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Evaluation of serum Fibroblast growth factor-23 in patients with beta-thalassemia major compared to healthy population

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Abstract

Background: The role of phosphate hemostasis in development of thalassemia bone disease has not been extensively studied yet. Due to the lack of sufficient human studies about the changes of serum Fibroblast growth factor-23(FGF23) in patients with beta-thalassemia major as the first step of investigating the role of FGF23 in thalassemia bone disease, the present study aimed to investigate the serum level of FGF23 in patients with thalassemia major.

Material and Method: In this case-control study, 25 patients with beta thalassemia major and their age- and sex-matched healthy volunteers were enrolled. Serum phosphorous, calcium, parathyroid hormone (PTH), 25(OH) D, erythropoietin (EPO), serum intact FGF23 (iFGF23) and 1,25 (OH)2 D were checked and analyzed.

Result: Patients with beta-thalassemia major had lower 1,25 (OH)2D, ($p = 0.025$), higher phosphate ($p = 0.002$), and higher PTH ($P < 0.001$) compared to the control group; however, all of them were in their normal blood range. They also had higher serum FGF23 ($p = 0.007$) and higher EPO ($P<0.001$). Serum FGF23 had an independent association with serum Iron ($p=0.016$), 1, 25(OH)2 Vitamin D ($p<0.001$), and hemoglobin ($p=0.002$).

Conclusion: Serum FGF23 was associated with serum Iron, 1, 25(OH)2 Vitamin D, and hemoglobin in beta-thalassemia major patients. Hence, it seems that regular transfusions and chelating agents which can decrease the serum iron and increase hemoglobin level can be associated with lower iFGF23.

Keywords: Erythropoietin, Fibroblast growth factor-23, Hemoglobin, Iron, Thalassemia

Introduction

Fibroblast growth factor 23 (FGF23) is a glycoprotein secreted by the osteocytes and mature osteoblasts (1). It utilizes α-klotho to carry out its physiological role in kidneys to reduce renal phosphate reabsorption and inhibition of vitamin D activation (2). An interesting axis called bone-kidney-intestinal axis has a crucial role in regulating mineral metabolism by altering the tubular absorption of serum calcium and phosphate through key modulators of FGF23, parathyroid hormone (PTH), and 1,25-dihydroxy vitamin D (1,25(OH)2D)(3, 4). It is well known that during the early stages of chronic kidney disease, the expression of the renal FGF23-receptor, αklotho, declines in response to renal damage; this decline is progressively continued along with the loss of functional nephrons that induces a partial resistance state to FGF23's physiological actions (5-8). To compensate this, serum FGF23 rises 1000-fold above the normal ranges to maintain a neutral phosphate distribution (9, 10), which suppresses the 1,25(OH)2D production and secondary hyperparathyroidism (11). However, the effect of iron deficiency, ferritin, and anemia on serum FGF23 is still under investigation (12-16). Some investigations showed that FGF23 increased in Iron deficiency anemia (17-19) and oral iron replacement could decline the serum FGF23 (17, 20-22). However, intravenous iron supplements could increase the serum FGF23 (14, 20, 23, 24), and this difference in serum FGF23 between the two routes of Iron replacement is still under investigation.

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Homozygous beta-thalassemia, called beta thalassemia major, is an inherited hemoglobinopathy, which requires a frequent red-cell transfusion, leading to iron overload and extensive harmful deposition of cytotoxic iron in several body tissues. Hence, iron chelating therapy is an important part of its treatment (25). Bone disease in these patients, which includes bone deformities and osteoporosis, has multiple causes such as hypoparathyroidism, vitamin D deficiency, hemosiderosis, hypogonadism, growth hormone deficiency, and side effects of iron chelating agents (26, 27).

The role of phosphate hemostasis in the development of thalassemia bone disease has not been extensively studied yet. In light of various studies that have investigated the relationship between serum iron and FGF23, this point is gaining increased interest. A study showed that there was a strong positive correlation between FGF23 and serum ferritin in patients with thalassemia major (28). Hanudel et al. showed that FGF23 production and cleavage were enhanced in high endogenous erythropoietin concentrations, irrespective of iron status in wild-type mice (29). Due to the lack of sufficient human studies about the changes of serum FGF23 in patients with beta-thalassemia major as the first step of investigating the role of FGF23 in thalassemia bone disease, the present study aimed to investigate the serum level of FGF23 in patients with thalassemia major, a condition with anemia and iron overload.

Materials and Methods

The present case-control study was carried out on 25 patients with beta thalassemia major who were visited and followed in thalassemia clinic of Shiraz University of Medical Sciences in Fars province in the south of Iran. A total of 25 age- and sex-matched healthy volunteers who had normal physical examination and normal blood profiles were selected as the control group.

The patients with beta-thalassemia major had the routine follow up of a hematologist and endocrinologist and received routine blood transfusion every 3-4 weeks to maintain their hemoglobin level in the range of 9-10.5 g/dl. In these patients, iron chelating agents like deferasirox, deferiprone, and deferrioxamine were used in those with a serum ferritin more than 1000 ng/ml. The exclusion criteria in both cases and controls were renal failure (glomerular filtration rate less than 60 ml/min), hypoparathyroidism, liver disease, chronic inflammatory disease, thyroid dysfunction, diabetes mellitus, and metabolic bone diseases such as rickets.

Blood samples were taken after overnight fasting and at least 15 days after the last blood transfusion. All the samples were centrifuged and stored at -70°c at the Endocrinology and Metabolism Research Center laboratory of Shiraz University of Medical Sciences. Serum phosphorous (mg/dl), calcium (mg/dl), albumin (g/dl), and alkaline phosphatase (Iu/L) levels were measured in SA auto-analyzer (Biosystem SA, Spain) using colorimetric method. Serum PTH (pg/ml) and 25(OH)D were measured by Cobas E411 (Roche, Germany) using Elecro-chemiluminescence method. Serum intact FGF23 (iFGF23) in pg/ml and 1,25(OH)2D (pg/ml) were checked by ELISA method using an ELISA kit (Bioassay Technology, Spain). Serum ferritin level was measured with an E170 analyzer (Roche Diagnostics, Germany) using Electro- chemiluminescence's immunoassay (ECLIA) method. The IMMULITE Erythropoietin (EPO) assay (Siemens Healthcare Diagnostics, Tarrytown, NY, USA) was used to evaluate serum EPO (mIU /mL).

Ethical Consideration

The present study was approved at Shiraz University of Medical Sciences Local Ethics Committee with ID: 1396-01-01-15-805. All the patients signed a written

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informed consent form for participation in the study and any possible publication of their data, after explaining the aim, method and goal of the study for the participants.

Statistical analysis

The SPSS statistical software (SPSS 22, IBM SPSS software, Armonk, NY) was used for analysis. Data are shown as mean ± SD. Sample size formula was used to compare the two independent groups ($\alpha = 0.05$, $\beta = 0.2$) with 25 participants in each. Normality of data was checked by Kolmogorov-Simonov test. Student T-test and Mam-Whitney U test was used to compare normal and not-normal distributed data. The correlation between normal and not-normal distributed data was analyzed using Pearson and Spearman test. Multiple regression analysis model was used to evaluate the effect of the independent factors on serum FGF23.

Results

In the present study, 25 patients with beta-thalassemia major were compared to 25 age- and sex-matched healthy volunteers. General characteristics and laboratory data of both groups are displayed in Table I. Beta-thalassemia major patients had lower 1,25(OH)2D, ($p = 0.025$), higher serum FGF23 ($p = 0.007$), higher phosphate ($p = 0.002$), and higher PTH ($P < 0.001$); however, all of them were in the normal blood range. Also, these patients had lower fractional excretion of phosphate ($p = 0.003$), higher iron ($p < 0.001$), lower total iron binding capacity ($p = 0.008$), lower hemoglobin ($p < 0.001$), and higher serum ferritin level ($p < 0.001$) compared to healthy volunteers. In univariate Pearson analysis, the serum FGF23 was associated with 1,25 (OH)2D, Serum iron, and hemoglobin, as shown in Table II. However, after performing regression analysis to omit those dependent and confounding factors, serum FGF23 had a positive correlation with serum iron ($p=0.016$) and 1,25 (OH)D ($p<0.001$), and negative correlation with hemoglobin ($p=0.002$) (Table III).

Table I: General characteristics and laboratory data of thalassemia patients compared with the control group

Parameter	Patients with thalassemia major	Healthy controls	P value
Age (y)	25.8 ± 8.1	24.8 ± 9.9	0.693
Height (cm)	157.6 ± 8.8	161 ± 11.2	0.149
Weight (kg)	50.5 ± 9.3	58.8 ± 15.9	0.033
BMI (kg/m^2)	21.5 ± 7.5	22 ± 4.1	0.73
1,25$(OH)_2$D(pg/ml)	6.3 ± 4.4	9.3 ± 4.7	0.025
25(OH)D(ng/ml)	23.2 ± 21.1	16 ± 10.3	0.145
FGF23(pg/ml)	33.2 ± 21.9	19.4 ± 8.9	0.007
Calcium(mg/dl)	10.1 ± 0.9	9.7 ± 0.65	0.145
Phosphorous(mg/dl)	5.1 ± 1.1	4.2 ± 0.6	0.002
Alkaline phosphatase(Iu/L)	233 ± 122	160 ± 130	0.54
PTH(pg/ml)	55.7 ± 15.7	39.1 ± 14.5	<0.001
FEph(%)	9.3 ± 5	14.5 ± 6.5	0.003
Urine ca/cr	0.16 ± 0.2	0.13 ± 0.1	0.494
Iron(micg/dL)	387 ± 142	107 ± 34.3	<0.001
TIBC(micg/dL)	208 ± 71	253 ± 33	0.008
Hemoglobin(g/dL)	8.9 ± 0.5	12.7 ± 0.56	<0.001
Ferritin(ng/ml)	4014 ± 2661	66 ± 73	<0.001
Erythropoietin(mIU/mL)	158±21.5	6.5±2.9	<0.001

BMI: Body mass index, PTH: Parathyroid hormone, FEph: Fractional excretion of phosphate, TIBC: Total Iron binding capacity

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Table II: Univariate analysis of the correlation of the possible factors associated with serum intact FGF23 in the patients and controls

Variable	Pearson correlation	P value
Age (y)	0.021	0.89
BMI(kg/m^2)	-0.037	0.804
Ferritin(ng/ml)	0.285	0.05
1,25(OH)$_2$D(pg/ml)	0.37	0.01
25(OH)D(ng/ml)	0.094	0.526
Calcium(mg/dl)	-0.018	0.47
Phosphorous(mg/dl)	-0.119	0.42
PTH(pg/ml)	0.148	0.315
FEph(%)	-0.28	0.057
Iron(micg/dL)	0.314	0.04
TIBC(micg/dL)	-0.012	0.941
Hemoglobin(g/dL)	-0.395	0.005
Erythropoietin(mIU/mL)	0.295	0.042

BMI: Body mass index, PTH: Parathyroid hormone, FEph: Fractional excretion of phosphate, TIBC: Total Iron binding capacity

TableIII: Regression analysis of the possible factors associated with serum intact FGF23 in the patients and controls

Variable	Beta	P value	Coefficient standard Error
Age (y)	-0.028	0.878	0.357
Sex	0.044	0.773	5.4
BMI(kg/m^2)	-0.195	0.185	0.43
1,25(OH)$_2$D(pg/ml)	0.517	<0.001	0.499
25(OH)D(ng/ml)	0.031	0.8	0.132
Ca(mg/dl)	-0.155	0.231	2.88
Ph(mg/dl)	-0.136	0.064	3.08
PTH(pg/ml)	0.019	0.88	0.143
FEph(%)	-0.185	0.18	0.390
Hemoglobin(g/dL)	-0.525	0.002	1.45
Iron(micg/dL)	0.508	0.016	0.022
Ferritin(ng/ml)	0.216	0.132	0.001
Erythropoietin(mIU/mL)	0.208	0.132	0.017

R Square = 0.512, Adjusted R = 0.377, SE = 14.32

Discussion

The present study revealed that serum iFGF23 was associated with the serum level of ferritin, hemoglobin, serum iron, and serum 1,25 (OH)2D in β-thalassemia patients independently. This study also revealed that beta-thalassemia major patients had a higher serum FGF23, higher serum phosphate, higher PTH level, higher EPO, and lower serum 1,25 (OH)2D, as compared to normal population.

Previous studies showed that serum phosphate increased in patients with beta-thalassemia major due to chronic hemolysis and transfusions, hypoparathyroidism, and impaired renal function (30-33). In the present study, patients with hypoparathyroidism and renal insufficiency were excluded; hence, high phosphate might be due to chronic hemolysis, and PTH might be increased secondary to higher phosphate level in chronic hemolytic state of thalassemia patients. It was revealed that PTH and serum FGF23 was increased, probably due to their role in decreasing serum phosphate

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(31, 32); however, they showed relative success as the serum phosphate was still higher in patients than the controls. The other possible mechanisms suggested for high serum FGF23 in beta-thalassemia major patients were anemia (34), higher serum ferritin (19, 33, 34), increased erythropoietin level (29, 35), and decreased FGF23 receptor expression in the kidneys which resulted in partial FGF23 resistance during renal impairment (5, 6).

Rabadi et al. showed that acute loss of 10% total blood volume in mice could increase FGF23 mRNA expression in the bone marrow to 20-fold higher than before, which was accompanied by acute elevation of serum FGF23 and erythropoietin level (35). Also, Hanudel et al. showed that beta-thalassemia intermedia in mice showed a significant elevation in the serum FGF23 following a single intraperitoneal injection of exogenous erythropoietin (29). The present study revealed that serum erythropoietin was associated with serum FGF23 in univariate analysis; however, this association depended on other factors because its association disappeared in the regression analysis. Hence, we suggested that the association of serum EPO with FGF23 might be secondary to its relationship with the hemoglobin level. Yang et al. showed that serum FGF23 9.1% of their studied beta-thalassemia major patients had elevated serum FGF23 which was associated with serum iron (30). Some studies showed that intravenous injection of iron preparations could increase the serum FGF23 in chronic kidney disease (14, 23, 24, 33). However, using oral iron supplements could decrease the serum FGF23 (14, 17, 20-22). Fukao et al. showed that both oral and intravenous routes of iron administration resulted in similar increases of pro-inflammatory cytokines, IL6 and TNF-α, but their effects on the serum FGF23 was different. Oral iron supplementation could reduce both serum intact FGF23 and c-FGF23. However, intravenous administration of iron could reduce c-FGF23 and increase the serum intact FGF23 (30). Stefanopoulos et al. showed that serum iFGF23 was increased in Beta-thalassemia patients, who had iron overload (32). The present study showed that serum iFGF23 had a positive association with serum ferritin, serum iron, and 1,25(OH)2D and negative association with hemoglobin. It indicates that regular transfusions and chelating agents which decrease the serum iron and increase the hemoglobin level could be associated with lower iFGF23 compared to those who had low hemoglobin and high serum iron and ferritin level. We also hypothesized that thalassemia-associated osteopathy might be more progressive in those patients who had not received regular transfusions and iron chelating therapy because of higher serum FGF23 level which should be investigated in future investigations.

This study had several strong points; it is one of the few human studies which investigated the serum FGF23 in beta-thalassemia major patients without hypoparathyroidism or other renal and hepatic insufficiency. However, it had some limitations. We suggest that the severity of thalassemia-associated osteopathy, e.g. bone mineral density, should be checked in future investigations to find out the association between serum iFGF23 and osteopathy in beta-thalassemia major patients. We suggested that this study should be performed on two groups of thalassemia major patients with and without osteopenia/osteoporosis.

Conclusion

The present study revealed that serum iFGF23 was associated with serum level of ferritin, hemoglobin, serum iron, and serum 1,25(OH)2D in β-thalassemia patients independently. This study also revealed that beta-thalassemia major patients had higher serum FGF23, higher serum phosphate, higher PTH level, higher EPO, and lower serum 1,25(OH)2D,

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compared to normal population. We suggested that regular transfusions and chelating agents which can decrease the serum iron and increase the hemoglobin level can be associated with lower iFGF23. Hence, we hypothesized that thalassemia-associated osteopathy might be more progressive in those patients who had not received regular transfusions and iron chelating therapy because of higher serum FGF23 level, which should be investigated in future investigations.

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Conflict of interest

The authors declare no conflict of interest.

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