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ORIGINAL ARTICLE

Study of Fibroblast Growth Factor-23 in Iron Deficiency Anemia in Group of Egyptian Children

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ABSTRACT

Background: Iron deficiency anemia (IDA) is a common disorder in children in Egypt.in various ages. Fibroblast growth factor 23 (FGF 23) is a hormone produced by osteocytes promotes phosphate excretion; It inhibits vitamin D metabolism and has pathological cardiac consequences. Also its level possibly affects serum iron and hemoglobin level.

AIM The study aims to study the level of FGF-23 in iron deficiency anemia in group of Egyptian children and its relation to vitamin D metabolism , bone health and other sequels

Methods: The study was conducted on 66 patients diagnosed as IDA. Automated complete blood count (CBC) was done. Serum iron, total iron binding capacity (TIBC) was measured by spectrophotometer. Calcium, phosphorous and alkaline phosphatase were measured by VTTos 350. Serum C reactive protein (CRP), ferritin, 1,25 OH vitamin D and FGF 23 were done by enzyme linked immune assay (ELIZA).

Results:IDA cases showed higher serum alkaline phosphatase, FGF 23 and lower 25 OH vitamin D compared to controls. (P was 0.004, 0.044 and 0.01 respectively), while no differences in serum calcium and phosphorous (P was 0.055, 0.144 respectively). FGF 23 showed no relation to age, height or weight. (P was 0.488, 0.38 and 0.439 respectively). It showed negative correlation with serum ferritin, and Hb (P was 0.000, 0.000) respectively), and positive correlation with alkaline phosphatase in IDA cases. (P was 0.000). Bone deformities like rickets was associated with 14 cases with IDA (21.22 %) In cases without bone deformities like rickets (BDLR) no correlation was found with Hb or alkaline phosphatase but still present with serum ferritin (P was 0.183,0.484 ,0.000) In both groups , no relation was found to serum iron or TBIC in (P was 0.654 ,0.336 & 0.184 ,0.244 respectively). Also no relation to serum calcium, phosphorous or 25 OH vitamin D was found in both groups (P was 0.491, 0.609 and 0.129 & 0.283, 0.213 and 0.197 respectively).

Conclusion:FGF 23 is increased in cases with IDA compared to controls. Cases showed BDLR had higher values of FGF 23, alkaline phosphatase and lower values of 25 OH vitamin D. It showed negative correlation with Hb and serum ferritin and positive correlation with alkaline phosphatase in IDA cases. The relation to Hb and alkaline phosphatase was lost when cases with BDLR were excluded but still present with serum ferritin. These results may have clinical implication on management of IDA and its consequences in children.

Keywords : Fibroblast growth factor; Calcium; Phosphorous; Iron deficiency anemia; Rickets

INTRODUCTION

Anemia resulting from severe iron deficiency (IDA) is the most prevalent and widespread nutrition problem in infants and young children in the developing world**. [1].** It has been associated with adverse cognitive and motor development **[2–4].** It is a common health problem among Egyptian children especially low socioeconomic classes reaching to 64% in some localities [**5].** In pediatric populations IDA is not only separate entity but also associates and perpetuates other diseases as prematurity, cyanotic heart diseases. And asthma **(hy6)**

Fibroblast growth factor 23 FGF-23) is a hormone produced by osteocytes acts on the kidney by inhibiting phosphate reabsorption and renal synthesis of active form of vitamin D (1, 25-dihydroxyvitamin D) **[7]**

Apart from bone health, FGF-23 has been investigated in adult population regarding

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relation to immune function **[8]** related to vitamin D metabolism .Also higher FGF-23 was associated with increased mortality risks due to cardiovascular diseases **[9]** and progression of chronic renal diseases **[10]** in adult population. The explanation of this association is still not clear , possibly due to vascular effects**[11],** impaired immune response **[8].** FGF-23 activates hypertrophic gene program, promoting cardio-myocytes growth, stimulating the release of natriuretic peptides [**12].**and induced left ventricular hypertrophy and heart failure events **[13]**

In experimental animals it found that, induced iron deficiency was associated with increased intact FGF 23 and decreased serum phosphate. Also, acute inflammation induced functional iron deficiency and increase FGF 23 production **[14]**

A recent association between iron status and FGF-23 was observed by some investigators. Farrow EG et al demonstrated induction of iron deficiency in mice has late autosomal dominant hypophosphatemic rickets "ADHR" accentuates and accelerates biochemical and clinical manifestation of the disease through increasing FGF-23. [**15].** they hypothesized that onset of the late form of the disease possibly precipitated by increase in iron requirement at puberty. Neonatal iron deficiency induced elevation of FGF23 in normal mice without ADHR and was associated with hypophosphatemia .and decreased level of 1, 25 OH vitamin D and rachitic changes **[16].** These changes were normalized by iron repletion. Maternal iron deficiency during pregnancy was associated with increased FGF-23 and alkaline phosphatase during 1st 2 years of life **[17]**. In Gambia where IDA and rickets are endemic inverse correlation was found between hemoglobin concentration and FGF-23. This correlation was pronounced in children with rickets like bone deformities than local community children. **[18]**

Because IDA is community health problem and has many consequences on general health and development, we investigated FGF 23 in children with IDA to evaluate its role in development of complication and relation to growth, development, calcium hemostasis and other possible squeals

METHODS

Patients group:

Sixty six (66) children diagnosed as IDA was chosen from Al ahrar Teaching Hospital from outpatient clinic who came for routine check , or have minor complains were included in the study .They were subjected. To detailed history : perinatal (preterm delivery ,small for gestational age) , nutritional (bottle or breast feeding ,weaning practice) , developmental history and history of other diseases . Also history of possible cow milk intolerance, gastro esophageal reflux disease (GEORD) was evaluated. .Physical examination included measurement of weight and height percentile, bone deformity was done. .

Anemia was defined as reduction in hemoglobin level, hematocrit or number of red blood cells per cubic millimeter below the lower limit of the normal range is set at two standard deviations below the mean for age and sex for the normal population " below 10.5 gm/dl at 28 days-2 years age, below 11.5 gm /dl at 2-12 ys age " **[19]]**

Exclusion criteria:

Cases with delayed mile stone other than rickets, cases with bone diseases other than rickets, cases with anemia other than IDA and cases with renal failure, or childhood malignancy for possible hypophosphatemia were *excluded.* .Also, cases showed evidence of infection were excluded. These cases were compared with 15 healthy controls age, sex matched**.**

CRP was determined by ELIZA "high sensitive CRP". Automated CBC was also done. Serum iron, TIBC was measured by spectrophotometer. Serum ferritin was measured by ELIZA kits provided from immune spec cooperation 7018 Owens mouth Ave. suit *103 Congo Bank, C.A.91303).

Serum calcium, phosphorus, alkaline phosphatase were measured by VTTos 350 and 25 OH vitamin D was estimated using ELIZA.

Stool analysis was done for all cases and control.

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***Measurement of FGF 23*:**
Human fibroblast growth factor 23 (FGF23) was measured using quantitative sandwich enzyme immunoassay technique (CUSABIO). Antibody specific for FGF23 had been pre-coated onto a micro-plate. Standards, samples were added into wells, after washing a biotin-conjugated Horseradish Peroxidase (HRP) was added to wells, following a wash a substrate was added to the wells and color development is stopped and the intensity of the color was measured at 450 nm with correction wave length at 570 nm

Plain x ray was done for cases with bone deformity or suspected old rickets

Legal aspect: Written informed consent was obtained from all participants parents. The study was approved by the research ethical committee of General Organization for Teaching Hospital and Institutes in Cairo. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans**.**

Statistical Analysis: Data were analyzed using SPSS 20 computer program (IBM, Endicott, Broome County, New York, United States). Data were expressed as mean ± SD for categorized variables. Tests of significance "Chi-square and T tests" and correlation study were done where appropriate $P < 0.05$ was statistically significant

RESULTS

In this study we selected 66 children with IDA and 15 healthy children as a control. IDA cases showed similar age, sex, height distribution and lower weight values (P was 0.643, 0.567, 0.697 and 0.045 respectively) compared n to controls (Table 1).

Among 66 patients with IDA 14(21.2%) patients had bone deformity like rickets (BDLR). Fifty two (52) cases had no BDLR.Fourteen patients had cow milk indolence (21.2%) ,4 (6.1%) had history suggest gastro-esophageal reflux disease (GEORD) ,15 cases has symptom of gastritis (22.7%), 7 cases (10.6 %) had history of improper weaning practice , 8 cases (12.1%) born small for gestational age ,14 cases (21.2%) had history of nutritional deficiency , 9 cases(13.6 %) born preterm (data not shown).

Cases with IDA has no significant differences in platelets, WBCs, serum iron calcium and. phosphorous in relation to control (P was 0.363,0.135,0.16 , 0.055 and 0.144) respectively (Table (2).Also they showed lower RBCs, HB , , serum ferritin(P was 0.015, 0.000 0.002) and higher TIBC, alkaline phosphatase and FGF 23 in relation to controls (,0.000,0.004 and .0.001 respectively).

Among IDA cases , 7 cases "10.6 % " with vitamin D < 20 mg/dl (deficiency) , 22 cases "33.3 %" with level 20 -29 mg/dl(insufficiency).compared with 2 of 15 "13.33 % " controls had insufficiency (p was 0.044) (table 2).

IDA cases with BDLR showed no significant differences with IDA without BDLR regarding RBCs ,HB, MCH ,HTC, MCV,MCHC, WBCs , serum iron ,calcium and phosphorous (P was 0.23,0.366,0.374 ,0.962,0.537,0.672,0.109 ,0.989.0.401 and 0.074 respectively). However they showed higher values of RDW, Platelets, TIBC, ALKP and FGF 23 (P was 0.004, 0.042, 0.037, 0.000 and 0.000 respectively) and lower values of vitamin D and serum ferritin (P was 0.005 and 0.001 respectively}) compared to cases without BDLR [table 3].

Multiple linear regression analysis showed no significant relation regarding FGF 23 with age, sex and height.(table 4 ,Figure 1) . Also, FGF 23 showed significant negative correlation with HB, WBCs and serum ferritin (P 0.00,0.001,0.00 respectively) and positive correlation in relation to platelets count and alkaline phosphatase (P was 0.011 ,0.002 respectively) with no significant relation to other parameters . It showed no relation with calcium, phosphorous or 25 OH vitamin D (P was 0.49, 0.609 and 0.129 respectively) [table 5, Figure 2]. When cases with BDLR were excluded no significant relation to alkaline phosphatase, and Hb were fount- but still presents with serum ferritin. [Table 6, Figure 3]

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Table (1): Comparison between Cases with IDA and Control Regarding Demographic Data

	Cases (66)		Control (15)		p
	Mean	SD	Mean	SD	T test
Age(months)	31.42	11.630	29.93	8.85	0.643
Height	86.21	8.93	87.2	8.35	0.697
Weight	12.94	2.47	14.33	1.95	0.045
					Chi-Square Test
Sex M	45		10		0.567
F	21		5		

Table (2): Comparison between Cases and Control Regarding Laboratory Data

	Cases (66)		Control (15)			
	Mean	SD	Mean	SD	T test	
					T	P
MCH	21..87	2.84	25.48	2.79	-4.32	.001
MCV	64.46	6.14	70.66	6.79	-3.37	000
MCHC	32.02	2.42	34.99	2.21	3.15	.000
RDW	14.99	1.09	13.85	0.67	3.77	.000
HTC	26.81	4.87	33.48	5.08	4.61	.000
RBCs	3.36	0.85	3.96	0.68	-2.48	.015
WBCs	8674.24	3949.5	7557.14	5046.05	0.914	0.363
Platelets	306.79	132.75	250.93	81.95	1.51	0.135
Serum iron	79.26	47.03	60	41.69	1.42	0.16
TIBC	323.65	75.35	236.14	75.35	3.94	.000
Serum ferritin	38.65	24.57	64.07	27.37	-3.52	.002
	Median	Range	Median	Range	Mann-Whitney Test	
					z	p
HB	8.9	3.5-10.8	10.85	10-11.50	-5.007	.000
Calcium	10.5	8.5-11.5	11	8.5-11.5	-3.36	0.055
Phosphorus	5	4-6.5	5	4.5-6.5	-3.69	0.144
Alk. phosphatase	240	130-450	160	130-350	-2.88	.004
	Value	Cases	Controls		Chi-Square Test	
25 OH Vitamin D	≥30	37	13		Phi	-.227
	< 30	29	2		P	0.044
FGF-23	8.1	.48-45	1.29	.6-15.1	-.3.83	.001

Table (3): Comparison between IDA Cases with BDLR and Without BDLR Regarding Laboratory Data

	IDA without BDLR (52)		IDA with BDLR (14)			
	Mean	SD	Mean	SD	T test	
					T	P
MCV	64.22	5.94	65.37	8.32	.-.62	.537
MCHC	32.09	2.03	31.78	3.6	.426	.672
RDW	14.79	.97	15.72	1.2	-3.025	.0.004

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	IDA without BDLR (52)		IDA with BDLR (14)			
RBCs	3.43	0.82	3.12	0.92	1.211	0.23
Platelets	289.6	122.38	370.64	154.25	2.08	.042
Serum iron	79.25	47.03	79.29	47.51	-.003	.989
TIBC	313.65	76.91	360.79	58.16	-2.13	.037
Calcium	9.75	1.18	8.8	1.37	2.585	.0401
Phosphorus	5.15	79	4.474	1.01	2.425	.0074
Alk. Phosphatase	224.73	69.1	343.86	80	-5.538	.000
25-OH vitamin D	41.23	14.79	28.29	14.41	2.923	.005
FGF23	7.43	6.77	22.71	11.62	-6.349	.000
	Median	Range	Median	Range	Mann-Whitney Test z	p
HB	8.95	.65-10.8	8.95	3.5-10.80	-.904	.366
MCH	22	18-30.4	21.45	17.60-27.60	-.888	.374
HTC	27.9	20-34	26.35	10-36	-.047	.962
WBCs	7.35	4-20	6.6	4.2-13	-1.602	.109
Serum ferritin	40	9-90	12.5	9-43	-3.408	.001

Table (4): Multiple Linear Regression Models For FGF 23 in relation To Age, Sex , Height

Parameter	β coefficient	P Value	95% Confidence Interval	
			Lower Bound	Upper Bound
Age	-.157	.577	0.351	0.426
Weight	-.144	.553	-.251	1.355
Height	.041	.875	-.532	0.613

Table (5): Multiple Linear Regression Models for FGF 23 in relation To Laboratory Data in IDA

Parameter	B Coefficient	P Value	95% Confidence Interval	
			Lower Bound	Upper Bound
HB	-.433	.000	-5.385	-.702
MCH	-.170	0.218	-1.58	.368.338
MCV	.339	0.00	.338	1.123
MCHC	-.027	0.750	-.683	.851
RDW	.033	.736	1.695	1.935
RBCs	.154	1.402	1.125	4.179

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Parameter	B Coefficient	P Value	95% Confidence Interval	
HTC	-.020	0.167	0.597	4.179
WBCs	-.319	0.001	-.001	.000
Platelets	.244	0.011	.004	.033
Serum iron	-.037	.654	-.043	.029
TIBC	-.0970	.336	.036	.014
Serum Ferritin	-.558	0.000	-0.310	0.147
Calcium	-.177	0.491	-2.605	-.214
Phosphorous	-.036	0.609	-2.055	1.214
Alkaline phosphatase	.0.044	0.002	.073	.113
25 OH VITAMIN D	.031	0.129	-.097	.137

Table (6): Multiple Linear Regression Models for FGF 23 in Relation to Laboratory Data in IRA without BDLR

Parameter	B Coefficient	P Value	95% Confidence Interval	
			Lower Bound	Upper Bound
HB	-.905	0.183	-2.26	-.45
MCH	-.164	0.2501	.652	.325
MCV	0.462	0.00	0.23	0.694
MCHC	0.125	0.65	0.00	0.23
RDW	0.707	0.172	-.322	1.736
RBCs	-.198	0.788	-1.678	1.281
WBCs	0.000	0.015	0.000	0.001
Platelets	0. 016	0.000	0.024	0.007
HTC	0.197	0.249	-.144	0.539
Serum iron	0.013	.184	0.006	.032
TIBC	-.007	0.224	-0.017	0.004
Serum Ferritin	-0.92	0.000	-.135	-0.048
Calcium	-1.788	0.283	-2.170	0.351
Phosphorous	-0..324	0.213	-1.568	.920
Alkaline phosphatase	0.099	0.484	0.056	0.095
25 OH VITAMIN D	0.0.63	0.197	0.034	0.161

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Figure (1): Multiple Linear Regression Models for FGF 23 in Relation to Age, Weight and height

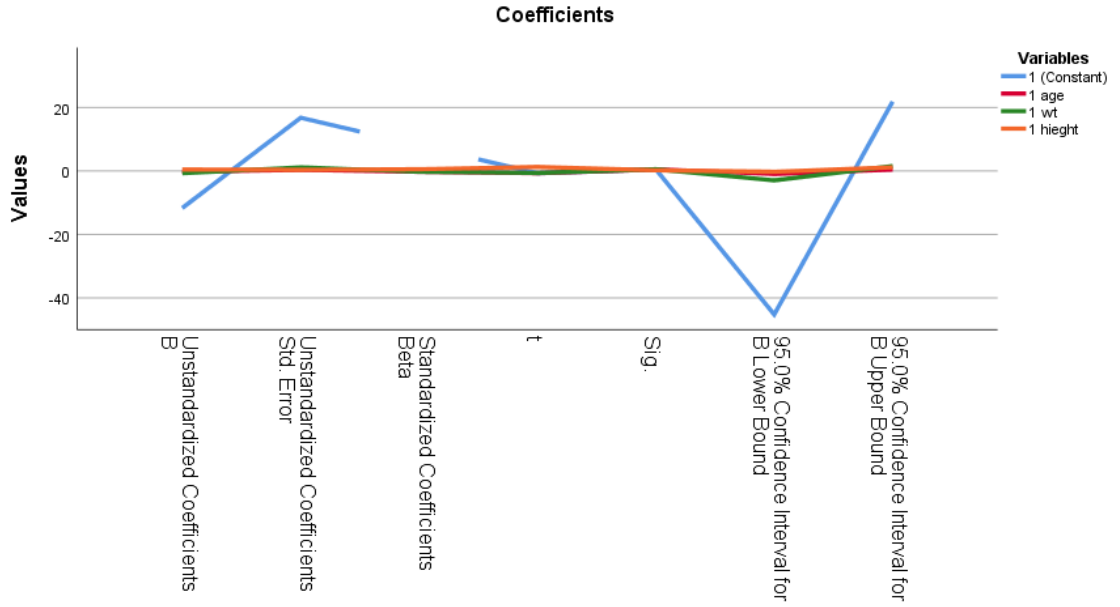

Figure (2): Multiple Linear Regression Models for FGF 23 in relation to Laboratory Data in IRD

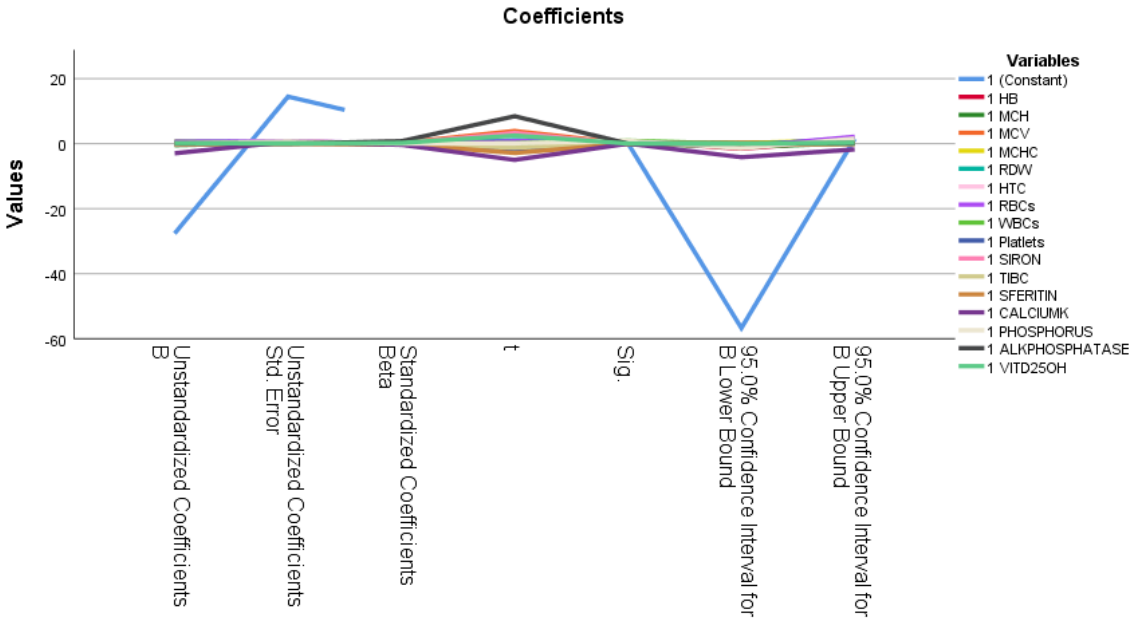

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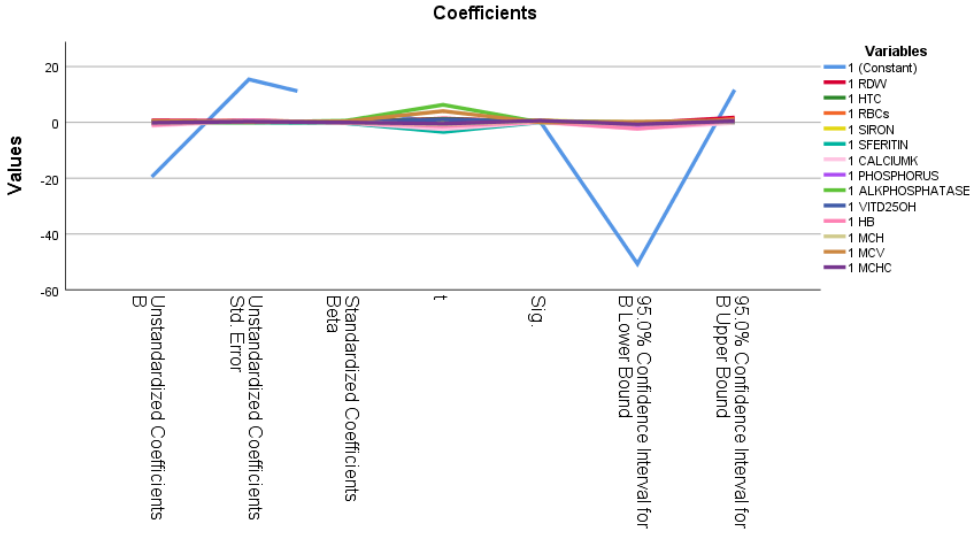
Figure (3): Multiple Linear Regression Models for FGF 23 in relation To Laboratory Data in IRD without BDLR



DISCUSSION

In this study we estimated FGF 23 level in children with IDA for possible its role in vitamin D and calcium, phosphorous metabolism and its effect on bone health and development in children. Very little studies are available in this subject .We investigated most markers of iron and calcium metabolism. We estimated 25 OH vitamin D rather than 1, 25 OH vitamin D "the active form" because the former gives better estimation of level of vitamin D in the blood because it's steady level. The active form is produced at local site of action of vitamin D and not reflects vitamin D level**. [20].**

IDA cases showed no significant difference in age, sex, height while showed lower weight values in relation to controls, P was 0.643, 0.567, 0.697 and 0.045 respectively. It is expected that IDA cases to have lower weight and height compared to controls **[21& 22].** The difference of our study in matching height between cases and controls possibly because of relative younger age group of our patients and possible shorter duration of anemia.

Cases with vitamin D deficiency (VDD) (10.6 %) ,or insufficiency (VDI) (33.3 %) was significantly higher in IDA cases compared with controls (13.33%) , also alkaline phosphatase was higher in these cases relative to controls (P was 0.044 ,0.005 respectively) . No significant differences in serum calcium, phosphorous between anemic cases and controls (0.055&0.144 respectively). Different studies described association between 25 OH vitamin D level and IDA . **HJ et al [22]** found that VDD, VDI was found in 67 % and 20 % in children with IDA under 24 months old and in 29% and 23% in healthy subjects with same age group respectively (P was 0.008). Similar to our study, they found no significant difference between anemic and healthy children regarding serum calcium and phosphorous (P was 0.896 and 0.376 respectively) .Youm JW et al **[23]** found that 25 OH vitamin D deficiency (39 %), insufficiency (48%) in IDA cases .The difference in proportion of vitamin D deficiency and insufficiency from our study may be due to different age group and dietary, environmental factors. Anemic cases with BDLR showed lower RBCs. Hb, 25 OH vitamin D and higher alkaline phosphatase compared with cases without BDLR. Multiple explanations about 25 OH vitamin D deficiency in IDA. First explanation is IDA may result from dietary deficiency of decrease intake of iron and vitamin D sources **[6].** Anemia may be a risk factor for vitamin D deficiency because of causing fatigue, decreased activity and consequently decreased

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exposure to sunlight **[24]**. Also vitamin D is required in erythropoiesis **[25].**

FGF 23 was higher in IDA cases compared to controls who were age, sex, height matched. Also it correlated negatively with Hb .This correlation lost when cases with BDLR were excluded. Most studies about FGF 23 were done in adult patients with end stage renal diseases with cardiovascular complications [**10, 11.13**].Very little reports done about its relation to iron and IDA in children. Braithwaite V et al **[26**] found negative correlation between Hb and FGF 23 IDA cases in rural localities in Gambia where IDA and rickets are endemic. Similar to our study when cases with BDLR were excluded, this correlation was non-significant. In our study negative correlation was found between FGF 23 and serum ferritin in IDA with and without BDLR. No correlation found with serum iron or TIBC. Similar results in adults undergoing hemodialysis were founded by Honda H et al **[27]** who found negative correlation between FGF 23 and serum ferritin and serum transferrin saturation (TSAT) and positively with serum calcium and phosphorous. The difference from our study regarding calcium and phosphorous may be attributed to different age, and associated renal disease which leads to altered calcium hemostasis. Acidosis and associated hyperparathyroidism. Also Braithwaite V et al [**27]** found inverse relationship between iron status and FGF 23. In this study serum ferritin was the strongest inverse predictor of FGF 23 in subjects with and without. Evidence of infection, FGF 23 level decreased with iron supplementation. Contrarily to our study, Schouten et al **[28]** demonstrated intravenous iron administration was associated with elevation of FGF 23 and hypophosphatemia. The difference from our study possibly attributed to method of administration of iron through intravenous access may has rapid effect than oral rout and resulted in direct effect on renal tubule and hypophosphatemic effect and consequently elevate FGF 23 [**29]** Different explanations hypothesized inverse relation of iron to FG 23, *first* by inhibiting the cleavage of the intact FGF23 molecule and *secondly* by assisting the clearance of FGF23 fragments by the kidney **[30].**

FGF 23 had positive correlation with alkaline phosphates .with no relation to calcium, phosphorous or 25 OH vitamin D. This correlation was lost in cases without BDLR. Similar results were found in Gambian children by Braithwaite V et al **[18]**. They found positive correlation between FGF 23 and alkaline phosphatase despite absence of such correlation with both calcium and phosphorous. Also they found higher number of cases with high FGF 23 in anemic children with BDLR compared to those without BDLR. The relation of FGF 23 to bone disease and rickets was studied in many literatures. **FG**F 23 induced renal phosphate wasting and hypophosphatemia in tumor induced osteomalacia **(TIO)** and X-linked hypophosphatemic rickets (XLH). **[30, 31]** Abnormal mutation in FGF 23 was associated with ADHR **[32].** ADHR symptoms and disease severity was likely to fluctuate with FGF23 concentrations **(33).** Also it inhibit active form 1,25 OH vitamin D synthesis **[7]** In our study FGF 23 was higher in anemic cases compared to controls and was higher in cases with BDLR compared to cases without BDLR. Also, despite positive correlation between FGF 23 and alkaline phosphatase no relation found to phosphate, calcium and 25 OH vitamin D. Normal calcium level .is maintained by calcium hemostasis through parathyroid hormone. Normal phosphate is explained possibly due to dietary factors of high phosphate in diet or high cow milk intake **[18].** Lack of correlation with 25 OH vitamin D possibly because that FGF 23 inhibit synthesis of the active form 1, 25 OH vitamin D locally rather than 25 OH vitamin D **[7]**

The limitations in our study that relative small number of cases included in the study with high frequency of I DA in our locality. We did not assessed parathyroid hormone, glomerular filtration rate .and the active form of vitamin D 1, 25 vitamin D because of financial costs and this require comprehensive study with better facility.

This study reflects the possible role of IDA in bone health and development of bone

deformities It has multiple clinical implications. IDA is very common disorder nearly endemic in some localities. Screening of serum, calcium, phosphorous alkaline phosphatase and vitamin D is very essential for maintenance of bone health and prevention of deformities. In patient with chronic renal disease undergoing renal dialysis, positive correlation was found between FGF 23 and left ventricular mass index (LVMI) [**34**] It was increased in association with LVH and chronic heart diseases **[35,36]** .The effect was thought to be due direct effect on myositis through FGF 23 receptors or through inhibition of formation of active vitamin D **[37]** .In children with cyanotic, congenital and acquired cardiac diseases screening, treatment and prevention of IDA is mandatory for prevention of further deterioration and complication mediated through FGF 23 . Administration of 1, 25 OH vitamin D may decrease the cardiovascular complication through decreasing FGF 23 (34) Data obtained from HD supports the survival benefit of active vitamin D therapy **[38]**

Further studies are required for detailed role of FGF 23 in IDA and its complications with large number of cases with different complications including cardiac, renal complications. Also extensive investigations of calcium metabolism including 1.25 OH vitamin D and parathormone hormone in IDA are required to understand more effect of the hormone on bone health

Conflict of interest: no conflict of interest
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