Association of vitamin D and FGF23 with serum Ferritin in hypoparathyroid thalassemia: A case control study

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Abstract

Background FGF23 controls serum l,25(OH) 2 D 3 levels and phosphate homeostasis. This study evaluates the effects of Ferritin on intact PTH, FGF23 and l,25(OH) 2 D 3 in patients with major thalassemia. It also evaluates FGF23 changes in patients with hypoparathyroidism to clarify the interaction between FGF23 and PTH in the absence of proper PTH function in human.

Methods In this case-control study, 25 patients with major-beta thalassemia with hypoparathyroidism and their age- and gender-matched patients with major-beta thalassemia having normal parathyroid function were enrolled. Biochemical studies assessed the serum calcium, albumin phosphorus, alkaline phosphatase, PTH, FGF23, 25(OH)D, 1,25(OH)2D3, Ferritin and Fractional excretion of phosphorous.

Results FGF23 was higher in the patients with hypoparathyroidism compared to the controls (p=0.002). Fractional excretion of phosphorous was lower in patients with hypoparathyroidism, despite the high level of FGF23(p=0.001). There was a correlation between serum1, 25(OH)2D3, and FGF23 with ferritin in the controls (P =<0.001and P =<0.001, respectively).

Conclusions The present study showed a strong positive correlation between serum ferritin and FGF23 and 1,25(OH)2D3. We hypothesized that ferritin could have stimulatory effect on production of 1,25(OH)2D3. Also, rise in FGF23 in patients with thalassemia, might be associated with either stimulating effect of PTH and 1,25(OH)2D3, or might be related to direct stimulating effect of ferritin.

Introduction

Thalassemia is an inheritable disease caused by abnormal hemoglobin production, resulting in ineffective erythropoiesis and increased peripheral hemolysis. The clinical outcomes of iron overload vary and reflect the key location of iron deposition. The concentration of ferritin in serum provides a quantitative measure for iron storage (1). In patients with major thalassemia, frequent blood transfusion and iron overload, despite intensive chelation therapy, prone them to many endocrine complications, such as hypogonadotropic hypogonadism, diabetes mellitus, hypothyroidism, and hypoparathyroidism (2, 3).

PTH is a potent stimulator in producing l, 25$(OH)_2D_3$ by increasing 1-alfa-hydroxylase activity in the proximal renal tubules. Reduced PTH secretion results in hypocalcemia and hyperphosphatemia (4, 5). PTH and Fibroblast growth factor 23 (FGF23) are the primary hormones that regulate the phosphate and calcium homeostasis (6). FGF23 is a member of FGF19 subfamily, produced by osteocytes in response to high serum phosphate and high l,25$(OH)_2D_3$ levels (7,8). FGF23 acts through FGFR-klotho co-receptors in the kidneys to provoke phosphaturia, and diminish 1-alfa-hydroxylase activity and controls the production of l,25$(OH)_2D_3$ (9–12).

Previous studies have shown the effects of dietary phosphate and serum phosphate on the release of FGF23 (13,14). The interaction between PTH and FGF23 on regulation of serum phosphate is not clearly understood. Recent studies have shown that both iron deficiency and iron transfusion have some effect

on the serum FGF23 (15–18). However, there is a lack of sufficient data evaluating the association or interaction between high serum ferritin and serum l,25$(OH)_2D_3$, FGF23 and PTH in patients with thalassemia. The aim of this study was to evaluate the association of Ferritin, intact PTH, FGF23, and l,25$(OH)_2D_3$ in patients with major thalassemia having normal parathyroid function and hypoparathyroidism.

Patience And Methods

Patients and Method

We studied 25 patients with major-beta thalassemia having hypoparathyroidism from October 2017 through March 2018 at Shiraz University of Medical Sciences affiliated thalassemia clinics in Fars province, southern Iran. A total of 25 age and gender matched participants were selected as the control who had major-beta thalassemia with normal parathyroid function. At the time of diagnosis, hypoparathyroidism was defined on the basis of hypocalcemia (Serum calcium less than 8.5 mg/dl) accompanied with a low or undetectable serum levels of intact parathyroid hormone (iPTH), and high serum phosphate level in thalassemia endocrine clinic. All patients with hypoparathyroidism had routine follow up by an expert endocrinologist, and received proper dose of calcium carbonate (500 mg tablet, manufactured Toliddaru pharmaceutical, Tehran, Iran), plus calcitriol (0.25 µg capsule, manufactured Zahravi pharmaceutical, Tehran, Iran). The range of daily dose of calcitriol was 0.5–2.5 µg/day to maintain albumin-corrected serum calcium level in the low-normal range of 8–9 mg/dl (5). The majority of transfusion-dependent thalassemia patients received routine blood transfusion therapy every 3–4 weeks to maintain their hemoglobin levels at 9-10.5 g/dL. In these patients, Iron chelating agents, such as Oral chelators (deferasirox and deferiprone) and Deferrioxamine injection were used. Deferoxamine subcutaneous injection was used in patients with thalassemia who had serum ferritin level greater than 1000 ng/mL with a dose of 20–40 mg/kg/day. The Exclusion criteria in both groups were renal failure (Glomerular filtration rate less than 60 ml/min), liver failure, and other metabolic bone disease (e.g., rickets), hyperthyroidism, and diabetes mellitus.

Blood samples were obtained from all participants for a minimum of 15 days after transfusion and overnight fasting. All blood samples were centrifuged for 15 min at 3000 rpm (1500 × g) and the sera were separated and stored at -70 °C until further analysis. All the biochemical studies were performed at the endocrinology and metabolism research center laboratory of Shiraz University of Medical Sciences. Colorimetric assays were used to analyze calcium (mg/dL), phosphorus (mg/dL), albumin (g/dL) and alkaline phosphatase (IU/L) levels, using Biosystem SA auto-analyzer, made in Spain. Electrochemiluminescence methods were used to measure serum parathyroid hormone (PTH) (pg/ml) and 25(OH)D (ng/ml) levels using Cobas E411, Roche, Germany. Sensitivity, intra- and inter-assay CVs for 25(OH)D were 2 ng/ml, 3.3% and 5.1%, respectively. ELISA method was used to determine the serum intact FGF23 (pg/ ml) and 1,25(OH)2D3 (pg/ ml) using Bioassay technology laboratory kit, Spain. Sensitivity, intra- and inter-assay CVs for 1,25(OH)2D3 were 3.14 (pg/ ml), < 8% and < 10%, respectively.

Sensitivity, intra- and inter-assay CVs for FGF23 were 2.4 pg/ml, < 8% and < 10%, respectively. Serum ferritin levels were recorded on Roche Diagnostic E 170 analyzer (Roche Diagnostics 1010/2010, Mannheim, Germany) by Chemiluminescence's Immunoassay (ECLIA) method.

Table 1
General characteristics and biochemical studies in both case and control groups and the related comparisons

Variable	control	case	P value
Age (y)	25.7 ± 5.1	26.9 ± 3.0	0.32
Weight(Kg)	50.5 ± 9.3	54.04 ± 10.2	0.213
Height(cm)	157.54 ± 8.832	162.40 ± 10.642	0.089
BMI(Kg/m^2)	21.4 ± 7.5	20.3 ± 2.4	0.479
PTH(pg/ml)	55.6 ± 15.7	13.93 ± 4.6	< 0.001
Ca(mg/dl)	10.1 ± 0.9	8.7 ± 1.6	0.001
Ph(mg/dl)	4.8 ± 0. 8	5.9 ± 1.6	0.005
Alk (IU/L)	279.3 ± 149.0	260.9 ± 121.5	0.65
1,25(OH)2D3 (pg/ml)	101.2 ± 38.1	94.7 ± 31.6	0.51
25 (OH)D (ng/ml)	21.6 ± 4.5	23.8 ± 7.8	0.22
FGF23(Pg/ml)	241.2 ± 121.0	381.9 ± 175.0	0.002
Ferritin(ng/ml)	1690 ± 548	1396 ± 638	0.086
FE phosphorous(%)	9.2 ± 5.0	5.1 ± 2.9	0.001
Urine Ca/Cr ratio	0.16 ± 0.2	0.17 ± 0.1	0.92

FGF_{23}: Fibroblast Growth Factor 23, Ph: phosphorus, Ca: Calcium, PTH: Parathyroid Hormone, FEph : fraction excretion of phosphorus, P = predictive value

Table 2

a. Multiple linear regression analysis of covariates of $1,25(OH)_2D_3$ in both case and control groups, performed with method of enter

Group	Associated factor	Beta	P value
Control (R square = 0.534) p < 0.001	Ferritin (ng/ml)	0. 71	0.016
	FGF23 (pg/ml)	-0.01	0.96
	PTH (pg/ml)	0.21	0.20
	Ca (mg/dl)	0.03	0.84
Case (R square = -0.081) p = 0.72	Ferritin (ng/ml)	0.08	0.68
	FGF23 (pg/ml)	0.27	0.20
	PTH (pg/ml)	0.036	0.88
	Ca (mg/dl)	0.168	0. 5

FGF_{23}: Fibroblast Growth Factor 23, Ca: Calcium, PTH: Parathyroid Hormone

Table 2

b. Multiple linear regression analysis of covariates of FGF23 in both case and control groups, performed with method of enter

Group	Associated factor	Beta	P value
Control (R square = 0.651) p < 0.001	Ferritin (ng/ml)	0. 77	0.001
	$1,25(OH)_2D_3$ (pg/ml)	-0.035	0.86
	PTH (pg/ml)	0.26	0.075
	Ph (mg/dl)	-0.072	0.65
Case (R square = -0.027) p = 0.52	Ferritin (ng/ml)	-0.17	0.42
	1,25(OH)2D3 (pg/ml)	0.27	0.19
	PTH (pg/ml)	-0.12	0.56
	Ph (mg/dl)	0.136	0. 5

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Results

In the present study, 50 patients with beta thalassemia including 25 cases with hypoparathyroidism and 25 controls with normal parathyroid function were enrolled. The patients' mean age in the case and

control groups was 26.9±3.09 years and 25.7±5.1 years, respectively. Hypoparathyroid group included 59.3% male participants. General characteristics and biochemical parameters of the patients are summarized in Table1. The mean serum calcium and PTH level was lower in patients with hypoparathyroidism in comparison with the controls (P=0.001 and P < 0.001, respectively). Serum phosphorus and FGF-23 level was significantly higher in patients with hypoparathyroidism compared to the control group (P=0.002 and P=0.005 respectively). The mean FE phosphorous was lower in the case group (5.1±3.1 %) in comparison with the controls (9.2±5 %) (P=0.001). There was no significant difference in serum alkaline phosphatase, 25(OH)D, ferritin, 1,25(OH)2D3, and Urine Ca/Cr ratio between the case and control groups (p= 0.65, p=0.22, p=0.08, p=0.51 and p=0.92, respectively).

In the control group, there was a positive strong correlation between serum ferritin and FGF23 (P <0.001, CC:0.801) and also between serum ferritin and 1,25(OH)2D3 (P <0.001, CC:0.754). However, serum ferritin level in patients with hypoparathyroidism did not correlate with those of serum FGF23, calcium, phosphorous, PTH, 25(OH)D, 1,25(OH)2D3, and FEPh (P>0.05). Table 2 shows multiple linear regression analysis of the covariates of FGF23 and 1,25(OH)2D3 in both case and control groups. It shows that association of ferritin with FGF23 or 1,25(OH)2D3 persisted after considering other contributing factors such as serum Ca, Ph, and PTH.

Based on the received Iron chelating agents, patients were divided into four groups according the daily dose of deferrioxamin and deferasirox (group1 <500 mg/day, group2 >500-1000 mg/day, group3 >1000-1500 and group4 >1500-2000). There was no significant difference in dosage and

kind of iron chelating agents received between the two groups.

Discussion

In the present study, we observed a high serum level of FGF23, 1,25OH2D and high normal PTH level in normo-parathyroid controls. We also detected a strong positive correlation between 1,25(OH)2D3, FGF23 and ferritin level in the control group. Expectedly in this study, low serum calcium in association with low serum PTH in patients with hypoparathyroidism was detected. In contrast, a high normal serum calcium and PTH in the control group was observed. This suggests that other factors might be involved in the stimulation of parathyroid secretion. It seems that high ferritin levels in patients with thalassemia might have had possible stimulatory effect on PTH secretion in intact parathyroid function, resulting in high normal serum PTH and calcium.

Kurtoglu et al. showed a high PTH level in major thalassemia patients more in the first two decades (2). Also, another study on 90 patients with thalassemia showed that more than 25% of them had high normal levels of PTH and calcium. They also found a significant correlation between ferritin and PTH in these patients (19). Pawlotsky et al. revealed a positive correlation between serum ferritin and high serum PTH 44-68 in patients with iron overload syndrome; however, there was no correlation with intact PTH

(20). On the other hand, some patients with thalassemia may develop parathyroid dysfunction at older age because of iron overload and iron deposition on the parathyroid glands (2). The iron overload could induce lysosomal and sarcolemmal membrane damage through free radical formation and lipid peroxidation and causes the destruction of parathyroid glands might be the underlying mechanism (21). And, cell surface transferrin receptors could able to play a role in protecting parathyroid glands against inorganic iron (22).

In the present study, we noticed that both case and controls had insufficient 25(OH)D serum level. Napoli et al. reported serum 25(OH)D deficiency in adult patients with beta thalassemia (23). In this study, we observed a high normal 1,25(OH)2D3 serum level, in spite of 25(OH)D deficiency in the control group. High normal serum PTH might be a potent factor to enhance alfa-1-hydroxylase activity in these patients. Also, this study showed a strong positive correlation between 1,25(OH)2D3 and ferritin level in the control group, which was not observed in patients with hypoparathyroidism. Therefore, we hypothesized that in the case of intact parathyroid function, high ferritin level might enhance 1,25OH2D production through direct stimulation of alfa-1-hydroxylase or indirectly through parathyroid hormone action. Some previous reports showed a significant low level of vitamin D in patients with thalassemia, but few of them evaluated serum 1,25(OH)2D3 in patients with thalassemia (1,23). Wood et al. showed a high serum level of 1,25(OH)2D3 in patients with thalassemia. He suggested that it could occur in spite of primary hyperparathyroidism or upregulation of extra-renal alfa-1 hydroxylase activity (24). Another study by Dandona et al. showed normal 1,25(OH)2D and PTH concentrations despite vitamin D deficiency in thalassemia patients and it claimed against an important role for vitamin D deficiency in the pathogenesis of thalassemia osteopathy (25). However, a high level of 1,25(OH)2D3 usually has not full function on intestinal calcium absorption in thalassemia patients. Moreover, Charoenphandhu.et al found that 1,25(OH)2D3 dependent intestinal calcium absorption was only observed in wild-type mice and not in the b-thalassemia mice. They concluded that in β-thalassemia mice, the 1,25(OH)2 D3 - dependent intestinal calcium absorption was impaired at the post-transcriptional level, that could lead to the dysregulation of body calcium metabolism and osteopenia. (26)

This study revealed a normal serum phosphate level in spite of high FGF23 and high urinary phosphate loss in the control group. It was suggested that high serum level of 1,25(OH)2D3 in patients with thalassemia could enhance the intestinal phosphate absorption, which leads to a normal serum phosphate even with high urinary phosphate loss (27). Another finding of the present study was the high level of serum FGF23 in patients with thalassemia. Two mechanisms could be put forward to explain the increase of serum FGF23 in these patients. The first is the stimulatory effect of PTH or 1,25(OH)2D3 on FGF23 production (28,29). Also, Moshayoff et al. showed that serum FGF23 levels were increased by PTH administration in both *in vivo* and *in vitro* (30). In addition, one study revealed that PTH had direct and indirect effects through 1,25(OH)2D3 on FGF23 secretion (31). As the result of strong positive correlation between ferritin and FGF23 in our patients with thalassemia, another possible mechanism could be

suggested by direct stimulatory effect of ferritin on FGF23 secretion, which should be further investigated in future studies.

There are controversies about the effects of iron deficiency or iron overload on the serum level of FGF23. Recent studies have shown that iron deficiency could increase the FGF23 degradation and administration of parenteral iron products, such as ferric carboxy-maltose increases FGF23 level (15,16,18). On the other hand, some studies have shown the association between iron deficiencies with increase in serum FGF23, and conversely iron transfusion resulted in decline of FGF23 level (17). Another research by Tangngam et al. showed that plasma level of FGF-23 in the normal controls was significantly higher than the thalassemia group(32).

Another finding of the present study was that, in our patients with thalassemia affected by hypoparathyroidism and hyperphosphatemia, in spite of the increase in the FGF23 serum level, there was no rise in urinary phosphate excretion. Recently, a few studies have been performed to evaluate the effect of PTH on FGF23 function in phosphate homeostasis (33). Yamashita et al. showed that FGF23 was increased in hypoparathyroidism and hyperphosphatemia, which was normalized along with serum phosphate normalization after parathyroid function improvement (34). The present study might suggest that FGF23 was not able to exert its full function in reducing serum phosphate in the absence of PTH. This could be due to the role of PTH in regulating FGF23 function.

In spite of many interesting findings in this study, we had some limitations; the first one was that the present study was descriptive with small number of patients and not a clinical trial. Future clinical trials are suggested on patients with hypoparathyroidism after PTH treatment to investigate the FGF23 functions more accurately. Also, investigating FGF23 and PTH gene expression could lead to more insight into the physiology, cause and effects. Further studies are also suggested to evaluate the role of ferritin on PTH, FGF23 in normal population with and without hypoparathyroidism and also in other genotypes of thalassemia.

Conclusions

The present study suggested that the rise in FGF23 in patients with thalassemia may be associated with either stimulating effect of PTH and 1,25(OH)2D3 on FGF23 production, or direct stimulating effect of ferritin. In addition, we hypothesized that in the case of intact parathyroid function, it is possible that high ferritin level might enhance 1,25OH2D production through direct stimulation of alfa-1-hydroxylase or indirectly by increasing the parathyroid hormone. Future clinical trials should be conducted on patients with hypoparathyroidism after PTH treatment to investigate the FGF23 functions more accurately.

Declarations

Ethical approval

Shiraz University of Medical Sciences local ethic committee and vice-chancellor of research at SUMS approved this study with the code number of 1396-01-01-15805. All the patients signed a written informed consent form after a session of explaining the aim, method and goal of the study for each participant.

Consent for publication: All the patients signed a written informed consent form for publication of any data from their results after a session of explaining the aim, method and goal of the study for each participant.

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests: Gholamhossein Ranjbar Omrani, Azita Salehifar, Seyed Reza Kassaee and Forough Saki declare that they have no conflict of interest.

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Authors' contributions

1. **Forough Saki:** Concept, design, data gathering, data analysis, preparing the manuscript
2. **Azita Salehifar,** design, data gathering, preparing the manuscript
3. **Seyed Reza Kassaee,** data gathering, preparing the manuscript
4. **Gholam hosein Ranjbar Omrani**: Concept, data gathering, preparing the manuscript and the correspondence

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Disclosure Summary

1. Saki, A. Salehifar, SR.Kassaee and GHR. Omrani have nothing to declare.

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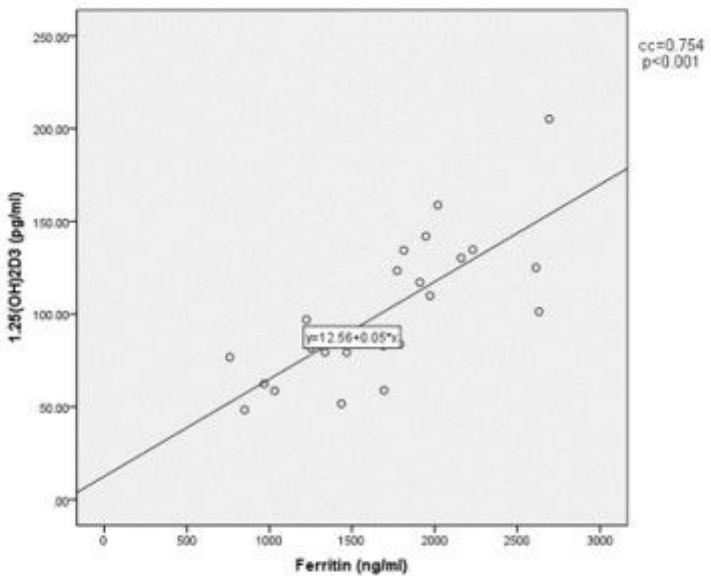
Figures



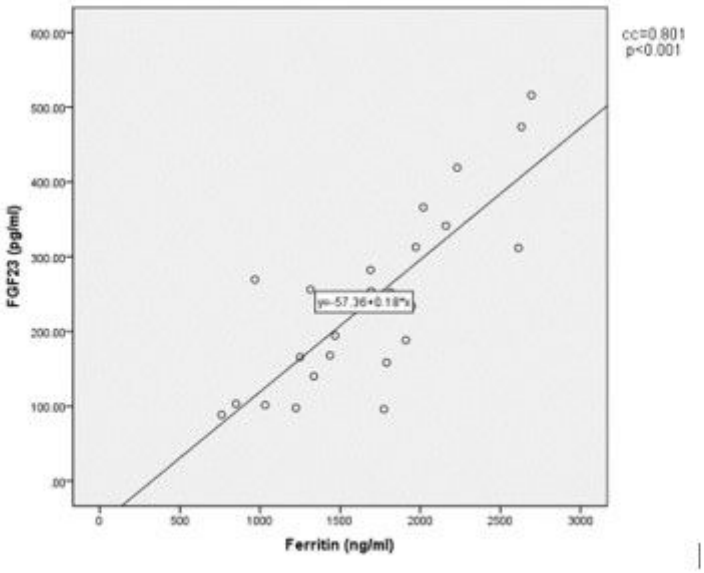


Figure 1

The correlation between values of serum Ferritin and 1.25(OH)2D3 (Fig1a) and the correlation between values of serum Ferritin and FGF23 (Fig1b) in the control group.