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Bone Mineral Density in Patients with Phenylketonuria in Iran

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Abstract

Background: Factors like low-protein diet may impose Phenylketonuria (PKU) patients to impaired skeletal disease. The present study assessed the status of Bone Mineral Density (BMD) among PKU patients on a low-protein diet.

Methods: A cross-sectional study was conducted (Tehran, Iran, 2019). Patients aged ≥ 4 years old with a definite diagnosis of PKU on a low-protein diet were included. BMD values of the lumbar spine and femoral neck were assessed. The primary objective was assessing femoral and lumbar BMD status in PKU patients.

Results: Forty-one PKU patients entered the study. The mean BMI was 20.712±4.833 Kg/m2. The mean bone age was significantly lower than chronological age (10.9 vs. 12.4 years; P=0.008). The results showed a bone mass reduction in 23.1% of all patients. A significant correlation was observed between lumbar and femoral BMD values (P=0.001; r=0.516). Most patients (about 77%) had lumbar Z-scores>-1 and 10.3% showed Z-scores in the range of osteoporosis. Age (P=0.004) and age at diagnosis (P=0.002) were the influencing factors on BMD status. The results showed a significantly inverse correlation between BMD lumbar levels with the patient's chronological age (P=0.016), age of PKU diagnosis (P=0.002), and phenylalanine level (P=0.025)

Conclusion: The results delineated impaired skeletal status among PKU patients on a low-protein diet. Lumbar Z-score values inversely correlated with the patient's chronological age, age at PKU diagnosis, and phenylalanine level. Hence, early PKU diagnosis and treatment during neonatal period, as well as controlling phenylalanine concentration may improve BMD status.

Key Words: Bone mineral density, Osteopenia, Osteoporosis, Phenylketonuria.

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1- INTRODUCTION

Phenylketonuria (PKU) with a prevalence of 1 per 10000 is an autosomal recessive disease that disturbs phenylalanine metabolism resulting in its accumulation. PKU is responsible for severe and long-term morbidities like brain dysfunction, epilepsy, behavioral, and neurodevelopmental complications. (1, 2). The prompt diagnosis and early treatment with a prescription of a low phenylalanine diet can alleviate adverse outcomes and improve the life quality of PKU patients (3).

Inadequate bone mass acquisition is also seen in PKU patients (4). Although the exact reason for the low bone mineral density (BMD) remains in a state of ambiguity, there are some explanations. It is thought that a low protein diet that is consumed to control metabolic disorders, may influence bone density (5, 6, 7). Low adherence to diet and inadequate control of plasma phenylalanine level may also be the other reasons (8, 9).

Although PKU screening has been implemented in Iran since 2007, there are factors like consanguineous marriage, region, and ethnicity-related mutations that may be responsible for the high frequency of PKU (10, 11). Herein, we assessed the BMD status among PKU patients. Furthermore, the effects of different demographic and clinical variables on BMD values were evaluated to find any risk factor for impaired skeletal status in PKU subjects on a low-protein diet.

2- MATERIALS AND METHODS

A cross-sectional study was conducted in the Endocrine and Metabolic Clinic, in the Children's Medical Center affiliated to Tehran University of Medical Sciences. (Tehran, Iran, 2019). Patient's ≥ 4 years of age with a definite diagnosis of PKU were included in the study. PKU was diagnosed in most of the participants through a screening program at the age of 3-5 days. However, in patients over 15 years of age (born before 2007), the diagnosis was delayed due to the lack of implementation of the PKU screening protocol. All included participants were on a low-protein diet from the time of PKU diagnosis. Congenital metabolic disease, skeletal dysplasia, dysostosis, osteogenesis imperfecta, neurologic and skeletal disorders causing limited mobility, and a positive history of receiving prolonged corticosteroid or stem cell therapy were considered as exclusion criteria.

The participants were invited for an interview after receiving written consent from them or their parents. Through history taking, data related to demographic characteristics were collected; anthropometric parameters were measured and the patient's puberty stages (classified in stages 1 to 5) (12) were also identified. Subjects were asked to respond to the questions regarding type of disease, time of treatment initiation, frequency of hospital admission, number of trauma-related or unrelated fractures, taking calcium supplements, and daily routine activity. Physical and mental exams were also performed. Accordingly, ambulation status was assessed based on modified Bleck criteria (13), scored 1-9 ranging from "Non-walkers" to "Community walkers without the use of rehabilitation facilities" (Supplementary 1). The patient's mental health was also evaluated based on clinical observation; the results of mental health examinations were recorded showing the severity of mental retardation (categorized in No, Moderate, and Severe retardation).

Then, the participants were scheduled for paraclinical examinations. To determine BMD and bone age, the patients were sent to the Radiology Department. Using stratose Dual-Energy X-ray Absorptiometry (DEXA) scanner, BMD values (g/Cm^2) of the lumbar spine and femoral neck were assessed. According to

the results, Z score ≥ -1, -1 >Z score> -2, and Z score ≤ -2 were defined as normal, osteopenia, and osteoporosis, respectively (1). Using the Greulich and Pyle method, an X-ray radiography examination of the left hand and wrist was also performed to determine the patient's bone age. The checked levels of blood phenylalanine during the last year were also extracted from the patient's medical record and the mean of phenylalanine was calculated for every patient. Accordingly, to evaluate treatment adherence and disease control, they were classified into 2 groups of good (mean phenylalanine level ≤6 mg/dL) and poor control (mean phenylalanine level>6 mg/dL). All demographic, clinical, and paraclinical data were gathered and recorded in a checklist.

The primary objective of the present study was to assess femoral and lumbar BMD status in PKU patients on a low-protein diet. The frequency of fractures, as well as the relationships between lumbar BMD and demographic variables, was also evaluated as the secondary objectives.

2-1. Sample size

Modan et al. (14) showed the frequency of low BMD in 20% of PKU patients. Considering the power of the study by 95% and alpha error of 0.05, the proposed sample size was calculated at 109. Due to the coincidence of the present study with the COVID-19 pandemic, 41 patients were included.

2-2. Data Analysis

Analyses of data were performed using the Statistical Package for the Social Sciences, version 18.0, SPSS Inc., Chicago, Illinois, USA (SPSS). Qualitative and quantitative variables were expressed in number (%) and mean ± SD, respectively. The relationships between qualitative variables were assessed with the Chi-square and Fisher's exact tests. Normal distribution of quantitative variables was not confirmed by Kolmogorov-Smirnov test. So Mann Whitney and Kruskal-Wallis tests were used to show associations between the quantitative variables and the correlation coefficients between the variables were determined by Pearson's correlation test. $p < 0.05$ was considered as the significance level.

3- RESULTS

Forty-one PKU patients including 19 males and 22 females entered the study. All participants had a low-protein diet. The mean BMI was 20.712±4.8334 Kg/m2 and BMI percentiles in 2 (4.9%), 20 (48.8%), 6 (14.6%), and 13 (31.7%) patients were <5, 5-85, 85-95, and >95. The mean age of the participants was 12.35±7.99 years; the youngest and oldest subjects were 4.5 and 31 years old, respectively. The mean bone age was significantly lower than chronological age (10.9 vs. 12.4 years; P = 0.008). The results showed a bone mass reduction in 23.1% of all patients. The mean age at diagnosis was 1.43±2.68 years (Min=0, Max=10). The pubertal stage of patients was proportionate to their age. Concerning mental health status, 5 cases suffered from severe, and 13 suffered from moderate mental retardation. According to the results of Bleck's modified criteria, motility condition was good in all subjects (mean score= 9). Of all, 2 female patients (4.9%), aged older than 12 years, had a history of fracture. Detailed demographic and clinical data are shown in **Table 1**.

Detailed data regarding femoral and lumbar BMD Z-scores in PKU patients are shown in **Table 2**. The scatter plot distribution of femur and lumbar BMD Z-scores is also shown in **Fig. 1**. The results showed a significant correlation between lumbar and femoral BMD values among PKU patients (P=0.001; Spearman correlation coefficient = 0.516). Of all included PKU participants, the majority of them (about 77%) had lumbar Z-scores>-1 and 10.3% showed Z-scores in the range of osteoporosis.

Table-1: The patients' detailed demographic and clinical data

Variables		Number (N=41)	Percent (%)
BMI percentile (Mean ±SD)		60.24±34.916	-
BMD status	Normal	30	76.9
	Osteopenia	5	12.8
	Osteoporosis	4	10.3
Coordination of bone and chronological ages	Normal	8	19.5
	Delayed	33	80.5
Disease control (based on mean phenylalanine level)	Good	17	42.5
	Poor	23	57.5
Mental health status	Severe retardation	5	12.2
	Moderate retardation	13	31.7
	No retardation	23	56.1
Tanger stage	1	20	48.8
	2	4	9.8
	3	2	4.9
	4	8	19.5
	5	7	17.1
Lumbar Z-score (Mean ±SD)		0.16±1.65	-
Femur Z-score (Mean ±SD)		-0.85±1.34	-
Height (Mean ±SD)		140.44±23.33	-
Height percentile (Mean ±SD)		56.34±27.47	-
Weight (Kg; Mean ±SD)		43.54±21.25	-
Weight percentile		61.93±30.84	-
Phenylalanine during the last year (mg/dL; Mean ±SD)		7.61±4.3462	-

Table-2: Femur and lumbar spine BMD in PKU patients with different ages

Variable		Age group (Years)		
		4-11	12-18	19-31
Femur BMD (g/Cm)	Number (%)	23 (56.1)	10 (24.4)	8 (19.5)
	Mean	-0.6	-0.3	-1.0
	Median	0	0	-1
	Lowest	-3	-2	-2
	Highest	1	0	0
	Range	4	2	2
	SD	0.2	0.7	0.9
Lumbar spine BMD (g/Cm)	Mean	0.7	-0.2	-1.0
	Median	0	0	-1
	Lowest	-2	-2	-2
	Highest	4	1	0
	Range	6	3	2
	SD	1.4	0.8	0.9

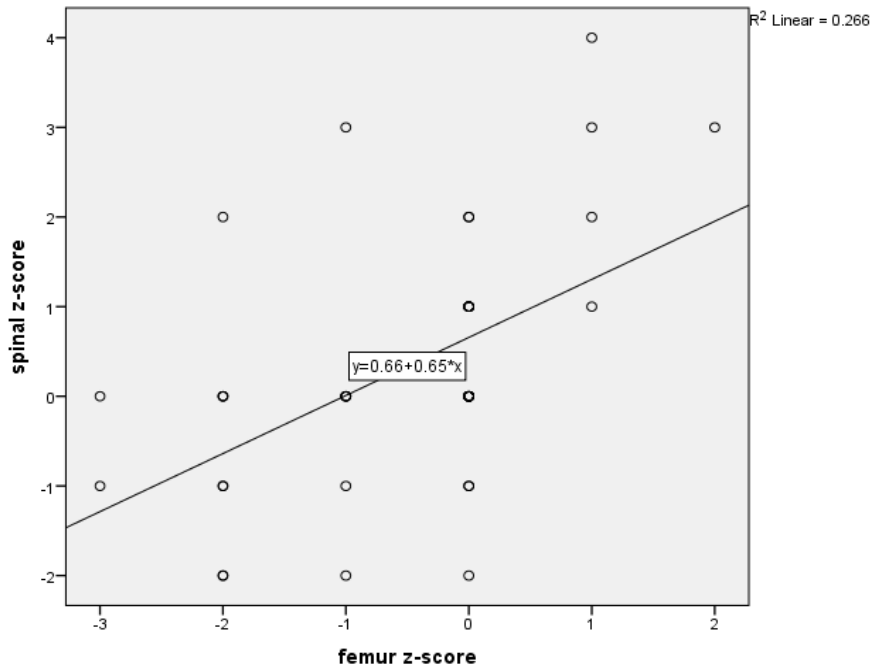

Fig. 1: Scatter plot diagram showing bone mineral density distribution in PKU patients

Using Mann Whitney and Kruscal-Walis tests, it was found that age was an influencing factor on BMD status. The frequency of osteopenia or osteoporosis was significantly lower among younger patients (P=0.004) or those who were diagnosed earlier in the neonatal period (P=0.002). On the other hand, there were no statistical differences between BMD Z-score groups regarding patient's gender (P=0.77), mental status (P=0.425), BMI (P=0.502), bone fracture (p=0.729), or mean phenylalanine level (P=0.182). Detailed data are shown in **Table 3**.

Table-3: Comparison of variables between three groups of normal BMD (-1<Z-score), osteopenia (-1<Z-score<-2), and osteoporosis (Z-score>-2)

BMD (n %)		Z-score<-2	-1<Z-score<-2	-1<Z-score	P value
Age (years)	4-11	0	3 (13)	20 (87)	0.018
	12-18	0	2 (20.0)	8 (80)	
	19-31	4 (66.4)	0	2 (33.2)	
Gender	Male	2 (11.1)	3 (16.7)	13 (72.2)	0.777
	Female	2 (9.5)	2 (9.5)	17 (81)	
Fracture		0	0	2 (5.7)	0.729
Disease control	Poor	3 (18.8)	2 (12.5)	11 (68.8)	0.342
	Good	1 (4.3)	3 (13.0)	19 (82.6)	
Age at diagnosis	Neonatal	1 (3.3)	2 (6.7)	27 (90.0)	0.002
	Non-neonatal	3 (33.3)	3 (33.3)	3 (33)	
Mental status	Severe	1 (25)	2 (16.7)	1 (4.3)	0.425
	Moderate	1 (25)	2 (16.7)	2 (8.7)	
	No	2 (50)	8 (66.7)	20 (87.7)	
phenylalanine	Mean	12.47	7.960	6.63	0.182

The correlations between BMD lumbar levels and different quantitative variables were also assessed by Spearman's analysis. The results showed a significantly inverse correlation between BMD lumbar levels and the patient's chronological age (P=0.016). Lumbar Z-score was also significantly correlated with age of PKU diagnosis (P=0.002) and phenylalanine level (P=0.025) (**Table 4**).

Table-4: Correlations between the patients' lumbar Z-scores and different quantitative variables

Variables	Correlation Coefficient	P value
Age (year)	-0.384	0.016
Age at diagnosis (year)	-0.485	0.002
Mean phenylalanine level	-0.360	0.025
BMI	0.111	0.502

4- DISCUSSION

The prevalence of PKU in Iran is about 1 in 5000 births, and annually 300-400 PKU neonates are born (15). To prevent severe morbidities, PKU subjects should take a low-protein diet. This diet may put them at risk of skeletal comorbidities (16). Hence, in the present study, we assessed femoral and lumbar BMD status in PKU patients on a low-protein diet and the results showed impaired skeletal status among our PKU cases.

According to the results, the frequency of bone mass reduction among included PKU patients was 23.1% (Osteopenia: 12.8%; Osteoporosis: 10.3%). Other studies revealed various ranges of low BMD frequency in PKU patients from 4.5% to 62% (5, 17, 18, 19). It seems that several factors like participants' age, assessed skeletal sites, BMD-evaluating techniques, implementation of newborn screening protocol, and identified criteria for osteopenia or osteoporosis could affect the reported frequency rates. Consistent with our finding, a systematic review study in 2020 (4) demonstrated low BMD values in PKU patients in all 8 included studies. Another systematic review and meta-analysis in 2015 (20) reported significantly lower BMD in PKU patients compared to the controls in 10 out of 11 included articles. Aggarwal et al. also observed osteoporosis in 14% of PKU subjects through assessing BMD in at least one skeletal site (17). On the other hand, Tansek et al. showed no significant difference in BMD status among the treated and untreated PKU patients (7).

The results of the present study showed that most of the participants had normal lumbar Z-scores (>-1). In line with our finding, Lubout et al., in a multicenter investigation, demonstrated a normal range of BMD values in PKU cases but significantly lower levels in comparison with BMD status in the general population (21).

Our findings, further, revealed that mean bone age was significantly lower than chronological age. This growth restriction may be related to the presence of another underlying disease, malnutrition or modified diet (low protein food and protein substitutes), or hormonal alterations (6). In contrast, Castro et al. showed that BMD values in PKU patients were not lower than the expected values for patients' ages (4).

Assessing BMD status, different skeletal sites like spine, femoral neck, radius, hip, and total body have been reported (4, 17, 21). Our results showed a significant linear

correlation between lumbar and femoral BMD values among PKU patients. This finding may show the importance of the femoral neck in assessing BMD status. In addition, it may propose no need for measuring BMD at different sites that impose extra economic and interventional burdens; however, further investigations with larger sample sizes are needed to confirm our findings.

The present study found that the patient's age and age at diagnosis were significantly different between the groups of normal and low BMD status. Accordingly, older age and delayed diagnosis were the risk factors of impaired bone density. Eighty-seven percent of 4-11-year-old PKU patients had normal BMD Z-scores while about 66% of 19-31-year-old patients had Z-score<-2. Moreover, 90% of the patients with PKU diagnosis at the neonatal period had normal BMD Z-scores. In accordance with our findings, de Castro et al. in their systematic review (4) demonstrated the beginning of mineralization defects in the neonatal period of PKU patients and disease deterioration through childhood, adolescent, and older-aged periods. Otherwise, early PKU screening at birth and dietary treatment result in profoundly improved outcomes (22).

Based on the results, there were inverse correlations between the lumbar Z-score level and the patient's chronological age, age at PKU diagnosis, and phenylalanine concentration. Regarding the correlation between the lumbar Z-score and the patient's chronological age, de Groot (23) confirmed our results. Barta et al., (24) also demonstrated the deterioration of skeletal complications with advances in age among PKU cases. Concerning age at PKU diagnosis, several investigations have pointed to a higher risk of osteopenia in PKU patients with earlier diagnosis and treatment (20, 24, 25), while our results demonstrated that early diagnosis could improve BMD values in patients. It is speculated that early PKU diagnosis and administration of minerals-fortified formulas could decrease the risk of low BMD in our participants.

Although we could not find any significant difference in phenylalanine levels among three groups of normal and low BMD statuses, further analyses demonstrated a reverse correlation between the quantitative value of lumbar Z-score and phenylalanine concentration. Barat et al. (19) reported that PKU patients with BMD Z-scores<-1 had higher levels of phenylalanine (p=0.006). Another investigation indicated that high phenylalanine concentration was the most inversely influencing factor on BMD status (26). On the other hand, de Groot et al. (23) showed that neither phenylalanine concentration nor its variation in the recent year were significant factors affecting BMD Z-scores. Furthermore, a systematic review indicated no relationship between phenylalanine level and BMD in 71% of the studied population (9).

Based on the results, the frequency of fracture among our participants was lower (4.9%) than the rates reported by other studies (about 20%) (9, 14). Furthermore, we could not find any relationship between fracture and bone density. This finding may be related to underestimation of fracture numbers in the included population, the small sample size with different age groups, and not evaluating the risk factors like lifestyle, nutritional status, or doing sports. Although this association has been observed in adult patients, it is still debatable in children. Other investigations have suggested an association between fracture and BMD, particularly in PKU patients with older ages (27, 28). A systematic review pointed to the results showing a higher risk of fracture in PKU patients older than 8 years (4) and another study showed 2.6 times higher fracture rates in PKU cases older

than 8 years compared to their health counterparts (9).

In contrast to the findings of Lubout et al. (21), we could not find any significant difference in gender between the groups of normal and low BMD status. Moreover, as the mean Bleck score in the included patients was high, no relationship was observed between BMD and motor ability in our study. The stage of puberty was also assessed in the present study, and it was found that this variable was proportionate to patients' ages.

It seems that implementing the PKU screening protocol as well as early neonatal treatment in Iran has alleviated disease consequences and improved the life quality of the patients (29, 30). Nonetheless, bone health is still a concern in patients with metabolic disease under certain diets. Considering nutritional status, supplementation, proper physical activity, and appropriate disease control may reduce the severity of skeletal complications.

4-1. Limitation of the study

The main limitation of the present study was the small sample size. To determine the possible association between bone density and fracture, investigations with prolonged follow-up periods are suggested. We assessed the mean of phenylalanine concentration during a year and we did not consider its alteration during a prolonged period. Finally, nutritional status and blood biochemical factors were not evaluated in the study. Including these variables will certainly provide more informative data.

5- CONCLUSION

The results of the present study delineated impaired skeletal status among PKU patients on a low-protein diet. Older-aged patients and delayed PKU diagnosis were at higher risks of low bone density. Lumbar Z-score values were inversely correlated with the patient's chronological age, age at PKU diagnosis, and phenylalanine level. Hence, early PKU diagnosis and treatment during the neonatal period, as well as controlling phenylalanine concentration may improve BMD status. Further investigations are needed to confirm our findings.

6- ETHICAL CONSIDERATIONS

Ethics approval was obtained from the institutional review board of Tehran University of Medical Sciences according to the Helsinki Declaration (Approval code; IR.TUMS.CHMC.REC.1399.013).

7- AUTHORS' CONTRIBUTIONS

Dr. A.S., Dr. S.O., and Dr. P.R. carried out the design and coordinated the study. Dr. A.R., Dr. F.A., Dr. F.S. and Dr. R.T., participated in most of the experiments, and prepared the manuscript. The authors read and approved the content of the manuscript.

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9- CONFLICT OF INTEREST

None.

10- AVAILABILITY OF DATA AND MATERIALS

The datasets related to our study are available from the corresponding author on reasonable request.

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