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Multifactorial Elements Affecting Bone Mineral Status and Growth in Children with Thalassemia Major

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TO DETERMINE the association between adipokynes such as leptin, and ghrelin, antioxidants as superoxide dismutase (SOD) and glutathione peroxidase(GSH Px) and iron overload and their effects on growth and on bone mineral density in patients with thalassemia major.Thirty patients and 30 healthy age and sex matched controls from the Hematology Clinic at Children Hospital, Cairo University. The range of age in both cases and the controls was 5-15 years, regarding as for sex in controls, there were 18 males (60%) and 12 females (40%) and in cases there were 21 males (70%) and 9 females (30%). All patients were receiving iron chelating agents either desferal or kelfer. Clinical examination and the anthropometric measurements were done in all subjects. Bone mineral density was assessed using dual-energy x-ray absorptiometry (DXA) machine on lumbar spine expressed in Z Score. Laboratory investigations, including SOD and GSH- Px, ferritin, leptin and ghrelin. The study showed that there was a significant difference between cases and controls regarding Body mass index (BMI), leptin, ghrelin, bone mineral density (BMD), super oxide dismutase (SOD) and glutathione peroxidase with p- values 0.003, <0.001, <0.001, <0.001, <0.001 respectively. Regarding the cases, there was no significant difference between cases on desferal (n=12) and cases on kelfer (n=18) except for leptin, which was higher in cases on kelfer than those on desferal with a *p*- value was 0.042. Regarding correlations there was a positive correlation between leptin, BMI, BMD and glutathione peroxidase. Ghrelin showed a positive correlation with BMI, BMD, SOD and glutathione peroxidase. Leptin/Ghrelin ratio showed a negative correlation with SOD, BMI showed a positive correlation with SOD, Glutathione peroxidase, and ferritin showed negative correlation with bone mineral density. This study confirmed that the adipocytes of beta thalassemic patients are unable to maintain adequate leptin production. These results suggest that the adipose tissue dysfunction may be one of the endocrinopathies together with ghrelin deficiency, antioxidant deficiency certainly affect growth and bone mineral status in Beta thalassemic children.

Keywords: Beta thalassemia, Leptin, Ghrelin, antioxidants, BMD.

Introduction

Thalassemia is the most prevalent hereditary disorder in the Mediterranean, African and Southeast Asian populations (Giardina *et al.*, 2008).

The genetic defect is caused most commonly by a mutation creating an abnormal splicing site or a mutation creating a premature translation termination codon. The manifestations of the disease usually appear at six months of age when a complete switch from fetal to adult hemoglobin synthesis occurs.

The prognosis of patients with thalassemia major is highly dependent on the patient's adherence to a long-term treatment program, namely hyper-transfusion program and lifelong iron chelation. Allogenic bone marrow transplantation may be curative (Kgriakou *et al.*, 2010).

The major causes of morbidity and mortality in beta thalassemia are anemia and iron overload. The severe anemia resulting from this disease if untreated, can result in high output cardiac failure, the

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intramedullary erythroid expansion which may result in associated skeletal changes such as cortical bone thinning.

Increased iron deposition, resulting from lifelong transfusion and enhanced iron absorption, results in a secondary iron overload. This overload causes clinical problems such as endocrine dysfunction, liver dysfunction, and cardiac dysfunction, however, these morbidities were markedly improved by regular transfusion and chelation therapy (Al-Naama *et al.*, 2016).

Leptin is the human obese (OB) gene product secreted by adipocytes specialized in storing energy as fat and has a direct relation with the weight gain and energy expenditure. It is regulated by glucocorticoids, thyroid and insulin (Smith *et al.*, 2002).

The hormone plays a role in the regulation of hematopoiesis and improves growth as well as it plays a role in inflammation and angiogenesis (Akhter *et al.*, 2007).

Ghrelin is an endogenous ligand of the growth hormone and it plays a role in the regulation of endocrinal function as well as reproduction and growth (Tena *et al.*, 2005).

Osteopenia or osteoporosis are considered of major morbidities in thalassemia.

This may be multifactorial either due to decreased bone formation or increased turnover (Pollack *et al.*, 2000 ; Christoforidis *et al.*, 2009).

Increased lipid peroxidation in the membrane of the red blood cells(RBCS) of thalaessmic patients with the increase in the malonyldehyde can cross-link phospholipids and proteins and alter lipid organization in the bilayer leading to oxidative stress (Voskou *et al.*, 2015).

This study aims to evaluate the effect of leptin, ghrelin, oxidative distress and changes in bone mineral density on the growth of thalassemic patients.

Patients and Methods

Subjects

The study is a case-control study which comprises 30 children aged from 10-11 years with thalassemia major and attending the Hematology Clinic at the Children's Hospital, Cairo University for follow up and 30 healthy age and sex matched controls. iInformed verbal consents were taken from all patients ~~of~~ in the study.

All patients were subjected to:

Questionnaires

All subjects were subjected to full history taking, including onset, course and duration of the disease.

-The incidence of complication as delayed puberty, hemolytic crisis, cardiac symptoms and bony complications including bony pains and repeated fractures.

-Therapeutic regimen including frequency of transfusion type of chelation therapy and compliance.

Anthropometric Measurements

Anthropometric assessment of body weight, height and body mass index (BMI) was calculated as weight/height^2 (kg/m^2).

Dual energy X-ray Absorptiometry (DXA) Bone mineral density (BMD) g/cm^2 was done on lumbar spine using DXA machine (DXA, Norland Bone Densitometer soft version: 3, 9, 617 Aug01).

Laboratory Investigations

-Serum leptin was measured using leptin RIA CT Diasource Belgium (KIPMR44).

-Serum Ghrelin using DIA source Belgium KIPMR 90 Ghrelin kit 100 tests by RIA.

-Serum ferritin was assayed as described by Marcus and Zinber (1975) using RIA.

Antioxidants

-Superoxide dismutase (SOD) in plasma was determined using an enzyme linked immunosorbent assay (ELISA) by Czapski and Goldstein (1991).

-Glutathione peroxidase ELISA Kit was derived from Abcam (ab193767); USA.

Bone Densitometry

BMD was measured for the lumber spine using the dual energy X ray absorptiometry (QDR-4500 W, Hologic BedFord MA, USA) expressed in the form of Z score at the out patients' clinic of the Institute of postgraduate childhood studies, Ain Shams University, Cairo, Egypt.

Statistical Analysis

Data were collected and analyzed with SPSS 20. Descriptive statistics are shown in frequency tables and for inferential statistics, independent t-tests, Analysis of variance (ANOVA), Z score for BMD, Pearson correlation, and $P < 0.05$ was considered significant level.

Results

Table 1 shows a comparison between cases and controls with a significant difference between them regarding BMI. leptin, ghrelin, BMD, SOD, Glutathione peroxidase.

Table (2) shows a comparison between cases on kelfer and those on desferal regarding laboratory findings with a significant difference in leptin and ferritin

In addition, there was a significant correlation between the leptin serum level, body mass index (BMI), BMD and glutathione peroxidase in patients with major beta thalassemia (P value=0.030 and 0.001 respectively) (Fig.1A-D). Moreover, there was a significant relationship found between ghrelin serum level, BMI, BMD, SOD and glutathione peroxidase in patients with major beta thalassemia (Fig. 1 E-G). Figs. H & I showed a significant correlation between leptin/Ghrelin ratio and BMD & BMI (P = 0.001 & 0.023 respectively).

Negative correlations were reported between ferritin and BMD and also between ferritin and serum leptin both with a P value<0.001 as shown in Figs. J and K respectively.

Ferritin also had a negative correlation with serum glutathione peroxidase SOD with a P-value 0.505 and with SOD with a P- value 0.405 shown in Figures (L and M).

TABLE 1. Comparison between cases and controls .

	Group	Number of cases	Mean	SD	p value
Age	Controls	30	11	1-9	0.102
	Cases	30	10	2-9	
BMI (kg/m^2)	Controls	30	18.61	2.51	0.003*
	Cases	30	16.09	3.72	
Leptin (ng/ml)	Controls	30	3.23	0.783	< 0.001*
	Cases	30	2.34	0.872	
Ghrelin (pg/ml)	Controls	30	336.8	23.51	< 0.001*
	Cases	30	293.8	18.04	
BMD Z score	q15	30	-0.687	0.594	0.001*
	Cases	30	-1.893	1.70	
SOD (U/ml)	Controls	30	50.28	6.32	< 0.001*
	Cases	30	42.47	6.55	
Glutathione Peroxidase (ng/ml)	Controls	30	44.47	2.88	< 0.001*
	Cases	30	37.30	2.31	

Data are described in mean ±SD; * statistically significant difference

TABLE 2. Comparison between cases on kelfer and those on desferal.

	Treatment	Number of cases	Mean	SD	p value
BMI (kg/m^2)	Desferal	12	16.11	1.54	0.977
	Kelfer	18	16.08	4.70	
Leptin (ng/ml)	Desferal	12	1.95	0.66	0.042*
	Kelfer	18	2.61	0.91	
Ghrelin (pg/ml)	Desferal	12	290.8	16.4	0.467
	Kelfer	18	295.8	19.3	
BMD (gm/cm^2)	Desferal	12	-1.808	0.64	0.827
	Kelfer	18	-1.950	2.15	
Ferritin (ng/ml)	Desferal	12	2493	2228	0.040*
	Kelfer	18	958.7	824	

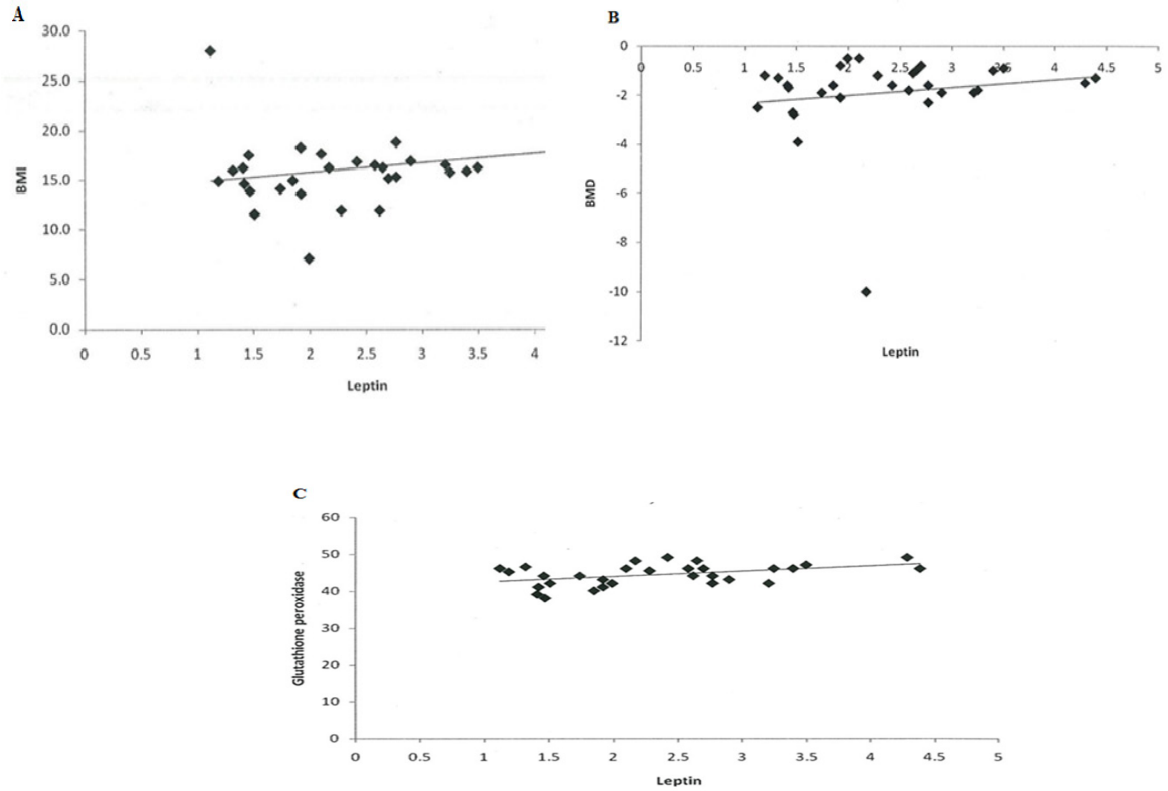

Fig. (1: A) Correlation between serum leptin(ng/ml) and BMI (kg/m2) among cases (P= 0.030). B) leptin and BMD (P= 0.001) C) leptin and glutathione peroxidase (ng/ml) (P= 0.001).

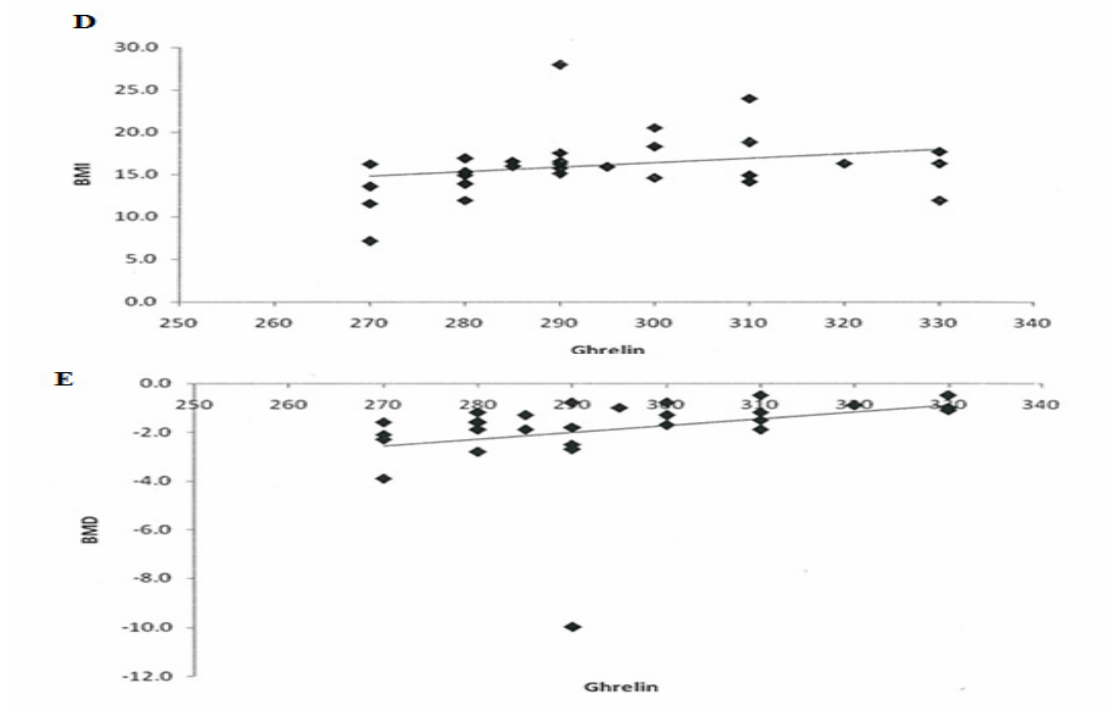

Fig. (1: D) Correlation between serum Ghrelin(pg/ml) and BMI (kg/m2) among cases (P= 0.030). E) Ghrelin and BMD (P=0.001).

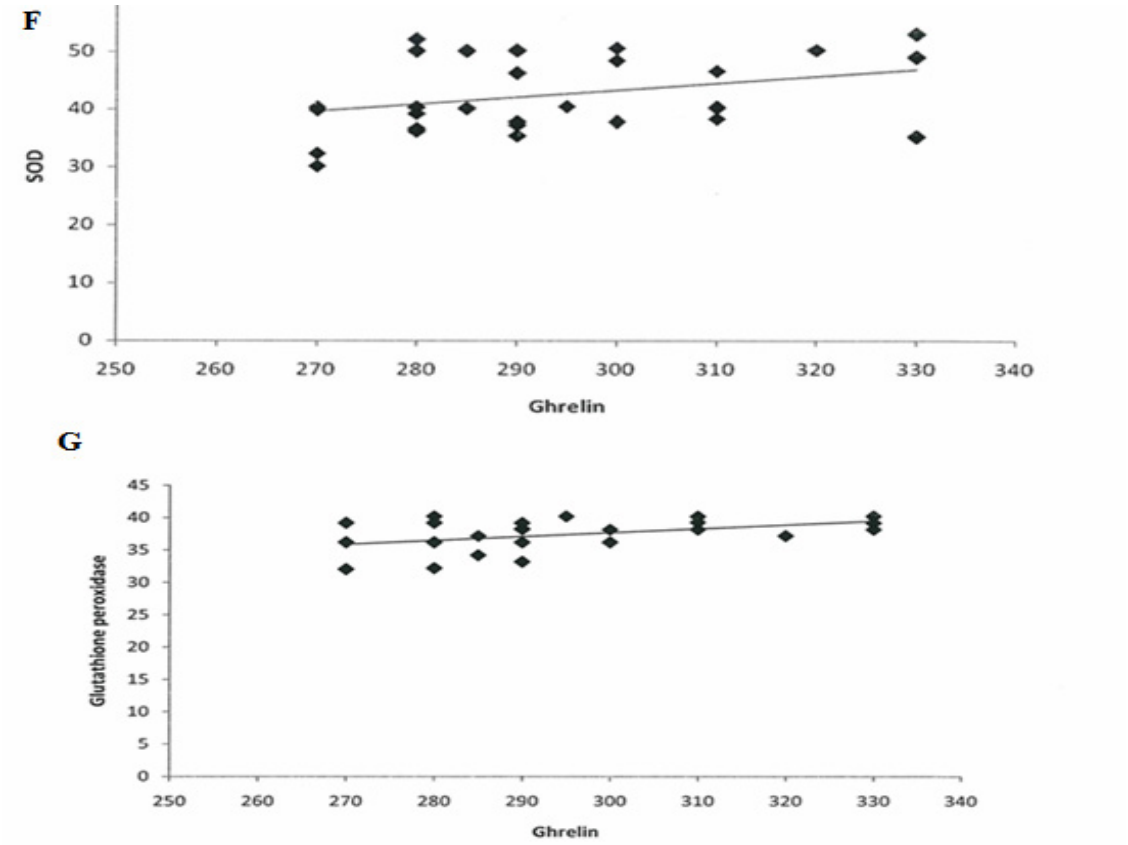

Fig. 1: F) Correlation between serum Ghrelin(pg/ml) and SOD (U/ml) among cases (P= 0.046). G) Ghrelin and glutathion peroxidase (P= 0.001).

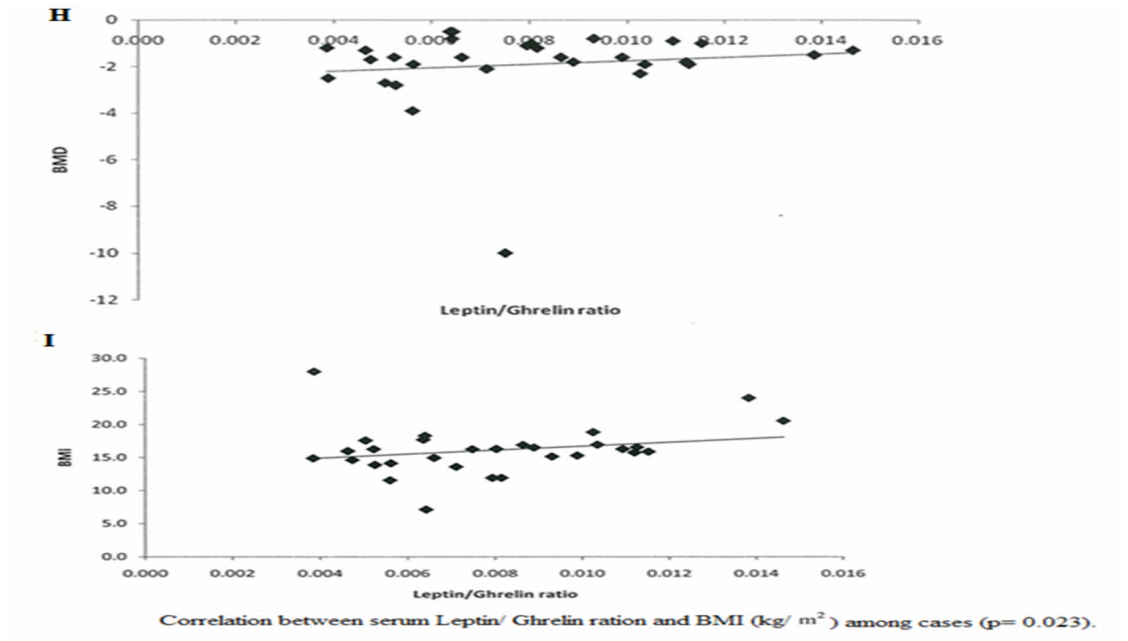

Fig. (1: H) Correlation between leptin/Ghrelin ratio and BMD (kg/m2) among cases (P= 0.001). I) leptin/ Ghrelin and BMI (P= 0.023).

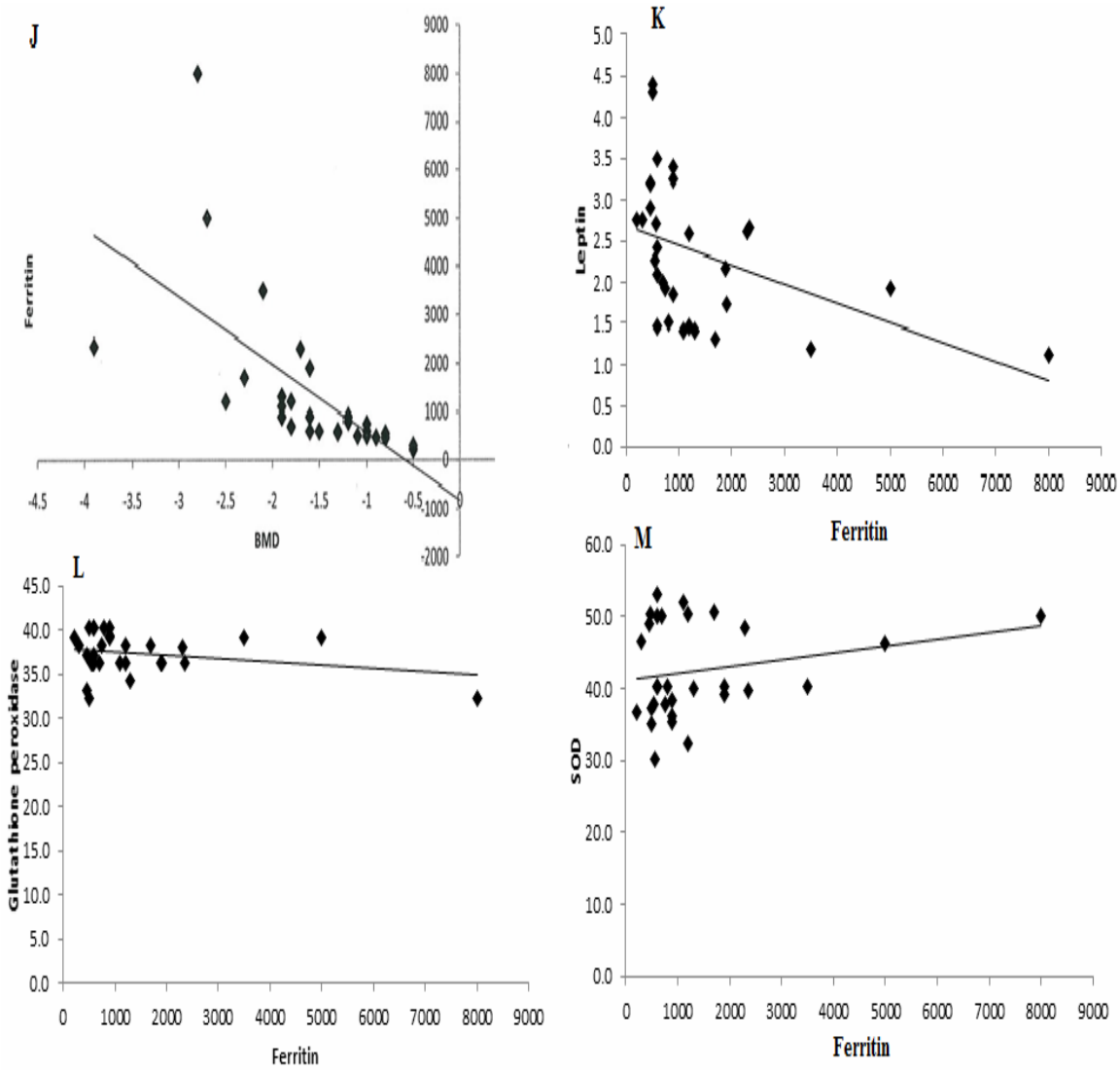

Fig. (1: J) Correlation between ferritin and BMD (kg/m2) among cases (P= 0.001). K) leptin and ferritin (P= 0.001). L) serum ferritin (ng/ml) and serum glutathione peroxidase (ng/ml) among cases (p = 0.505). M) serum ferritin (ng/ml) and serum SOD (U/ml) among cases (p = 0.405).

(Discussion

Thalassemia is one of the major health problems, especially in the developing countries. Recently, the survival of thalassemics increases and the prevalence of complications due to iron overload and other morbidities also increases (Cappellini *et al.*, 2010).

In this study leptin and ghrelin were significantly lower in thalassemic patients than the control p<0.001. In addition, there was a direct correlation between BMI and Leptin with a P- value <0.001 and direct relation between leptin and bone mineral density with a P value <0.001 and between leptin and glutathione peroxidase with a P-value <0.001.

These findings are similar to those reported by kashanian *et al.*, (2009) who reported decreased leptin in beta-thalassemic patients and it was reported to decreased leptin/ghrelin ratio in thalassemic females than those of the control. In this study, the lower values of leptin and ghrelin were considered a part of the hormonal imbalance, which may contribute to the phenotype of impaired growth and sexual maturation encountered in these patients. Body mass index of thalassemic patients in

these studies was less than the controls and similar finding was reported in this study (Kashanian *et al.*, 2010).

The low serum leptin levels in thalassemic may be multifactorial either due to iron toxicity or hypogonadism. Iron overload, resulting from multiple transfusion in thalassemics causes toxicity to the adipocytes decreasing their activity causing decreased serum leptin and altering the physiological role of leptin in sexual maturation and fertility (Elias *et al.*, 2013).

The present finding shows that ghrelin hormone in thalassemics decreased significantly compared to the controls. Gonadal expression of acetylated ghrelin receptors in the gonadal cells showed that ghrelin could inhibit Gonadotropin-releasing hormone

(GnRh) pulse activity and GnRh secretion leading to impaired growth and hypogonadism (Fernandez *et al.*, 2005).

In this study, there was a significant difference in bone mineral density in thalassemics compared to the controls. These results are similar to those obtained by Somnuek *et al.*, (2003). Somnuek *et al.*, (2003) also reported that a significant decrease in serum 25-hydroxyvitamin D [25(OH)D] and decreased serum insulin like growth factor 1(IGF-1). These hormones were proven to stimulate skeletal growth velocity by cell proliferation, and differentiation. The decrease of IGF-1 together with iron toxicity may be the most acceptable cause of decreased bone mineral density and osteoporosis (Perrottas *et al.*, 2000).

There was a positive correlation between leptin and BMI and, between leptin and BMD. These findings are similar to those reported by Shams *et al*., (2006). They showed a significant positive correlation between leptin and both BMI and BMD in healthy individuals. The results were explained by the fact that leptin may promote bone growth as it has angiogenic character and osteogenic influence on cortical bone. It increases bone growth, and inhibits the bone remodeling to make a balance between bone formation and bone turnover (Shams *et al.*, 2006). In a study done by Shahramian *et al.*, (2013) about serum leptin concentrations in thalassemia major, it was proven that there was a significant difference regarding leptin concentrations in patients with thalassemia major and the controls. In addition, there was an inverse correlation between serum level of ferritin and leptin with a P-Value<0.05 (Shahramain *et al.*, 2013). Similarly, in the present study there was an inverse correlation between serum levels of leptin and ferritin in thalassemics with a P<0.01.

This could be explained by the fact that the body is unable to produce leptin due to the toxic effect of iron overload besides leptin secretion affected by other hormones as insulin and thyroid hormones whose production is decreased in thalassemics, due to iron deposition in thyroid and pancreas (Guzelbey *et al.*, 2016).

In this study, there was a significant decrease in bone mineral density (BMD) in thalassemics compared to the controls. These results are similar to those reported by Rafsanjani *et al.,* (2009).

In 2005, a study was conducted on patients with thalassemia major and intermedia by Karimi *et al.*, (2005). This study proved to decreased BMD in thalassemics compared to the controls, and that there was a positive correlation between hemoglobin levels and BMD. Decreased BMD and osteoporosis may be reflection of endocrine abnormalities in thalassemia secondary to iron overload and iron toxicity (Karimi *et al.*, 2011).

Some studies reported that the central action of leptin was proposed to target osteoblasts and not osteoblasts. This is because these authors found normal osteoblast function in the absence of leptin signaling. Other *in vitro* studies suggested a direct positive effect of leptin on osteoblast differentiation (Elefteriou *et al.*, 2005).

In another study done by Turner *et al.*, (2013) it was proven that leptin enhanced both bone formation and bone resorption and this happens primarily via peripheral pathways (Turner *et al.*, 2013).

In the current study, a negative correlation was reported between BMD and ferritin with a P<0.001 , and ferritin was significantly lower in patients on desferral than those

on kelfer. These results are similar to those obtained by voskaridou *et al.* (2004), and to the results of the study done by Olivier (1992).

In the present study, serum ferritin levels were found to have a negative correlation with SOD and glutathion peroxidase. On the other hand, another study on children observed no correlation between serum ferritin and anti-oxidant capacity (Voskou *et al.,* 2015; Ally *et al.,* 2016).

Oxidative stress is defined as an imbalance between antioxidant formation and formation of reactive oxygen species (ROS) (Birben *et al.,* 2012).

Oxidative stress leads to increasing formation of reactive oxygen species such as superoxide anions, hydrogen peroxide and hydroxyl radicals leading to excessive peroxidation of lipids and proteins (Rao *et al.*, 2007).

Formation of ROS helps in the development of osteoporosis (Xie *et al.*, 2011). ROS formed by the osteoclasts helps in the destruction of calcified tissues and bone remodeling only under physiological conditions (Xie *et al.,* 2011), but under pathological conditions ROS damages tissues via lipid peroxidation leading to formation of malodialdehyde (MDA) which is a marker of osteoclastic activity (Sandukji *et al.*, 2011).

The decreased activity of superoxide dismutase (SOD) and GSH-P_X lead to increase production of superoxide radicals by osteoclasts represented by an increased level of MDA in the serum (Birben *et al.,* 2012).

Osteoporosis can be mediated through the production of ROS and the decreased levels of superoxide dismutase (SOD) and catalase, glutathione peroxidase (Smietana *et al.*, 2010). Therefore, oxidative distress and decreased antioxidants reported in this study may be a contributing factor to osteoporosis and this explains the negative correlation between SOD, glutathione peroxidase and bone mineral density (BMD).

In this study ferritin was significantly higher in patients on Desferal than in those on kelfer which indicates that kelfer is a better chelator. These results are similar to those obtained by Delea, et al. in 2007 who proved that the compliance of Desferal is worse than that of kelfer (Delea *et al.*, 2007).

Conclusion

1-Monitoring of iron overload and proper chelation therapy are mandatory to improve growth and development of thalassemics especially with the increased survival .

2-The adipose tissue of thalassemic children is unable to maintain adequate leptin production .

3-Adipose tissue dysfunction as well as ghrelin deficiency and oxidative distress certainly affect growth and bone mineral status in thalassemics .

4-Regular monitoring of BMD in thalassemics is required for early diagnosis of osteopenia and osteoporosis .5-Addition of Antioxidants and other track elements as calcium in the therapeutic regimen is recommended.

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العناصر المتعددة العوامل التي تؤثر على حالة كثافة العظام ونمو الأطفال المصابين بالثلاسيميا الكبرى

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تهدف هذه الدراسة إلى تحديد الارتباط بين الأديبوكينز مثل اللبتين، وغريلين، ومضادات الأكسدة مثل سوبر والجلوتاثيون بيروكسيداز والحديد الزائد وتأثيرها على النمو وكثافة العظام لدى (SOD) أكسيد ديسموتاز .مرضى الثلاسيميا الكبرى

استخدمت في هذه الدراسة ثلاثين مريضا وثلاثين فردًامن الأصحاء حيث العمر والجنس يتفق مع المجموعة الضابطة من مستشفى أمراض الدم للأطفال، جامعة القاهرة. وكان معدل العمر في كلتا الحالتين (المرضى والضوابط)٥-١٥ سنة فيما يتعلق بالجنس في المجموعة الضابطة كان هناك ١٨ ذكور (٦٠٪) و ١٢ إناث (٤٠٪) وفي الحالات كان هناك ٢١ ذكور (٧٠٪) و ٩ إناث (٣٠ ٪). وكان جميع المرضى الذين يتلقون عوامل خلب الحديد إما ديسفرال أو كيلفر. تم إجراء الفحص السريري والقياسات البشرية في مجاميع الدراسة. تم تقييم كثافة العظام باستخدام مقياس امتصاص الأشعة السينية ثنائي البواعث على العمود الفقري القطني و الذي والجلوتاثيون بيروكسيداز، (SOD) الفحوصات المعملية، بما في ذلك سوبر أكسيد ديسموتاز .Z عبر عنه في .الفريتين، اللبتين و غريلين

أظهرت نتائج الدراسة وجود فرق معنوي بين الحالات المرضية والضوابط المتعلقة بمؤشر كتلة الجسم بتقدير معنوي قيمته (٠,٠٠٣) والبتين وغريلين و كثافة العظام و الديسميوتاز الفائق و جلوتاثيون بيروكسيداز بتقدير معنوي أكبر من ٠,٠٠١. فيما يتعلق بالحالات، لم يكن هناك فرق معنوي بين الحالات التي كانت تتعاطى ديسفرال (عددهم = ١٢) والحالات التي كانت تتعاطى كيلفر (عددهم = ١٨) باستثناء اللبتين، والتي كانت أعلى في الحالات التي كانت تتعاطى كيلفرمقارنةً بتلك التي تعاطت ديسفرال حيث كانت القيمة المعنوية (٠,٠٤٢). فيما يتعلق بالارتباطات كان هناك ارتباط إيجابي بين اللبتين، مؤشر كتلة الجسم، كثافة العظام والجلوتاثيون بيروكسيداز. أظهرت النتائج أن هناك ارتباطا ايجابيا بين الغريلين و مؤشر كتلة الجسم، سوبر أكسيد ديسميوتاز، والجلوتاثيون بيروكسيداز. كما أظهرت النتائج أن هناك ارتباطا سلبيا بين نسبة اللبتين / غريلين و سوبر أكسيد ديسميوتاز، و كذلك كان هناك علاقة إيجابية بين مؤشر كتلة الجسم مع سوبر أكسيد ديسميوتاز، الجلوتاثيون بيروكسيداز، وأظهرت النتائج وجود علاقة سلبية بين الفيريتين و كثافة العظام.

أكدت هذه الدراسة أن الخلايا الدهنية في مرضى الثلاسيميا بيتا غير قادرة على إنتاج اللبتين بدرجة كافية. وتشير هذه النتائج إلى أن خلل الأنسجة الدهنية قد تكون واحدة من اعتلالات الغدد الصماء جنبا إلى جنب مع نقص الغريلين، ونقص المواد المضادة للأكسدة تحديدا تؤثر بالتأكيد على النمو و حالة كثافة العظام في الأطفال المريضة بالثلاسيميا بيتا.