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Predictors of Osteopathy among Adult Patients with Thalassemia Major

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Authors' contributions

This work was carried out in collaboration between all authors. Author MABAA designed the study and approved the protocol. Author HMZEA interpreted data and wrote discussion. Author GME performed laboratory analysis of blood samples. Author AAMG performed data collection, statistical analysis and wrote the first draft of the manuscript. Author AAH managed the literature search, wrote the final manuscript and acted as corresponding author. All authors read and approved the final manuscript.

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ABSTRACT

Background: Beta thalassemia comprises a group of inherited (autosomal recessive) hematologic disorders characterized by decreased or absent synthesis of β-globin chains. Beta thalassemia patients exhibit an unbalance in bone mineral turnover with increased resorptive rates and suppression of osteoblast activity, resulting in diminished bone mineral density (BMD).
The Aim of Study: The aim of study was to determine the prevalence of low BMD in patients with β-thalassemia and to find a possible relationship between osteopathy among adult thalassemic patients and multiple variables as different endocrinal disorders, iron chelation therapy, calcium and vitamin D levels, ferritin levels and history of splenectomy.
Subjects and Methods: The current study had been conducted on 80 patients with β-thalassemia major. Thirty seven were males (46.2%) and 43 patients were females (53.8%). Their ages ranged

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from 15 to 33 years with a mean of 20.6 ± 4 years. All patients were subjected to full medical history, full clinical examination and investigations that included total calcium, 25 (OH) vitamin D, FBG, 2hPPBG, TSH, free T4 and ferritin levels. Assessment of BMD was done by DEXA scan at three sites (AP-spine, left femur and right forearm).

Results: Seventy-nine (98.7%) patients had abnormal BMD where 34 (42.5%) patients were osteoporotic, 6 (7.5%) were osteopenic and 39 (48.7%) had both osteopenia and osteoporosis. Bone mineral density positively correlated with vitamin D levels at left femur and AP spine, and Calcium levels at RT forearm, LT femur and AP spine. BMD negatively correlated with 2-hour postprandial blood glucose and ferritin levels at RT forearm, LT femur and AP spine. There was a statistically significant difference with p-value of 0.02 between number of sites affected and history of splenectomy, where (40.6%) of these who underwent splenectomy had affection in the three sites.

Conclusions: The prevalence of low BMD in patients with β-thalassemia is high. Many factors contribute to the development of such complication. BMD is a good index of bone status in patients with thalassemia. Regarding the high prevalence of osteopenia/osteoporosis in patients with thalassaemia major, all patients should be screened periodically for bone disease. Future studies including larger number of patients with different types of hemoglobinopathies are recommended.

Keywords: β-thalassemia major; bone mineral density; osteopathy; 25(OH) vitamin D.

1. INTRODUCTION

Thalassemia is the most common monogenic disorder in the world. Thalassemia major (β-thalassemia) affects a significant segment of the population in certain areas of the world. Alterations in migration patterns have changed the geographic distribution of this disease and made it a worldwide health problem with a high frequency in Africa, India, Southeast Asia and the Mediterranean area [1].

The management of patients with thalassemia has improved markedly over the past few decades with the use of optimized transfusion programs and chelating therapy. With prolongation in the life expectancy, it has been observed that this hemoglobinopathy is associated with a variety of bone disorders like deformities, bony pains, delayed bone age, growth failure, rickets, scoliosis, spinal deformities, nerve compression, pathologic fractures, osteopenia, and osteoporosis [2].

Dual X-ray absorptiometry (DEXA) is an excellent non-invasive choice for repeated measurements of any temporal changes of BMD because of its low radiation exposure [3].

2. SUBJECTS AND METHODS

This study included 80 patients with β-thalassemia major who attended the outpatient clinic at Fayoum university hospital, Fayoum city, Egypt. Patients in the study were subjected to:

- Full history taking stressing on regularity of blood transfusion and compliance with iron chelation therapy (if any).
- Thorough clinical examination.
- Laboratory investigations including complete blood count , serum Ca (total), FBG and 2h PPBG , serum ferritin and 25(OH) vitamin D. Blood samples were taken from patients using wide-bore needle slowly from ante cubital vein to avoid hemolysis of RBCs by careful venipuncture. These samples were divided into two aliquots, first aliquot was added to EDTA tube for CBC counts, second one was added to a plain tube, allowed to be clotted for 15 minutes, and then separated by centrifugation at 1000 rpm for 15 minutes for the other measurements. Serum 25 (OH) vitamin D levels were determined by Enzyme linked immunosorbent assay (ELISA).
- Dual energy X-ray absorptiometry (DEXA) to detect osteopenia (which is a BMD as a T-score -1 to -2.5) or osteoporosis which is designated at a bone density value at least 2.5 SDs below the mean value for young adults, i.e. the T-score is -2.5 [4]. In our study, BMD was assessed by DEXA in three sites: right forearm, left femur and AP- spine.

Informed consent was obtained from all participants in the study. The study was conducted following the approval of the ethical committee at Fayoum University in keeping with the guidelines of Helsinki.

2.1 Statistical Analysis

Collected data were computerized and analyzed using Statistical Package for Social Science (SPSS) version 16. Descriptive statistics were used to describe variables; percent proportion for qualitative variables. Mean ± SD and range for

Quantitative variables. Student's t-test was used to compare measures of two independent groups of quantitative data. Chi square test was used to compare two or more than two qualitative groups. P values with significance of less than 5% were considered statistically significant.

3. RESULTS

The current study had been conducted on 80 patients with β-thalassemia major. Thirty-seven were males (46.2%) and 43 patients were females (53.8%). Their ages ranged from 15 to 33 years with a mean of 20.6 ± 4 years. Two (2.5%) patients only were diabetics. None of our patients had abnormal thyroid function. Splenectomy was found in 69 (86.3%) patients. Nineteen (23.8%) patients were on regular blood transfusion every 4-6 weeks. As regard to iron chelating agents (IV deferoxamine 30-50 mg/kg which was taken by 55 patients and oral deferiprone75-100 mg/kg in 3 divided doses, which was taken by 21 patients), 21 (26.3%) patients were compliant with treatment, while 55 (68.7%) patients were not, and 4 (5%) patients did not receive iron chelating therapy at all. As shown in Table 1, 48 (60%) patients were found to have severe vitamin D deficiency (<10 ng/ml), 12 (15%) patients had low calcium levels (< 8.5 mg/dl) and 62 (77.5%) patients had ferritin levels more than 1000 ng/dl. With respect to DEXA scan, we found the following results: DEXA score at right forearm ranged between (-7.6 and 0.60) with a mean of (-4.2 ± 1.8), DEXA score at left femur ranged between (-3.6 and 0.90) with a mean of (-1.3 ± 1.1) and DEXA score at AP-spine ranged between (-6.9 and 2) with a mean of (-3.04 ± 1.5). See also Fig. 1.

Table 1. Vitamin D, calcium, and ferritin levels among the study group

Variables	Number (n=80)	%
Vitamin D level		
Severe deficiency (< 10 ng/ml)	48	60%
Deficiency (< 20 ng/ml)	21	26.3%
Insufficiency (< 30 ng/ml)	4	5%
Sufficiency (30-100 ng/ml)	6	7.5%
Toxicity (> 100 ng/ml)	1	1.3%
Low calcium levels	12	15%
High ferritin levels (>1000 ng/ml)	62	77.5%

As shown in Table 2: there was statistically significant difference between number of sites affected and history of splenectomy, where (40.6%) of those who underwent splenectomy had affection in the 3 sites examined.

Twenty-five (31.2%) patients had symptoms of hypogonadism (8 males and 17 females). Table 3 illustrates the relation between hypogonadism and DEXA scan results among the study group.

As we found hypocalcemia (< 8.5 mg/dL) in 12 patients (15%), we tried to investigate its impact on DEXA results in the 3 sites where we found statistically significant difference with p-value of 0.002 and 0.009 between hypocalcemic patients and those having normal calcium levels as regard DEXA score at left femur, and AP-spine respectively with high mean DEXA score among normocalcemic patients in these 2 sites (see Table 4).

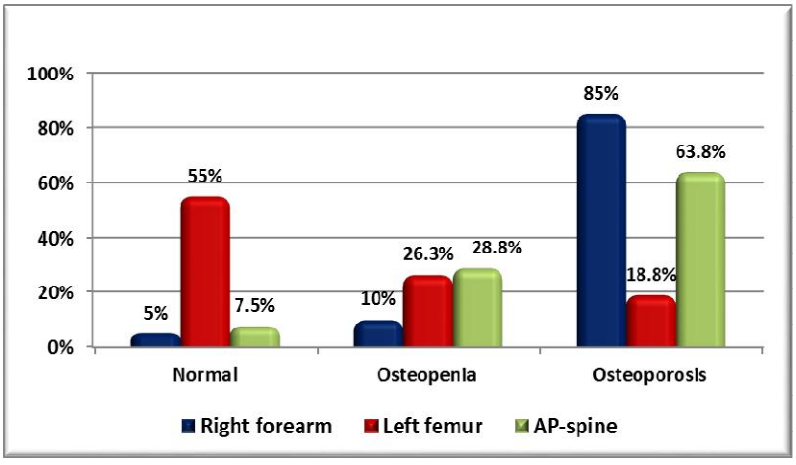

Fig. 1. Description DEXA scan results at different sites among the study group

Table 2. Relationship between DEXA results at different sites and history of splenectomy

Variables	Splenectomy				p-value	Sig.
	No (n=11)		Yes (n=69)			
	No.	%	No.	%		
Number of sites						
No	1	9.1%	0	0%	0.02	S
One site	1	9.1%	6	8.7%		
Two sites	8	72.7%	35	50.7%		
Three sites	1	9.1%	28	40.6%		

Table 3. Relation between hypogonadism and DEXA scan results among the study group

RT–forearm DEXA results			P-value
Normal (n=4)	**Osteopenia (n=8)**	**Osteoporosis (n=68)**	
Mean ±SD	**Mean ±SD**	**Mean ±SD**	
Males 0/1 (0%)	0/3 (0%)	8/33 (24.2%)	<0.001
Females 0/3 (0%)	0/5 (0%)	17/35(48.6%)	<0.001
LT- femur DEXA results			
Normal (n=44)	**Osteopenia (n=21)**	**Osteoporosis (n=15)**	
Mean ±SD	**Mean ±SD**	**Mean ±SD**	
Males 1/21(4.8%)	2/10(20%)	5/6(83.3%)	<0.001
Females 3/23(13%)	5/11(45.5%)	9/9(100%)	<0.001
AP-spine DEXA results			
Normal (n=6)	**Osteopenia (n=23)**	**Osteoporosis (n=51)**	
Mean ±SD	**Mean ±SD**	**Mean ±SD**	
Males 0/3(0%)	0/10(0%)	8/24(33.3%)	0.06
Females 0/3(0%)	2/13(15.4%)	15/27(44.4%)	0.01

Table 4. Relation between serum calcium levels and DEXA scan results among the study group

Variables	Hypocalcemic (<8.5mg/dl) (N=12)		Normocalcemic (≥8.5mg/dl) (N=68)		p-value
	Mean	SD	Mean	SD	
Right forearm	-4.9	2.1	-4.1	1.7	0.1
Left femur	-2.2	1.2	-1.1	0.9	0.002
AP-spine	-4.1	1.7	-2.9	1.4	0.009

Moreover, we noted a statistically significant difference with p-value of 0.02 between vitamin D levels and different DEXA results at right forearm while the difference was statistically non-significant in the other 2 sites as shown in Table 5.

Regarding the relation between blood glucose levels and DEXA scan results in our patients, results are shown in Table 6.

In addition, we investigated the relation between different types of treatment and DEXA scan results in our thalassemic patients. The results are shown in Table 7.

There was statistically significant difference with p-value of 0.05 between results of DEXA scores at right forearm and compliance with iron chelating agents where 62.5% of osteopenic patients had been receiving iron-chelating agents regularly. 73.5% of patients with osteoprosis were not compliant with treatment.

There was also a statistically significant difference with p-value of 0.04 between results of DEXA scores at right forearm and blood transfusion as 75% patients who received regular blood transfusion showed normal DEXA results, 79.4% patients who received irregular blood transfusion had osteoporosis at right forearm.

On the other hand, there was non- statistically significant difference with p-value of 0.1 between results of DEXA scores at left femur and compliance with iron chelating agents.

There was statistically significant difference with p-value of 0.02 between results of DEXA scores at left femur and blood transfusion where (38.6%) of patients who received regular blood transfusion had normal DEXA results, 100% of patients who received irregular blood transfusion had osteoporosis at left femur.

We also found a statistically significant difference with p-value of 0.03 between results of DEXA scores at AP spine as regards to blood transfusion with high percentage of osteopenia among patients who received regular blood transfusion (47.8%). 45 patients (88.2%) who received irregular blood transfusion had osteoporosis at AP-spine.

As shown in Table 8: there was statistically significant positive correlation (r=0.29, p=0.008) between right forearm DEXA scores and calcium levels, and significant negative correlation with 2 hours post-prandial blood glucose and ferritin levels.

Regarding DEXA scores at left femur, a significant positive correlation was observed with vitamin D (r= 0.3, p= 0.001) and calcium (r=0.32, p= 0.05) levels, and a significant negative correlation with the following variables: FBG, 2h postprandial blood glucose and ferritin levels.

Table 5. Comparison between DEXA results and vitamin D levels among study group

	RT–forearm DEXA results			**P-value**
	Normal (n=4)	**Osteopenia (n=8)**	**Osteoporosis (n=68)**	
	Mean ±SD	**Mean ±SD**	**Mean ±SD**	
	12±19	14±13.6	12.1±15.7	0.9
	LT-femur DEXA results			**P-value**
Vitamin D	**Normal (n=44)**	**Osteopenia (n=21)**	**Osteoporosis (n=15)**	
	Mean ±SD	**Mean ±SD**	**Mean ±SD**	
	15.1±20	9.7±5.6	7.5±6.1	0.2
	AP-spine DEXA results			**P-value**
	Normal (n=6)	**Osteopenia (n=23)**	**Osteoporosis (n=51)**	
	Mean ±SD	**Mean ±SD**	**Mean ±SD**	
	32±42.7	14.3±14.2	9±7.1	0.002

Table 6. Comparison between DEXA results in relation to FBG and 2hPPBG levels among study group

	RT–forearm DEXA results			**P- value**
	Normal (n=4)	**Osteopenia (n=8)**	**Osteoporosis (n=68)**	
	Mean ±SD	**Mean ±SD**	**Mean ±SD**	
FBG (mg/dl)	85.5±6.2	80.1±5.4	86.4±35.6	0.9
2 hours PPBG (mg/dl)	106±11.6	102.5±9.6	113.6±52.9	0.8
	LT-femur DEXA results			**P-value**
	Normal (n=44)	**Osteopenia (n=21)**	**Osteoporosis (n=15)**	
	Mean ±SD	**Mean ±SD**	**Mean ±SD**	
FBG (mg/dl)	79.9±5.9	83.4±16.4	106.2±71	0.02
2 hours PPBG (mg/dl)	102.6±11.7	110±27	142.8±104.1	0.02
	AP-spine DEXA results			**P-value**
	Normal (n=6)	**Osteopenia (n=23)**	**Osteoporosis (n=51)**	
	Mean ±SD	**Mean ±SD**	**Mean ±SD**	
FBG (mg/dl)	78±5.4	80.3±6.5	89.1±40.7	0.5
2 hours PPBG (mg/dl)	93±6.7	102.7±10.5	118.5±60.2	0.02

Table 7. Relation between different types of treatment and DEXA scan results among study group

	Rt-forearm DEXA results			P-value
	Normal (n=4)	Osteopenia (n=8)	Osteoporosis (n=68)	
	No. (%)	No. (%)	No. (%)	
Iron chelation therapy				
No	1(25%)	0(0%)	3(4.4%)	0.05
Irregular	2(50%)	3(37.5%)	50(73.5%)	
Regular	1(25%)	5(62.5%)	15(22.1%)	
Blood transfusion				
Regular	3(75%)	2(25%)	14(20.6%)	0.04
Irregular	1(25%)	6(75%)	54(79.4%)	
	Lt-femur DEXA results			**P-value**
	Normal (n=44)	Osteopenia (n=21)	Osteoporosis (n=15)	
	No. (%)	No. (%)	No. (%)	
Iron chelating therapy				
No	1(2.3%)	2(9.5%)	1(6.7%)	0.1
Irregular	27(61.4%)	15(71.4%)	13(86.7%)	
Regular	16(36.4%)	4(19%)	1(6.7%)	
Blood transfusion				
Regular	17(38.6%)	2(9.5%)	0(0%)	0.002
Irregular	27(61.4%)	19(90.5%)	15(100%)	
	AP-spine DEXA results			**P-value**
	Normal (n=6)	Osteopenia (n=23)	Osteoporosis (n=51)	
	No. (%)	No. (%)	No. (%)	
Iron chelating agents				
No	1(16.7%)	0(0%)	3(5.9%)	0.07
Irregular	2(33.3%)	14(60.9%)	39(76.5%)	
Regular	3(50%)	9(39.1%)	9(17.6%)	
Blood transfusion				
Regular	2(33.3%)	11(47.8%)	6(11.8%)	0.003
Irregular	4(66.7%)	12(52.2%)	45(88.2%)	

Table 8. Correlation between different DEXA scores with age and different laboratory data among study group

Variables	DEXA score					
	RT-forearm		LT-femur		AP-spine	
	R	p-value	r	p-value	r	p-value
Age (years)	-0.21	0.06	-0.03	0.8	0.03	0.8
HB	0.16	0.1	0.21	0.07	0.14	0.2
FBG	-0.21	0.06	-0.28	0.01	-0.31	0.006
2 hours PPBG	-0.23	0.04	-0.30	0.007	-0.34	0.002
Vitamin D	0.14	0.2	0.30	0.008	0.36	0.001
Calcium	0.29	0.008	0.32	0.004	0.22	0.05
Ferritin	-0.42	<0.001	-0.46	<0.001	-0.37	0.001

As regards AP-spine DEXA scores there was a significant positive correlation with p-value of 0.001 and 0.05 between AP-spine DEXA scores and vitamin D and calcium levels, and a significant negative correlation with fasting and 2 h post prandial blood glucose and ferritin levels.

4. DISCUSSION

Osteoporosis represents a prominent cause of morbidity in patients with thalassemia [5].

Many factors contribute to the etiology of low bone mass in patients with β-thalassemia major

including: ineffective erythropoiesis, which leads to bone marrow hyperplasia, growth hormone and sex steroid deficiencies, hypothyroidism, vitamin D deficiency and severe anemia with presumed, but poorly characterized reduced physical activity. Even well transfused patients with normal gonadal function who are supplemented with calcium have been shown to have low bone mass by dual x-ray absorptiometry, suggesting other factors are also involved [6].

In our study, 79 (98.7%) patients had abnormal DEXA findings in the form of: 34 (42.5%) patients were osteoporotic, 6 (7.5%) were osteopenic and 39 (48.7%) had both osteopenia and osteoporosis. These findings were supported by Hashemieh and colleagues [3] who reported abnormal DEXA findings in 274 (84.2%) thalassemia patients (214 (65.5%) patients had osteoporosis and 60 (18.7%) patients had osteopenia).

Our study revealed a statistically significant difference (p = 0.02) between number of sites affected and splenectomy where 28 patients (40.6%) of those who underwent splenectomy had affection in the three sites. Up to our knowledge, no other study correlated BMD with history of splenectomy.

In addition, our study showed non-statistically significant correlation between age and different DEXA scores at RT forearm, LT femur and AP spine (r -0.21, p= 0.06 & r -0.03, p=0.8 and r 0.03, p=0.8 respectively). On the contrary, Izadyar and colleagues [7] reported that there was a significant decrease in the BMD with age (p = 0.001) and they explained this finding based on that normally, peak bone mass is attained shortly after completion of puberty and is stable until the third decade of life. It is just after the age of 30 that age-related bone mineral loss starts. However, in thalassemic patients, this process starts much sooner and progresses more swiftly. Therefore, they concluded that BMD (Z score) significantly deteriorates with age.

In our study, there was statistically significant difference (p = 0.04 and 0.002) between DEXA scores at right forearm and left femur as regard sticking to regular blood transfusion programs with high percentage of normal results being found among patients who received regular blood transfusion.

Nakhakes and colleagues [8] found that mean BMD score in patients with dependent blood transfusion is generally less than in those with independent blood transfusion.

Our study found a statistically significant difference (p = 0.05) between DEXA scores at right forearm and compliance with iron chelating agents where osteopenic changes (62.5%) were more prominent in those who were compliant with treatment (this may be explained by the adverse effect of these agents on osteoblasts), while osteoporotic changes (73.5%) were more evident among those who were not. This finding was inconsistent with Izadyar and colleagues [7] who found that there was no association between the frequency or regularity of treatment with iron chelating therapy and BMD (p = > 0.2).

Vitamin D deficiency is prevalent in many patients with β-thalassemia major and vitamin D replacement therapy has been shown to increase IGF-I secretion which is vital for skeletal health [9]. As regards 25 (OH) vitamin D levels, our study revealed that 48 (60%) patients had severe deficiency, 21 (26.3%) had deficiency, while 4 (5%) had insufficient and 6 (7.5%) had sufficient levels, and 1(1.3%) had toxic level.

Similar results were obtained by Meena and colleagues [2], their study demonstrated that none of the subjects had normal 25(OH) vitamin D levels.

Our study showed a positive correlation between DEXA scores (at AP-spine and left femur) and vitamin D levels (r = 0.36 and r = 0.30). Supporting our results, Singh and colleagues [1] showed a significant influence of serum vitamin D on Z score of BMD at lumbar spine in their studied group of patients (r = 0.422, P =0.031). In addition, Meena et al., [2] observed a positive correlation between BMD and vitamin D levels at the three sites (r =0.086, 0.0236 and 0.0236 at lumbar spine, distal radius and left femur respectively) but it was not statistically significant (p = 0.641, 0.193 and 0.194 at lumbar spine, distal radius and left femur respectively). In contrast, Merchant and colleagues [10] found no difference in vitamin D levels between thalassemic patients with or without evidence of osteopathy.

Moreover, Tzoulis and colleagues [11] found no association between vitamin D status and low bone mass.

In our study, there was a negative correlation between BMD and ferritin levels at RT forearm, LT femur and AP spine (r -0.42, p = <0.001& r -0.46, p=<0.001 and r -0.37, p=0.001 respectively). Morabito and colleagues [12]

demonstrated that, BMD on lumbar spine and femoral neck was inversely related to serum ferritin levels which could account for direct or indirect bone damage by iron overload status. Meanwhile, Wong and colleagues [13] found that there was no significant relationship between serum ferritin levels and *Z*-scores at the lumbar spine or femur neck.

In addition, we found a negative correlation between the following variables:

- 2HPP blood glucose and DEXA scores at RT forearm, LT femur and AP spine (r-0.23, p = 0.04& r-0.30, p=0.007 and r-0.34, p=0.002 respectively).
- FBG and DEXA scores at LT femur and AP spine (r-0.28, p=0.01 and r-0.31, p=0.006 respectively).

The contribution of diabetes mellitus in the pathophysiology of bone complications in thalassemic patients was not well evaluated, and we found few studies in literature, which correlate diabetes mellitus and BMD. One study showed that thalassemic patients with diabetes had higher rates of very low BMD compared to those with normal blood glucose levels [14]. While Baldini and colleagues [15] found that the presence of diabetes did not distinguish thalassemic patients without osteopathy from osteopathic ones.

Our study showed statistically significant difference (p = 0.001) between DEXA score at left femur and hypogonadism among males and females and a statistically significant difference at right forearm and AP spine among females only (p = 0.04 and 0.01), with higher evidence of osteoporosis among patients with history of hypogonadism. This is supported by Izadyar and colleagues [7] who found a significant relationship between bone mineral loss and history of gonadal dysfunction and stated that the anabolic effects of sex steroids in bone are essential, not only for the acquisition of bone mass during adolescence and puberty, but also for the maintenance of peak bone mass during adulthood.

In our study, 12 (15%) patients had low calcium level. Merchant and colleagues [10] evaluated the prevalence of osteopathy in β-thalassemia major patients by bone mineral densitometry and biochemical indices on 42 regularly transfused Indian thalassemic patients, found that 7 (16%) patients had hypocalcemia and 16 (37%) patients had high alkaline phosphatase levels. In contrast, Modi and colleagues [16] reported no alteration in the calcium and phosphate levels in thalassemia patients.

We also found a positive correlation between calcium levels and BMD at all three sites, namely, lumbar spine (r = 0.22, P = 0.05), RT forearm (r = 0.29, P =0.008) and LT femur (r = 0.32, P = 0.004). This was supported by Meena and colleagues [2] who reported a positive correlation between calcium levels and BMD at all three sites, namely, lumbar spine (r = 0.116, P = 0.526), distal radius (r = 0.063, P = 0.733) and neck of femur (r = 0.392, P = 0.026). While Izadyar and colleagues [7] reported that there was no significant correlation between serum concentrations of calcium and BMD of hips and spines (all p values were more than 0.1).

5. CONCLUSIONS

Our study concluded that:

- Seventy-nine (98.7%) patients had abnormal DEXA findings (osteopenia and osteoporosis) with high prevalence in the right forearm and lumbar spine.
- 15 % of the patients had low calcium level with higher mean DEXA score among patients with normal level of calcium. BMD positively correlated with calcium on RT forearm, LT femur and AP spine.
- Vitamin D deficiency/insufficiency prevalence was detected in 73 patient (91.2%) and BMD positively correlated with vitamin D on left femur and AP spine
- BMD negatively correlated with ferritin in RT forearm, LT femur and AP spine and negatively correlated as well with 2HPP blood glucose levels in RT forearm, LT femur. Twenty-five (31.2%) patients had hypogonadism with statistically significance difference between DEXA results at left femur as regards to hypogonadism among males and females.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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