Evaluation of Reproductive Hormones in Patients with β-Thalassemia Major in Misan Province, Iraq

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Abstract

Assessment of serum ferritin, FSH, LH, estradiol, testosterone levels in β-thalassemia major patients. A total 50 (30 male and 20 female) children with β- thalassemia major patients with ages range 11- 16 years and 50 age and sex matched healthy adolescents as control group were included in this study. The study subjects divided into 2 more subgroups: 11-13 years, and 14-16 years to measure mean serum ferritin, FSH, LH, testosterone, estradiol hormones. There was significant increase ($P < 0.05$) in serum ferritin level in male and female patients as compared to control groups. Male patients have significant decreased ($P<0.05$)serum levels of FSH, LH, testosterone and estradiol, while female patients have non-significant ($P > 0.05$) high serum FSH and testosterone levels, but LH, estradiol levels were non-significant ($P>0.05$) lowas compared to control. In age subgroup 11–13 years, male patients have significant ($P<0.05$) decreased reproductive hormones levels as compared to control, however in 14 – 16 years subgroups serum FSH,LH and estradiol levels in male patients were significantly decreased as compared to control ($P<0.05$), whereas,hormones levels in female patients didn't show significant differences in comparison to female control in both age subgroups ($P>0.05$). Serum ferritin had an inverse correlation with serum FSH, LH, testosterone, estradiol hormones levels. Patients with β- thalassemia major have iron overload with inverse correlation between gonadal hormones and serum ferritin.

Keywords: *β-thalassemia major, serum ferritin, reproductive hormones.*

Introduction

Beta-thalassemia is a hereditary blood disorder characterized by reduced (β^+) or absent (β^-) synthesis of the beta globin chains of the hemoglobin, resulting in reduced hemoglobin in red blood cells,decreased red cells production and anemia[1].

Before the introduction of regular blood transfusion and before the availability of iron chelation therapies β-thalassemia major patients died within the first few years[2,3]. This bad prognosis changed since the survival rates, and life expectancy started to improve progressively and patients may survive until 4^{th}-5^{th} decades due to the implementation of continuous and significant advent of diagnostic and therapeutic method, consisting mainly of an intensive transfusion program combined with chelation regimes and imaging method[4,5,6,7].

The most serious disadvantage of life-saving transfusions is the inexorable accumulation of iron within tissues and high incidence of endocrine abnormalities in children, adolescents and young adults[4,5].

Hypothalamic-pituitary-gonadal (HPG) dysfunctions are the most frequently registered endocrine complication in β- thalassemia major despite regular transfusions and optimal chelation therapy ranges between 30 and 80% of patients [5,8].

The current study was designed for assessment of

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serum ferritin and reproductive hormones (FSH, LH, estradiol, testosterone) in β-thalassemia major patient.

Materials and Method

Over a six-month period, from 1st of December 2018 to the 31st of May 2019, a total 50 (30 male and 20 female) children with β- thalassemia major patients with ages range between 11 to 16 years attended Misan Thalassemia Center, and an equal number of age and sex matched healthy adolescents as control group were included in this case control study. The cases and control were further divided into 2 more subgroups based on age from 11-13 years, and 14-16 years to measure the serum ferritin, FSH, LH, testosterone, and estradiol. The assay principle combines an enzyme immunoassay sandwich method with a final fluorescent detection Enzyme Linked Fluorescent Assay (ELFA) was used [9, 10, 11].

Statistical analyses were reports as mean estimation ± standard error, t test, and correlation using Statistical Package for Social Science (SPSS) version 23 for windows.

Results

The present study revealed a highly significant increase ($P < 0.05$) in serum ferritin level (4094.78±492.55ng/ml) in male and female (3603.20±564.88 ng/ml) patients in comparison to male and female in control groups (94.96±8.17 ng/ml, 74.82±6.44 ng/ml respectively), (table 1).

Table (1): Comparison of serum ferritin in control and β-thalassemia patients regarding gender

Variable	Gender	Control Group	Patients Group	P Value	T test
Ferritin (ng/ml)	Male	94.96±8.17	4094.78±492.55	0.000	8.119
	Female	74.82±6.44	3603.20±564.88	0.000	6.246

Value represented mean ± SE.

According to the age subgroups in control and patients groups, male patients in both age subgroups have a highly significant increase ($P<0.05$) in serum ferritin level (11–13 years =3716.03±535.76 ng/ml, and14-16 years = 4473.50±835.21ng/ml) in comparison to male control groups (86.86±10.51 ng/ml, and 103.07±12.53 ng/ml respectively), and so female patients in both age subgroups have a high statistically significant increase ($P<0.05$) in serum ferritin (11-13 years = 3894.90±894.56 ng/ml, and 14-16 years=3311.40±726.72 ng/ml) as compared to controls, (table, 2).

Table (2): Serum ferritin value according to gender and age groups in control and β- thalassemia patients

Variables	Gender	Age	Control Group	Patients Group	P Value	T test
Ferritin (ng/ml)	Male	11-13	86.86±10.51	3716.03±535.76	0.000	6.773
		14-16	103.07±12.53	4473.50±835.21	0.000	5.232
	Female	11-13	79.77±8.45	3894.90±894.56	0.000	4.265
		14-16	69.88±9.91	3311.40±726.72	0.000	4.460

Value represented mean ± SE.

The results of ours study revealed male patients have highly significant ($P<0.05$) decreased levels of serum FSH (1.52±0.26 mIU/ml), LH (0.92±0.16 mIU/ml), testosterone (1.31±0.20 ng/ml) and estradiol (23.67±3.54 pg/ml) levels in comparison to male patients in control group. However, in female serum FSH (3.38±0.60 mIU/ml), and testosterone (1.08±0.20 ng/ml) in patients was not significantly high as compared with control group ($P>0.05$), while serum LH (2.54±0.78 mIU/ml), and estradiol (48.13±6.57 pg/ml) levels were not significantly low in patients in comparison to control ($P >0.05$), (table, 3).

Table (3): Comparison the values of reproductive hormones in control and β-thalassemia patients regarding gender

Hormone	Gender	Control Group	Patients Group	P Value	T test
FSH (mIU/ml)	Male	2.67±0.17	1.52±0.26	0.000	3.688
	Female	2.72±0.21	3.38±0.60	0.316	1.015
LH(mIU/ml)	Male	2.64±0.20	0.92±0.16	0.000	6.560
	Female	2.73±0.18	2.54±0.78	0.806	0.248
Testosterone(ng/ml)	Male	5.64±1.62	1.31±0.20	0.01	20649
	Female	0.80±0.10	1.08±0.20	0.225	1.233
Estradiol (pg/ml)	Male	54.79±5.18	23.67±3.54	0.000	4.957
	Female	72.92±17.83	48.13±6.57	0.200	1.305

Value represented mean ± SE.

Regarding age subgroups; (table 4) showed that there were significant (P < 0.05) decreased levels of serum FSH (1.47±0.39mIU/ml), LH (0.88±0.25 mIU/ml), testosterone (1.40±0.37 ng/ml), and estradiol (23.89±5.13 pg/ml) in male patients compared with control in 11 – 13 years subgroups, and so in female of same age subgroup serum FSH (2.71±0.84 mIU/ml), LH (1.24±0.42 mIU/ml), and estradiol (59.45±9.42 pg/ml) levels were decrease in patients as compared with control, but FSH and estradiol levels had no significant (P>0.05) difference, while testosterone level in female patients group (1.52±0.31 ng/ml) was higher than in control (0.92±0.12 ng/ml) without significant difference (P>0.05).

In 14 – 16 years subgroups our results showed that serum FSH, LH and estradiol levels in male patients were significantly (P<0.05) decreased (1.57±0.35 mIU/ml, 0.96±0.20 mIU/ml, and 23.44±5.06 pg/ml respectively), as so testosterone level (1.21±0.17 ng/ml) was lower but without significant difference (P >0.05) as compared with male controls (2.66±0.26 mIU/ml,2.63±0.32 mIU/ml, 58.85±8.40 pg/ml and 7.30±3.21 ng/ml respectively). While in female of same age subgroup serum FSH (4.06±0.88 mIU/ml), and LH (3.83±1.41mIU/ml) levels have non-significant differences in comparison to control (P>0.05), but testosterone (0.65±0.18 ng/ml) and estradiol (36.81±8.06 pg/ml) levels were measured not significantly differed in female patients compared to same gender of control group (P>0.05), (table, 4).

Table (4): Evaluation of reproductive hormones values according to gender and age groups in control and β-thalassemia patients

Hormone	Gender	Age	Control Group	Patients Group	P Value	T test
FSH(mIU/ml)	Male	11-13	2.67±0.24	1.47±0.39	0.014	2.630
		14-16	2.66±0.26	1.57±0.35	0.019	2.496
	Female	11-13	3.06±0.35	2.71±0.84	0.706	0.002
		14-16	2.39±0.20	4.06±0.88	0.081	1.849
LH (mIU/ml)	Male	11-13	2.65±0.27	0.88±0.25	0.000	4.721
		14-16	2.63±0.32	0.96±0.20	0.000	4.401
	Female	11-13	2.64±0.18	1.24±0.42	0.007	3.022
		14-16	2.82±0.32	3.83±1.41	0.499	0.690
Testosterone (ng/ml)	Male	11-13	3.98±0.45	1.40±0.37	0.000	4.391
		14-16	7.30±3.21	1.21±0.17	0.069	1.891
	Female	11-13	0.92±0.12	1.52±0.31	0.093	1.776
		14-16	0.68±0.16	0.65±0.18	0.895	0.133

Hormone	Gender	Age	Control Group	Patients Group	P Value	T test
Estradiol (pg/ml)	Male	11-13	50.73±6.19	23.89±5.13	0.002	3.337
		14-16	58.85±8.40	23.44±5.06	0.001	3.609
	Female	11-13	93.93±34.21	59.45±9.42	0.344	0.972
		14-16	51.91±8.58	6.81±8.06	0.216	1.282

Value represented mean±SE

Serum ferritin as a dependent variable had an inverse correlation with serum FSH, LH, testosterone, and estradiol levels, (table, 5).

Table (5): Correlation between serum ferritin levels versus reproductive hormones levels in β-thalassemia major Patients

Variables	Ferritin	Testosterone	Estradiol	FSH	LH
Testosterone	-.123	1			
Estradiol	-.023	.000	1		
FSH	-.135	-.043	.044	1	
LH	-.124	-.033	-.011	.676*	1

* Correlation is significant at the 0.05 level (2-tailed).

Discussion

Although blood transfusions are crucial in the survival of β- thalassemia major, but the most serious disadvantage of life-saving transfusions is the inexorable accumulation of iron within tissues, and excess iron is extremely toxic to all cells of the body and can cause serious and irreversible end-organ damages as these β-thalassemia major children grow into adolescence and adulthood if untreated[12,13].

In Iraq thalassemia is a serious and real public health problem due to the unavailability of equipment and drugs during different periods of unrest and war and calls for an effective management plan, including public health education programsto facilitate early diagnosis and treatment[14,15,16].

Our study results showed that our patients have a high significant increase in serum ferritin levels among male and female patients compared with same genders in control group. This high serum ferritin level most likely due to frequent blood transfusions and hemolysis of red blood cells. Leecharoenkiat *et al*[12] and Gardenghi *et al* [14] mentioned iron overload in β-thalassemia major patients as predicted by high serum ferritin level due to frequent blood transfusions, hemolysis of red blood cells, and increased gastrointestinal iron absorption due to paradoxical hepcidin suppression from dyserythropoiesis.

In agreement to our findings Yaman*et al*[7] and Abdulzahra *et al*[18] found a significant increase in serum ferritin in thalassemia major patients in comparison with control children. As well as, Majeed[15] found a highly statistical significant increase in serum ferritin in male and female β-thalassemia major patients in comparison with control group.

Endocrine glands have extreme sensitivity to iron toxicity, because they have high levels of transferrin receptors that promote iron accumulation and hence increase vulnerability of these glands to iron toxicity. Iron stored in endocrine glands binds to intracellular transferrin and as the storage capacity of transferrin gets exceeded, pathological quantities of metabolically active iron catalyses formation of free radicals[6,19,20]. Joshi and Phatarpekar[21] mentioned most of the endocrine abnormalities in developed countries were after ten years of age, but in developing countries it is possible to have a high prevalence of endocrine complications at an early age due to suboptimal of transfusions and chelation therapy.

Analysis of our study documented abnormalities in gonadal hormones. Compared to healthy male control group, male patients group have significantly lower mean serum levels of FSH, LH, testosterone and estradiol. While female patients as compared to female control have statistically non-significant higher levels of

FSH and testosterone, but LH and estradiol levels were decreased without significant effect.

Regarding age subgroups, female patients have non-significant increased level of FSH, LH in 14 – 16 years, and so increased level of testosterone in 11 -13 years subgroup as compared to controls, while male patient have significant decreased levels of FSH, LH, testosterone and estradiol in both age subgroups, but testosterone level in age 14 – 16 years had non-significant effect as compared to respective gender in same age subgroups, (table 4).

In comparison to current results, Sutay*et al*[22] in their study found the difference was not significant in the FSH levels in the age group of 8-12 years, and the FSH values of cases >12 years were significantly lower than those of controls, but LH values were significantly lower in patients as compared to control in both age groups, and estrogen values were significantly lower in thalassemia patients as compared to control in both age groups. As well as, they found FSH, LH and estrogen levels were significantly lower in the girls with thalassemia as compared to control in age group of 12-16 years. While, Vahidi *et al* [23] found that mean levels of FSH and LH were significantly lower in cases than in controls for boys and girls, and mean testosterone levels were significantly depressed in male thalassemia major patients compared to controls, moreover a lower level of estradiol in female patients compared to female controls.

However, Majeed[15] reported that the mean of FSH levels in healthy male in control group were higher than patients group, but FSH levels of male and female patients were significant lower than the corresponding values in the healthy and the level of LH in male patients and control groups were comparable. While the values of estradiol, and testosterone in patients group were significant lower than in the control group.

Moreover, Yenzeel and Salih[16] reported a significant decrease in the levels of FSH, LH, and estradiol hormones when compared to control in their study of female β-thalassemia major patients.

Our study results indicated that serum ferritin had an inverse correlation with FSH, LH, estradiol, and testosterone hormones levels. These findings highlight the importance of iron overload in the development of endocrinopathy in the β-thalassemia major patients, due to iron deposition in secretory cell of endocrine glands leading to impairment of gonadal hormones. In agreement to our finding, Hagag *et al* [24] observed significant negative correlations between FSH, LH, and estrogen levels with serum ferritin level, while Abdulzahra *et al*[18] observed significant correlation between serum ferritin with LH and FSH levels, but no significant correlation between serum ferritin with testosterone level.

Conclusion

There was a highly significant increase in serum ferritin level β- thalassemia major patients in comparison to control groups. Male patients have highly significant decreased levels of serum FSH, LH, testosterone, and estradiol. While female patients have non-significant high serum FSH and testosterone levels, but LH and estradiol levels were non-significant low in comparison to control.

Acknowledgements: Much obliged to Dr. Assad Yahia, Muntaha Yacoub and Dr. Hummod Madhifor their assistance in performing the statistical analysis. Great thankful to the patients and control individuals and their families, for participation and facilitated in completion this study.

Financial Support and Sponsorship: Nil

Conflict of Interest: There are noconflicts of interest

Ethical Clearance: Permission to conduct this study was issued by the health institutional,Blood diseases and Thalassemia Center in Misanprovince, and the blood sampling from patients and control was carried out by a public health technician.

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