferritin, also non-significant negative correlation in PRL and FSH and ferritin were found in patients with β-thalassemia. From the above results it can be concluded that the iron overload may be the major cause of infertility in β-thalassemia male patients.

Keywords: Beta-thalassemia, Infertility, Sex hormones, Iron overload.

التغاير في مستويات بعض هورمونات الغدة النخامية والمناسل في الذكور المصابين بفقر دم البحر المتوسط في العراق

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الخلاصة

هدفت الدراسة الحالية الى التحري عن تاثير الزيادة في الحديد على مستوى الفرتين والهورمون المحفز للجريبات والهورمون اللوتيني وهورمون الحليب والتستوستيرون في الذكور المصابين بفقر دم البحر المتوسط.تم تحديد مستوى الفرتين والهورمونات الجنسية في خمسين من الذكور المصابين بفقر دم البحر المتوسط تراوحت اعمارهم بين 16−23 عاما وثلاثون من الذكور الاصحاء بنفس العمر خلال تواجدهم في مستشفى ابن البلدي في بغداد.استخدم جهاز Ichroma™ kits في تحديد مستوى الفرتين والهورمونات الجنسية.اظهرت النتائج ان مستويات هورمونات التيستوستيرون ومحفز الجريبات ,والهورمون اللوتيني قد انخفضت معنويا ($p\leq 0.05$) في الذكور المصابين مقارنة مع الاصحاء، في حين لوحظ ارتفاعا معنويا ($p\leq 0.05$) في مستويات الفرتين وهورمون الحليب في المرضى مقارنة مع السيطرة.لوحظ وجود ارتباطا معنويا موجبا ($p\leq 0.05$) بين الفرتين

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وهورمون اللوتيني وارتباط موجب غير معنوي ($p\leq0.05$) مع التيستوستيرون وارتباط سالب غير معنوي ($p\leq0.05$) بين الفرتين وهورمون الحليب ومحفز الجريبات . يمكن من النتائج التوصل الى ان الزيادة في الحديد قد تكون السبب الرئيس في عدم الخصوبة في الذكور المصابين بفقر دم البحر المتوسط.

Introduction

Thalassemia major is a hereditary disorder of hemoglobin synthesis and the homozygous state results in severe anemia. The homozygous condition was known to affect a large population in Mediterranean countries and the Middle East; however, migration has changed the geographic spread and made it a worldwide health problem. [1]. Blood transfusions are mandatory for survival of beta thalassemia major patients which leads to iron overload; subsequent oxidative stress and tissue damage [2]. Excessive iron is deposited in most tissues primarily in the liver, spleen, heart and the endocrine glands and other vital organs [3].

Chelation therapy and blood transfusion has dramatically extended the life expectancy of thalassemia patients but is complicated by toxicity and subsequent iron overload resulting in a high incidence of endocrine abnormalities in children, adolescents and young adults [1]. Disorders of sexual development, growth, & fertility, abnormal bone mineralization, diabetes mellitus, hypothyroidism and hypoadrenalism are the main important endocrine complications found in thalassemia patients [4]. Now many subjects with β- thalassemia major successfully survive into adult life due to the remarkable improvements in medical care and to a better understanding of clinical manifestations, pathogenesis, and prevention of endocrine complications [5]. Despite the improvement of the treatment, the involvement of the endocrine system still burdens the life of these patients. In fact, many studies have reported that as many as 50% to 65% of patients may have sexual dysfunction, pubertal failure, and infertility, due to hypogonadism [6].

The iron depositions in the endocrine glands classically considered to be the main causes of male infertility in β-thalassemia are result of [7]. The 'free iron' is a catalyst of the production of oxygen species that peroxidize membrane and damage cells and lipids, leading to cell destruction, also there are other possible causes of hypogonadism in β-thalassemia include chronic hypoxia, liver disorders, and associated endocrine complications, such as diabetes [3].

Materials and Methods:

Subjects: Blood samples were obtained from 50 adult male, (age 16–23 years) with β-thalassemia major. They were recruited from the Abin Al-Balady Hospital in Baghdad. The study was conducted during the period from January 2016 to March 2016.The patients had suffered from *β*-thalassemia major for various periods of time and take no medications except their daily Desferral supplementation. Blood sample obtained from 30 adult healthy male (ages 16–23) were used as controls.

Blood Collection: Five (ml) of blood were drawn for each biochemical and hormonal study. The samples were left at room temperature for about 30 minute, and then centrifugation was done at 3000 round per minute for 10-15 minute to separate the serum and stored at – 20ͦ C.

Assay methods: Determination of ferritin, and other hormones was carried out according to procedures recommended by: ichroma™ ferritin kit, ichroma™ PRL kit, ichroma™ testosterone kit, ichroma™ LH kit and ichroma™ FSH from Boditech Inc. Korea by using Enzyme -Linked Immunosorbent Assay (ELISA).

Statistical Analysis: Statistical analysis of the resultswas done using statistical package for social science (SPSS) . Analysis of variance (ANOVA) table was used and mean and standard deviation were calculated depending on basic statistic method.

Results:

The results showed a significant ($p\leq0.05$) increase in the level of serum ferritin and prolactin in patients with beta thalassemia major (3277.4 ± 622.7ng/ml) and (18.434 ± 4.13 ng/ml) respectively as compared to control (163.45 ± 32.63ng/ml) and (12.79 ± 3.16 ng/ml) Table-1 and Figures- 1 and 2. There was a significant ($p\leq0.05$) decrease in the level of serum testosterone (1.295 ± 0.66ng/ml), LH (0.811 ± 0.51mIU/ml) and FSH(2.226 ± 1.013 mIU/ml) in patients with beta thalassemia major as compared to control(5.134 ± 1.86 ng/ml),(4.045 ± 1.33 mIU/ml) and (6.239 ± 1.58 mIU/ml) respectively Table-1 and Figures - 2,3 and 4. The results in Table-2 showed a significant ($p\leq0.05$) positive correlation between ferritin and LH (r = 0.3834), while there was non-significant ($p\geq0.05$)

positive correlation between ferritin and testosterone (r= 0.1003). There was non-significant ($p \geq 0.05$) negative correlation between ferritin and FSH (r= - 0.1439) and prolactin (r = - 0.2404).

Table 1- Levels of ferritin, pituitary and gonadal hormones in male patients with beta-thalassemia major and control

Groups → / Parameters ↓	Healthy control	Beta-Thalassemia Major Patients
Testosterone (ng/ml)	**5.134 ± 1.86**	**1.295 ± 0.66***
Prolactin (ng/ml)	**12.79 ± 3.16**	**18.434 ± 4.13***
LH (mIU/ml)	**4.045 ± 1.33**	**0.811 ± 0.51***
FSH (mIU/ml)	**6.239 ± 1.58**	**2.226 ± 1.013***
Ferritin (ng/ml)	**163.45 ± 32.63**	**3277.4 ± 622.7***

Values are expressed as mean ± S.D

* Values are significant (P <0.05) when compared with control.

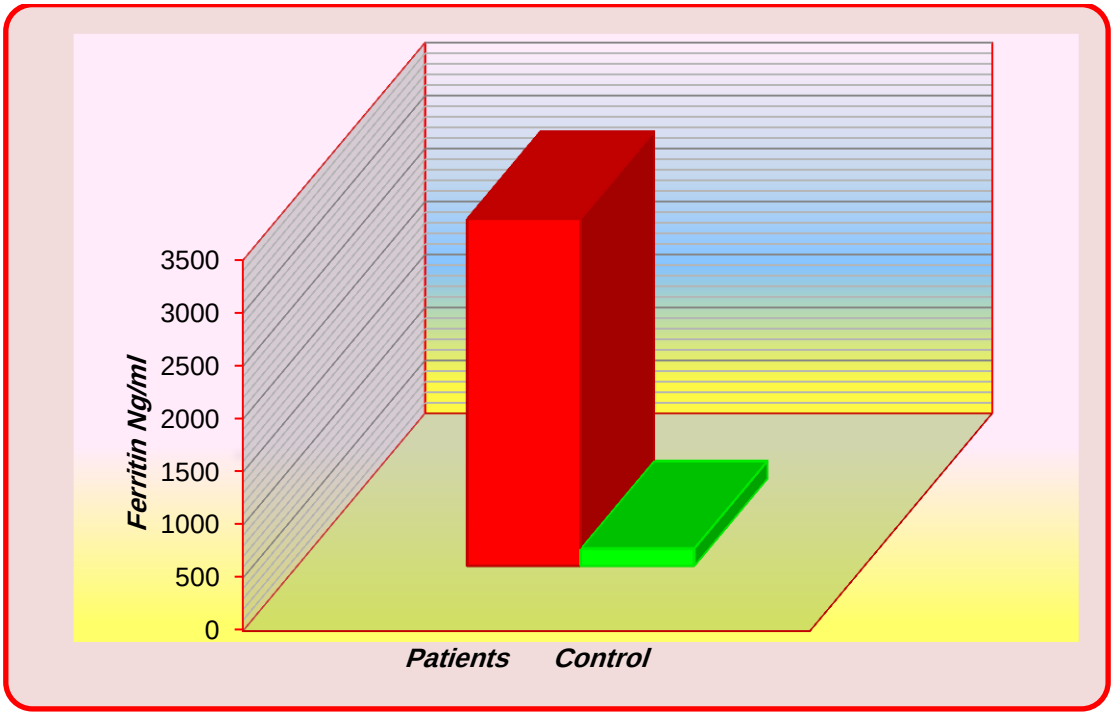

Figure 1- Level of ferritin in male patients with beta-thalassemia major and control

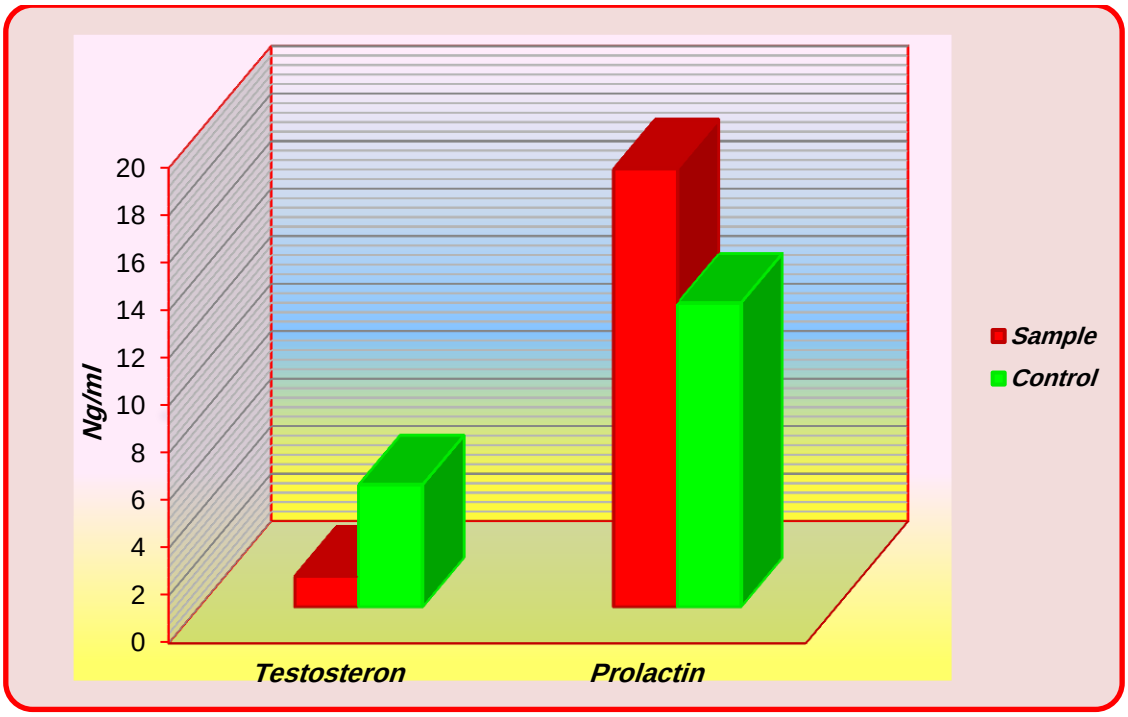

Figure 2- Level of testosterone and prolactin hormone in male patients with beta-bhalassemia major and control

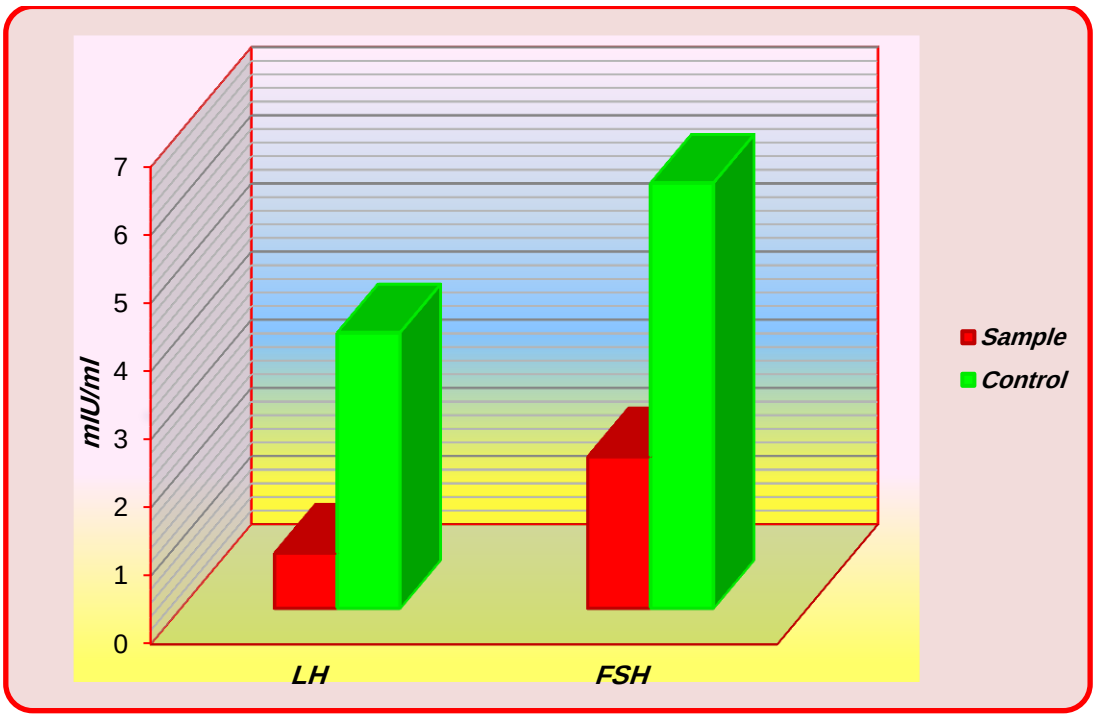

Figure 3- Level of LH and FSH hormone in male patients with beta-thalassemia major and control

Table 2-Correlation coefficient between ferritin and different pituitary and gonadal hormones in male patients with beta-thalassemia major

Correlation		r- value	Significant
Testosterone	**ferritin**	**0.1003**	**NS**
Prolactin	**ferritin**	**- 0.2404**	**NS**
LH	**ferritin**	**0.3834**	**Sig.**
FSH	**ferritin**	**- 0.1439**	**NS**

Sig.: Significant $p \leq 0.05$, NS: Non significant $p \geq 0.05$

Discussion

The results of this study showed significant decrease in the level of testosterone ,LH and FSH and this finding agree with the finding of the study that explain the failure of pubertal growth, amenorrhea, delay or absence of sexual development, sexual dysfunction and infertility due to hypogonadism are well-recognized disturbances of the hypothalamic "pituitary " gonadal axis in β-thalassemia patients [8].The significant increase in the level of ferritin in this study are agree with another multiple gonadal and pituitary-gonadal function studies have confirmed primary gonadal failure due to gonadal iron deposition .The secondary hypogonadism results from iron deposition on gonadotrophic cells of the pituitary gland as shown by limited response of LH and FSH to GnRH stimulation [9] or a combination of both primary and secondary hypogonadism [10]. Aberrant gonadotrophin response to gonadotropins releasing hormone (GnRH) administered in a pulsatile fashion strongly indicates failure of gonadotroph cells, which seem to be extremely vulnerable to iron damage [11].Patients with more severe defects have a greater rate of iron loading possibly due to increased vulnerability to free radical toxicity. Iron deposition in large amount is caused by chronic anaemia resulting in profound tissue hypoxia as well as compensatory responses, including increased intestinal iron absorption and increased bone marrow erythropoiesis. Despite the availability and activity of chelation therapy, iron overload remains problematic because of poor acceptability of the currently available agents, which require parenteral administration and close blood monitoring. [4].The anterior pituitary gland is particularly sensitive to free radical. Magnetic resonance imaging shows that the iron deposition within the anterior pituitary can interfere with its function [12]. Iron overload in the pituitary, hypothalamus and gonads is progressive even with used of chelation therapy [13]. Patients with low gonadotropin levels have significant unresponsiveness to gonadotropin releasing hormone compatible with a hypothalamic and pituitary damage [14]. Delayed onset of menarche, oligomenorrhoea, secondary amennorhoea, breast size at Tanner Stage 2 or 3, and attenuated testicular size (of 6 - 8) millimeter are common manifestations of significantly elevated serum iron and ferritin levels [15, 16]. Recent study has demonstrated a high prevalence of hypogonadotropic hypogonadism. The prevalence was 45% in boys and 39% in girls. Also there was delay or arrest in development of secondary sexual characters and menstrual cycle [17]. Another study reported puberty failure in 69% of thalassemia patients with low levels of FSH and LH (73.2% in males and 64.8% in females) [18]. Soliman *et al.* [19] have also reported lack of puberty in 73% males and 42% in thalassemia patients with age less than 21 yrs. Iron toxicity on adipose tissue has also been shown to cause impaired synthesis of Leptin which is a polypeptide hormone produced by adipose cells due to expression of the ob gene and acts as a permissive signal to initiate puberty, and consequently a delay in sexual maturation [20].

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