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Study of Serum Leptin in Children with Beta Thalassemia: Correlation with Iron Overload

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Abstract

Background: Beta thalassemia is a hereditary blood disorder with defective beta chain formation. *β*-thalassemia is a major public health problem in Egypt. Patients with multi-transfused thalassemia develop severe endocrine complications due to iron overload.

Aim of the Work: Was to study serum leptin in children with beta thalassemia and its correlation with iron overload.

Subjects and Methods: The current study included 30 patients with beta thalassemia under treatment and follow-up in Hematology Unit, Pediatrics Department, Tanta University Hospital. All studied children were subjected to complete history taking, thorough clinical examination and laboratory investigations including complete blood count, serum iron, TIBC, serum glucose, serum ferritin and serum leptin using ELISA.

Results: There were significant differences between patients and control group as regard BMI and Tanner staging with delayed puberty according to Tanner staging and significantly lower BMI in patients compared with controls. Significantly higher levels of serum ferritin and serum iron and significantly lower TIBC were found in patients compared to control group. Serum leptin was significantly lower in patients than controls. There was significant positive correlation between serum leptin and age in studied patients and significantly higher serum leptin in female patients compared with males. Significant negative correlation was found between serum leptin and serum ferritin, but non-significant negative correlation between serum leptin and BMI.

Conclusion: Decreased serum leptin in *β*-thalassemia patients with significant positive correlation with age with higher levels in females compared to males. There is significant negative correlation between serum ferritin and serum leptin.

Key Words: *Leptin – Iron overload – Thalassemia.*

Introduction

***β*-THALASSEMIA** is an autosomal recessive disorder caused by defect in beta globin chain synthesis of hemoglobin which is either complete absence of beta globin production or partial reduction of beta chain synthesis [1].

Thalassemia is prevalent in Mediterranean countries, the Middle East, central Asia, India, Southern China and the Far East as well as countries along the north coast of Africa and in South America. The highest carrier frequency is reported in Cyprus (14%), Sardinia (10.3%) and South East Asia [2].

β-thalassemia is considered a very critical public health issue in Egypt. Being in continuity with other countries of the Mediterranean region, enhanced the genetic material to mix up with those of the native Egyptians [3]. The carrier rate of thalassemia varies between 5.3% –>9%, so it was estimated that 1000/1.5 million per year live birth born with thalassemia disease [4].

Repeated blood transfusions lead to iron overload in these patients. Excess iron can deposit in body organs particularly in pancreas, liver, pituitary, and the heart [5].

Leptin is a 167 amino acid peptide that is mainly expressed in white adipose tissue, but is also found in a variety of tissues including placenta, mammary gland, ovary, skeletal muscle, stomach, pituitary gland and lymphoid tissue [6].

Leptin regulates appetite, thermogenesis, hematopoiesis, angiogenesis, bone metabolism, reproduction and glucose homeostasis. Also it links nutritional status with neuroendocrine and immune function [7].

Six leptin receptor isoforms (LepRa-f) are known. These isoforms share a common leptin binding domains. LepRe uniquely lacks a transmembrane domain and is a soluble LepR isoform [8]. The leptin receptor is available on the bone

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marrow cells and hematopoietic stem cells. In hemolytic anemia such as ß-thalassemia major this defect in the hematopoietic cells may lead to affected levels of leptin in these patients [9].

Aim of the work:

The aim of this work was to study serum leptin in children with beta thalassemia and its correlation with iron overload.

Subjects and Methods

This study was done after approval from ethical committee of research center of Tanta University and written consent from the parents of all children included in this study. The study was conducted on 30 thalassemic children under treatment and follow-up in Hematology Unit, Pediatrics Department, Tanta University in the period from June 2016 to May 2017 including 15 males and 15 females with their age ranged from 5 to 15 years and mean age value of 10.16 ±3.21. This study included also 20 healthy children as a control group including 9 males and 11 females with their age ranged from 5 to 15 years and mean age value of 10.70±3.37 years.

Inclusion criteria:

Children with beta thalassemia major.

Exclusion criteria:

Other types of chronic hemolytic anemia as sickle thalassemia, autoimmune hemolytic anemia, sickle cell anemia.

All the children in both groups were subjected to the following:

1- Full history taking with special emphasis on consanguinity between parents of patients with thalassemia and parents of controls, family history of thalassemia, age of diagnosis of thalassemia, frequency of blood transfusion and iron chelation therapy (types and regularity).

2- Clinical examination with special emphasis on pallor, jaundice, mongoloid facies, splenomegaly or splenectomy, hepatomegaly, cardiac manifestations, anthropometric measurements (weight, height, body mass index) and Tanner staging for assessment of puberty.

3- Investigations including:

- Complete blood count, Hb electrophoresis.
- Iron profile (serum iron, TIBC and serum ferritin).
- Serum glucose.
- Serum leptin.

Specimen collection and handling:

Seven ml venous pre-transfusion blood samples were collected at midnight from each patient by venipuncture under complete aseptic technique and were divided into four tubes as following:

One ml in a tube containing EDTA for CBC including differential WBCs and reticulocyte count which was done on Leishman stained peripheral blood smear with evaluation using ERMA PCE-210 N cell counter 10, one ml was added to two ml hemolysate for Hb electrophoresis, three ml were collected in a plain tube and centrifuged for serum iron, total iron binding capacity 11, serum ferritin using Accu Bind ELISA microwells from Monobind Inc 12 and serum glucose level which was done by using fully automated clinical chemistry auto-analyzer system 13 and two ml were collected in a plain tube, centrifuged and separated serums were stored at 20ºc till assay for assessment of serum leptin. The DRG Leptin ELISA Kit is a solid phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle 14. Samples were collected at midnight from non-fasting children.

Statistical analysis of the present study was conducted, using the mean, standard deviation and chi-square test by SPSS Version 17.

Results

Table (1) shows no significant difference between thalassemic patients and control group as regard age and sex, weight and height but significantly higher positive family history of thalassemia and positive consanguinity and significantly lower BMI in patients compared with control group with lower weight, height and BMI in patients compared with control group.

Table (2) shows that Pallor and jaundice were the most common presenting symptoms while hepatomegaly and splenomegaly were the most common presenting signs in studied patients.

Table (3) shows significant difference between patients and control group with delayed puberty in patients compared with control group.

Table (4) shows that microcytic hypochromic anemia with reticulocytosis was found in studied patients with significant differences in pre–transfusion complete blood count including hemoglobin level, reticulocytes, MCV, MCH, platelets and white blood cell count while non-significant difference as regard MCHC in patients compared with control group.

There was significantly higher levels of serum ferritin and serum iron and significantly lower TIBC and serum leptin level in patients compared with control group.

There was significant positive correlation between serum leptin and age and significant negative correlation between serum leptin and serum ferritin in studied patients.

There was non-significant negative correlation between serum leptin and BMI of studied patients.

There was significantly higher serum leptin level in females compared to males.

Table (1): Demographic data, anthropometric measurements and Tanner staging of studied groups.

Parameters	Groups		*t*-Test or Chi-Square	
	Patients (n=30)	Controls (n=20)	*t* or X^2	*p*-value
Age (Years):				
Range	5-15	5-15	–0.563	0.576
Mean ± SD	10.167±3.217	10.7±3.373		
Sex:				
Male	15 (50%)	9 (45%)	0.120	0.729
Female	15 (50%)	11 (55%)		
Family history of thalassemia:				
Negative	16 (53.33%)	20 (100%)	12.963	<0.001*
Positive	14 (46.67%)	0 (0%)		
Consanguinity between parents:				
Negative	6 (20%)	20 (100%)	30.769	<0.001*
Positive	24 (80%)	0 (0%)		
Weight (kg):				
Range	14-50	17-62	–1.779	0.082
Mean ± SD	32± 11.885	38.65± 14.431		
Height (cm):				
Range	105-153	106-167	–1.018	0.314
Mean ± SD	133.667± 15.548	138.650± 18.899		
BMI:				
Range	13.08-21.9	15.1-22.6	–2.607	0.012*
Mean ± SD	17.080±2.915	19.153±2.489		

BMI = Body mass index.

Table (2): Clinical data in studied patients.

Parameters	Patients (n=30)	%
Pallor	27	90
Jaundice	13	43.33
Hepatomegaly	26	86.67
Splenomegaly	16	53.33
Splenectomy	14	46.67
Mongoloid facies	12	40

Table (3): Tanner staging in studied groups.

	Patients (n=30)	Controls (n=20)	X^2	*p*-value
Tanner 1	16 (53.33%)	7 (35%)		
Tanner 2	8 (26.26%)	4 (20%)		
Tanner 3	6 (20%)	1 (5%)	15.028	0.005*
Tanner 4	0 (0%)	2 (10%)		
Tanner 5	0 (0%)	6 (30%)		

Table (4): Comparison between patients and controls as regard pre-transfusion complete blood count.

	Groups		*t*-Test	
	Patients (n=30)	Controls (n=20)	*t*	*p*-value
HB (g/dl):				
Range	4.7-8.2	11-13.4	–23.998	<0.001*
Mean ± SD	6.743±0.803	12.075±0.715		
MCV (/fl):				
Range	49.9-69.5	77-90.6	–15.144	<0.001*
Mean ± SD	61.080±5.808	83.960±4.210		
MCH (/pg):				
Range	21-26.3	28.2-32	–14.821	<0.001*
Mean ± SD	24.510± 1.339	29.835± 1.085		
MCHC (g/dl):				
Range	30-35	31-36	6.32	0.852
Mean ± SD	30.1±4.3	31.3±3.1		
Platelets (x10^3/mm^3):				
Range	146-475	164-420	2.241	0.030*
Mean ± SD	288.400±99.458	233.700±54.448		
TLC (x10^3/mm^3):				
Range	6.8-59	4.3-11	4.208	<0.001*
Mean ± SD	16.489± 10.736	6.250± 1.902		
Retic. %:				
Range	2.9-6.2	0.2-1.3	14.645	<0.001*
Mean ± SD	3.927±0.965	0.655±0.302		

HB = Hemoglobin.
MCV = Mean corpuscular volume.
MCH = Mean corpuscular hemoglobin.
MCHC = Mean corpuscular hemoglobin concentration.
TLC = Total leuccocytic count.
Retic. = Reticulocytes.

Table (5): Comparison between patients and controls as regard serum leptin and iron status.

Parameters	Groups		*t*-Test	
	Patients (n=30)	Controls (n=20)	*t*	*p*-value
Serum leptin (ng/ml):				
Range	0.13-5.2	1.59-6.2	–5.885	<0.001 *
Mean ± SD	1.481± 1.384	3.916± 1.505		
Serum Ferritin (ng/ml):				
Range	650-7100	39-122	8.071	<0.001 *
Mean ± SD	4069.533 ±2207.182	72.400±23.214		
Serum Iron (µg/dl):				
Range	123-388	65-126	7.008	<0.001 *
Mean ± SD	238.667±89.281	96.150± 19.220		
Total iron binding capacity (µg/dl):				
Range	149-230	263-320	–19.481	<0.001 *
Mean ± SD	181.100±20.042	282.850± 14.626		

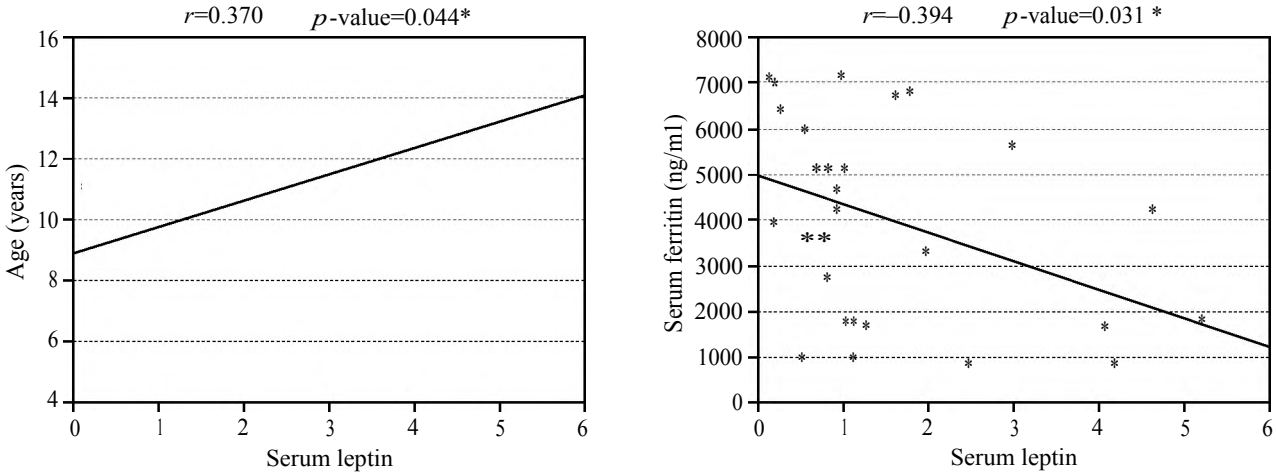

Fig. (1): Correlation between serum leptin and age (left) and serum leptin and serum ferritin (right) in studied patients.

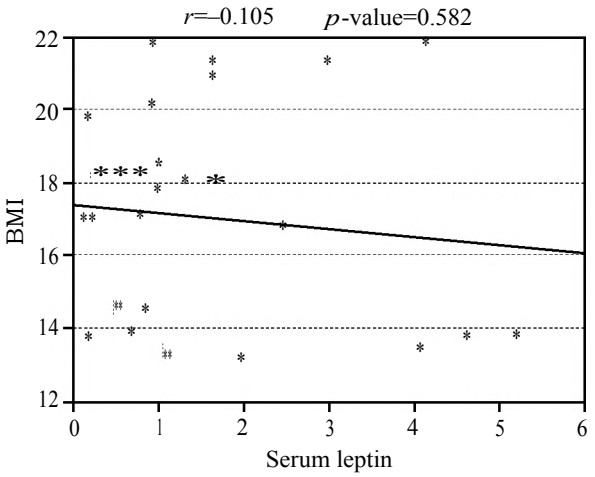

Fig. (2): Correlation between serum leptin and BMI in studied patients.

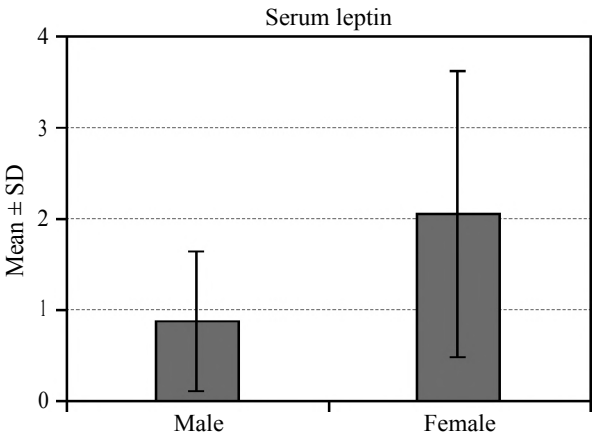

Fig. (3): Relation between serum leptin and sex in studied patients.

Discussion

Thalassemia results in severe anemia often requiring repeated blood transfusions. The fate of patients with transfusion-dependent thalassemia has improved substantially over the past 50 years. With the advent of regular transfusions, survival improved, but patients with thalassemia become iron overloaded [15].

Iron overload results in damage to the liver, endocrine organs, and most importantly to the heart without effective iron chelation, death occurs from cardiac failure or arrhythmia, usually in late childhood or in the teenage years [16].

Leptin is a polypeptide hormone which is mainly expressed in white adipose tissue [6]. The leptin receptor is available on the bone marrow cells, hematopoietic and stem cells [9].

The aim of the present work was to study serum leptin level in patients with beta thalassemia and its correlation with iron overload.

This study was carried out on 30 children with β-thalassemia major who were under treatment and follow-up in Hematology Unit, Pediatric Department, Tanta University Hospital and 20 healthy children as a control group.

In the present study, pallor and jaundice were the most common presenting symptoms in thalassemic patients, while hepatomegaly and splenomegaly were the most common signs. This is in agreement with Hagag et al. [17] who found the same results. This could be explained by chronic hemolysis, extramedullary erythropoiesis and iron overload as stated by Galanello and Origa [18] or hemosiderosis, extra medullary hematopoiesis, transmitted hepatitis B and C with subsequent cirrhosis as stated by Hashemizadeh et al. [19].

In the present study, there was significantly lower body mass index in patients compared with control group. This is in agreement with Eissa and El-Gamal [20] who explained low BMI in thalassemic children by chronic nature of the disease. As physical growth is affected in transfusion-dependent thalassemic patients, minimizing the iron overload in these patients should be warranted for them to have normal growth and development.

In the present study, there was microcytic hypochromic anemia with reticulocytosis with significantly lower Hb, MCV and MCH and significantly higher reticulocytes % in thalassemic patients compared with control group. This is in agreement with Mahmoud et al. [21], Winichagoon et al. [22] who demonstrated that decreased hemoglobinization of red cells resulting in hypochromia and microcytosis which are the main features of thalassemia syndromes and El-Shanshory et al. [3] who found reticulocytosis in thalassemic patients which could be explained by hemolytic nature of the disease causing hyperactive bone marrow with subsequently reticulocytosis.

In this study, there were significantly higher leucocytic and platelets counts in patients compared with control group. This is in agreement with El-Gammal et al. [23] and Fayed et al. [24].

In this study, there were significantly higher serum ferritin and serum iron and significantly lower serum total iron binding capacity in studied patients compared with controls which could be explained by frequent packed RBCs transfusion and irregular iron chelators intake. This is in agreement with Nasr et al. [20], Eissa and El-Gamal [25], Faruqi et al. [26] and Hagag et al. [27] who found the same results. Iron overload in beta thalassemia could be explained by two main mechanisms, increased iron absorption due to ineffective erythropoiesis and repeated blood transfusion [28].

In the present study, there was significantly lower serum leptin in patients compared to control group. This is in agreement with Shahramian et al. [9] who studied 45 cases of thalassemia children and stated that, serum leptin levels were significantly lower than normal participants, Choobineh et al. [29], Karami et al. [30] and Elsayh et al. [31] who found significantly lower serum leptin level in patients compared with control group. In fact, iron overload followed by iron deposition in fat cells can lead to toxic effects of iron which is the result of free radical formation and inhibits the activity of adiposities leading to destruction of the fat cell membrane and dysfunction in adipose tissue [18].

In the present study, there was delayed puberty as regard Tanner staging in studied patients compared with control group. This is in agreement with Hagag et al. [27] who found delayed puberty in patients with beta thalassemia major, Sayed et al. [32] who found the same results and revealed a decrease in serum leptin level together with delayed pubertal development in patients with beta-thalassemia major which may be due to the effect of iron overload on endocrinal glands and adipose tissue. The low serum leptin level might be a contributing factor for delayed puberty reported in beta thalassemia major patients and Kyriakou and Skordis [33] who stated that delayed puberty and hypogonadism are the most common endocrine complications in patients with thalassemia major.

In the present study, there was significant positive correlation between serum leptin level and age of the studied patients in which serum leptin level increase with age. Shahramian et al. [34] found the same results and demonstrated that since from the age of 10 years the cardiac involvement begins to increase, so there is a remarkable and positive association between leptin and cardiac involvement, but Shahramian et al. [9] found no significant relationship between leptin and age as increase of age could not result in an increase of fat mass as well as leptin production.

In the present study, there was significant relation between serum leptin and sex with higher leptin level in females than males. This is in agreement with Choobineh et al. [29], Shahramian et al. [9] and Al-Naama et al. [35] who found significantly higher serum leptin in females with beta thalassemia major compared with males with the same disease. Androgens are thought to provoke a reduction in leptin production, which may explain the low levels of serum leptin observed in male individuals. However, factors other than sex steroid hormones (e.g., fat mass in the body and energy expenditure) may cause a fluctuation in serum leptin concentrations [35]. Also lower levels of leptin in males may be explained by lesser mRNA expression of leptin in males compared to females [36].

In the present study, there was significant negative correlation between serum leptin level and serum ferritin of the studied patients. This is in agreement with Chaliasos et al. [37], Shahramian et al. [9] and El-Rasheidy et al. [38] who found significant negative correlation between the serum levels of leptin and ferritin in children with ß-thalassemia major.

In fact, iron overload in fat cells can lead to free radical formation and inhibits the activity of

adipose tissue. Along with the destruction of the fat cell membrane and the dysfunction in adipose tissue, it leads to a decrease in serum leptin level **[9]**.

It seems that adipose cells of thalassemia patients are not able to produce adequate leptin which might be due to deposition of iron in these cells. Therefore, the defect in adipose tissue function in thalassemic patients can be considered as an endocrine system dysfunction, although it seems other factors may interfere in the decrease of serum leptin level in thalassemic patients. As a patient is more underweight with less fat tissue so the ability to produce leptin would be lower **[39]**.

Conclusion:

Decreased serum leptin in ß-thalassemia patients with significant positive correlation with age with higher levels in females compared to males. There is significant negative correlation between serum ferritin and serum leptin.

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Conflicts of interest:

No conflicts of interest declared.

Authors contributions:

All authors had equal role in design, work, statistical analysis and manuscript writing. All authors have approved the final article work.

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دراسة مستوى اللبتين فى الأطفال المرضى بانيميا البحر المتوسط وعلاقته بارتفاع مستوى الحديد بالدم

البيتا ثلاسيميا هى أحد الإراض الوراثية التى يمكن تعريفها على نطاق واسع بإعتبارها متلازمة إضطرابات الهيموجلوبين الموروثه والتى تتميز بنقص كمى فى سلسلة البيتا جلوبين الوظيفية. تعتبر أنيميا البحر المتوسط هى الشكل الأكثر شيوعاً لفقر الدم الوراثى.

الهدف من البحث: هو دراسة مستوى اللبتين فى الأطفال المرضى بأنيميا البحر المتوسط وعلاقته بارتفاع مستوى الحديد بالدم.

المرضى وطرق البحث: أجريت الدراسة الحالية على ٣٠ طفل من مرضى أنيميا البحر الوسط بوحدة أمراض الدم، قسم طب الأطفال، مستشفى جامعة طنطا الذين تتروا ح أعمارهم ٥-١٥ من سنة. وقد تم اجراء الآتى لجميع المرضى: أخذ التاريخ المرضى للحالات وعمل فحص إكلينيكى شامل والاختبارات المعملية وتشمل صورة دم كاملة مع عد خلايا شبكية وقياس مستوى الفيرتين فى الدم، قياس مستوى الحديد فى الدم، إجمالى قدرة ربط الحدى قياس مستوى السكر بالدم ونسبة اللبتين بالدم.

النتائج: انخفاض مستوى اللبتين وتأخر فى البلوغ فى مرضى انيميا البحر المتوسط عن مجموعة الأصحاء ووجود علاقة طردية بينه وبين عمر المرضى وكذلك وجود علاقة عكسية بينه وبين نسبة الفيرتين بالدم ومؤشر كتلة الجسم وارتفاع نسبة اللبتين فى الاناث عن الذكور فى مجموعة المرضى.

الاستنتاج: انخفاض مستوى اللبتين فى مرضى أنيميا البحر المتوسط عن مجموعة الأصحاء ووجود علا قة طردية بينه وبين عمر المرضى وكذلك وجود علاقة عكسية بينه وبين نسبة الفيرتين بالدم وارتفاع نسبة اللبتين فى الاناث عن الذكور.

التوصيات: نوصى بالمتابعة المستمرة لمرضى أنيميا البحر المتوسط بالنسبة لانتظام نقل الدم وتناول مزيلات الحديد بجرعات وطرق سليمة وكذلك متابعة دقيقة لنسبة الحديد بالدم وعمل دراسات مكثفة على هؤلاء المرضى المصابين بتأخر فى البلوغ لمعرفة العلاقة التى تربط نقص اللبتين بتأخر البلوغ.