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Evaluation of bone mineral density and biochemical markers in pediatric patients with phenylketonuria

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ABSTRACT

Objectives: Phenylketonuria is a hereditary condition caused by the deficiency of the enzyme phenylalanine hydroxylase, leading to abnormal phenylalanine metabolism. Managing phenylketonuria involves implementing dietary interventions to control phenylalanine levels and prevent complications. However, these treatments can lead to long-lasting negative effects, including impacts on bone health and abnormal biochemical test findings. The aim of the study was to examine the relationship between biological markers and bone density in individuals with phenylketonuria.

Methods: This cross-sectional study was conducted out at Motahari Hospital in Urmia, Iran. The study involved 19 patients with phenylketonuria, examining their demographic information, laboratory findings, and bone density by statistical methods.

Results: The study examined the association between age and bone densitometry outcomes, along with the connection between different biochemical markers and bone densitometry results. The analysis showed no statistically significant link between age and bone densitometry data (P-value = 0.31). The p-values for correlation between bone densitometry and serum calcium, serum phosphorus, phenylalanine, alkaline phosphatase, and 25-hydroxyvitamin D_3 were found to be 0.30, 0.27, 0.57, 0.86, and 0.95, respectively. The only significant relationship was between the result of bone densitometry and alkaline phosphatase levels in the age group below 8 years with a correlation of 0.720 (P-value = 0.01).

Conclusions: The study revealed no association between bone densitometry and levels of serum calcium, serum phosphorus, phenylalanine, and 25-hydroxyvitamin D_3. The only meaningful association was between bone densitometry and alkaline phosphatase in the age group below 8 years.

1. Introduction

Congenital abnormalities encompass a wide range of illnesses that exhibit aberrant biochemistry or morphogenesis, manifesting at birth and resulting in various impacts on morbidity and mortality (1–3). Phenylketonuria (PKU) is a hereditary condition characterized by a dysfunction in the phenylalanine hydroxylase (PAH) enzyme, resulting in aberrant phenylalanine (Phe) metabolism (4). The inheritance pattern for this disorder is autosomal recessive, resulting from mutations occurring in the PAH gene (5). The enzyme in question facilitates the process of converting phenylalanine into tyrosine (Tyr). Untreated patients with PKU have increased amounts of Phe in their blood, which leads to the synthesis of phenylketones that are excreted in the urine (6). Conversely, these individuals generally have relatively low levels of Tyr (5). The management of this disease, as well as other disorders resulting from problems with amino acid metabolism, necessitates the manipulation of the impaired metabolic pathway through the restriction of substrate, the provision of specialized foods containing the necessary

Abbreviations: BMD, Bone Mineral Density; DXA, Dual-energy X-ray Absorptiometry; ICD, International Classification of Diseases; Phe, Phenylalanine; PAH, Phenylalanine Hydroxylase; PKU, Phenylketonuria; Tyr, Tyrosine; Y.O., Years Old.

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amino acids and nutrients, and the supplementation of essential enzyme cofactors (7–9). The primary objective of this intervention is to maintain plasma phenylalanine levels within the range of 120 to 360 μmol per liter until the individual reaches the age of 12 (10–12). Nevertheless, the dietary intervention for PKU has been associated with enduring adverse consequences in its therapy (13,14). A significant negative outcome is the occurrence of bone-related issues (15,16), since skeletal abnormalities were initially identified as one of the outcomes in patients who received initial and ongoing treatment in 1962 by Feinberg and Fisch (17,18). Numerous studies have consistently shown low bone mineral density (BMD) as a substantial risk factor for skeletal fractures in people with PKU (19,20). Due to the significant significance of effective dietary management in children diagnosed with phenylketonuria in mitigating the onset of fundamental complications (21–23), and the available evidence highlighting the adverse impact of this condition and its therapeutic diets on optimal bone mass development (24), it is imperative to identify biochemical factors that can be utilized for the purpose of identification and correction in order to prevent these complications.

2. Materials and methods

2.1. Study design

The current study is a cross-sectional study conducted at Motahari Hospital in Urmia, West Azerbaijan, Iran. The study was approved by The Ethics Committee of Urmia University of Medical Sciences.

2.2. Patient selection

The study selected patients based on precise inclusion and exclusion criteria. Patients were selected based on the following inclusion criteria: (1) confirmed diagnosis of phenylketonuria, (2) ongoing treatment with phenylalanine restriction diet without Sapropterin supplementation, and (3) complete records of bone densitometry and laboratory results.

Patients with age over 18 were excluded. Patients who hadn't given informed consent were removed since their voluntary decision to participate was essential for ethical research methods. Patients with incomplete medical data, particularly those missing bone densitometry and laboratory test findings, were not included. Participants were found through the institutional medical record search engine using the International Classification of Diseases (ICD) 9 and 10 codes for Phenylketonuria (25,26). There were 37 patients in the database between January 2012 and January 2024. Each patient's first medical record containing bone densitometry and complete laboratory test findings was chosen. All blood samples were collected after an overnight fast. Of the 37 cases, 17 lacked complete records with the necessary data. Furthermore, one patient was over 18 years old, leading to a total sample size of 19 patients for the study.

2.3. Data extraction

Demographic data (age and gender), laboratory parameters, and bone densitometry results were collected at a single time point. Laboratory measurements included serum calcium, phosphorus, alkaline phosphatase, phenylalanine, and vitamin D levels. Bone mineral density was assessed using dual-energy X-ray absorptiometry (DXA) scans of the spine, femur, and hip, with regions of interest selected according to patient age at a single time point. It is worth noting that 13 DXA scans were performed using Hologic Discovery Wi, 4 using Hologic Explorer, and 2 using Stratos DR.

2.4. Data analysis

This study employed the SPSS 27 statistical software to examine the data. A statistically significant result was defined as a p-value below 0.05. The Kolmogorov-Smirnov test (27) was employed to assess the normality assumption of the data distribution. In the bivariate correlation investigation, Spearman's correlation coefficient was applied for non-parametric variables (28), whereas Pearson's correlation coefficient was utilized for parametric variables (29). Additionally, a non-parametric Mann-Whitney U test was utilized to examine the data within two distinct age groups (30): individuals under the age of 8 and individuals aged 8 years and older.

3. Results

Table 1 provides a summary of the age, biochemical, and densitometry variables for the 19 patients diagnosed with phenylketonuria (PKU) in our study. The participants were categorized into two groups based on their age: those under 8 years old and those 8 years old and above. The biochemical variables examined include serum calcium, serum phosphorus, phenylalanine levels, alkaline phosphatase levels, and 25-hydroxyvitamin D_3 levels. The data for these variables are presented as mean values accompanied by their respective standard deviations.

In Table 2, a bivariate analysis was conducted to assess the correlations between all variables and the results obtained from bone densitometry. Since the variable *age* did not follow a normal distribution, Spearman's correlation coefficient was employed to examine the relationship between age and bone densitometry. Conversely, as the remaining variables were normally distributed, Pearson's correlation coefficient was utilized to evaluate their associations with bone densitometry. The results presented in Table 2 demonstrate that there was no significant correlation observed between age and bone densitometry results (P-value = 0.31). Similarly, no significant correlations were found between the biochemical indices (i.e., serum calcium, serum phosphorus, phenylalanine, alkaline phosphatase, and 25-hydroxyvitamin D_3) and bone densitometry results. Specifically, the correlation coefficients for serum calcium, serum phosphorus, phenylalanine, alkaline phosphatase, and 25-hydroxyvitamin D_3 were found to be $P = 0.30$, $P = 0.27$, $P = 0.57$, $P = 0.86$, and $P = 0.95$, respectively.

Subsequently, a non-parametric Mann-Whitney U test was employed to analyze the data within the age groups, and the data is shown in Table 3. The only significant relationship was between the result of bone densitometry and alkaline phosphatase levels in the age group below 8 years with a correlation of 0.720 (P-value = 0.01).

4. Discussion

Several research have investigated the correlation between bone density and parameters such as age, calcium, phosphorus, phenylalanine, alkaline phosphatase, and 25-hydroxyvitamin D3.

As an example, Al-Qadreh's research found a significant link between age and bone density (31). In contrast, De Groot's study did not discover a notable connection between age and Z-scores of bone mineral density (32). Miras also found no significant correlation between age and Z-scores of bone mineral density, regardless of the presence of mineral bone disease (33). Our investigation found no significant correlation between age and bone densitometry results (P-value = 0.31).

De Groot discovered a significant link between high blood calcium levels and decreased bone mineral density (32). Aggarwal's study showed a moderate connection between femoral and radial bone mineral density and serum calcium levels (34). Al-Qadreh's study did not find a significant correlation between bone density and calcium levels (31). Also, Adamczyk discovered no significant variations in total calcium and ionized calcium levels among different subgroups of bone mineral densitometry results (35). Lage's study also discovered that there was no link between calcium and bone mineral density (36). During our analysis, we did not find any notable correlations between calcium levels and bone densitometry results (P-value = 0.30).

De Groot found that individuals with reduced bone mineral density had significantly elevated blood phosphorus levels in comparison to

Table 1
Means and standard deviations of age, biochemical indices, and bone densitometry measurements for patients with phenylketonuria.

	< 8 y.o			≥ 8 y.o			All			Units
	Male ($n = 6$)	Female ($n = 5$)	Total ($n = 11$)	Male ($n = 2$)	Female ($n = 6$)	Total ($n = 8$)	Male ($n = 8$)	Female ($n = 11$)	Total ($n = 19$)	
Age	4.5 ± 2.63	5.60 ± 1.67	5.00 ± 2.21	13.50 ± 6.36	10.50 ± 3.72	11.25 ± 4.20	6.75 ± 0.29	8.27 ± 3.82	7.63 ± 4.43	years
Serum Calcium	9.65 ± 0.22	9.95 ± 0.31	9.79 ± 0.29	9.68 ± 0.16	9.88 ± 0.44	9.83 ± 0.39	9.66 ± 0.19	9.91 ± 0.37	9.80 ± 0.33	mg/dl
Serum Phosphorus	5.17 ± 0.43	4.36 ± 0.56	4.80 ± 0.63	4.21 ± 0.15	4.05 ± 0.92	4.09 ± 0.78	4.93 ± 0.58	4.19 ± 0.76	4.50 ± 0.76	mg/dl
Phenylalanine	2319.03 ± 1477.34	5708.00 ± 1218.24	3859.47 ± 2194.81	3474.00 ± 2242.94	2707.03 ± 2630.47	2898.77 ± 2405.65	2607.77 ± 1601.09	4071.10 ± 2551.36	3454.96 ± 2272.50	μmol/dl
Alkaline Phosphatase	522.83 ± 80.77	590.80 ± 111.96	553.73 ± 97.65	407.50 ± 364.16	290.67 ± 121.83	319.88 ± 180.20	494.00 ± 162.65	427.09 ± 192.36	455.26 ± 178.87	Iu/L
25-hydroxyvitamin D_3	33.60 ± 13.39	37.12 ± 13.97	35.20 ± 13.08	33.90 ± 4.66	35.90 ± 16.26	35.40 ± 13.88	33.67 ± 11.45	36.45 ± 14.51	35.28 ± 13.04	ng/ml
Bone Density	−2.11 ± 1.18	−0.54 ± 0.87	−1.40 ± 1.29	−0.90 ± 0.42	−0.93 ± 1.79	−0.92 ± 1.52	−1.81 ± 1.15	−0.75 ± 1.39	−1.20 ± 1.37	z-score

Table 2
Bivariate correlations between lab indices and bone mineral density expressed in terms of *Z*-score in PKU patients.

	Bone Density (Z-score)	
	Correlation Coefficient (r)	P-value
Age	0.24	0.31
Serum Calcium	0.24	0.30
Serum Phosphorus	−0.26	0.27
Phenylalanine	0.13	0.57
Alkaline Phosphatase	−0.04	0.86
25-hydroxyvitamin D_3	−0.01	0.95

Table 3
Non-parametric Mann-Whitney *U* test for analyzing the data within the age groups.

	Correlation with Bone Density			
	< 8 y.o		≥ 8 y.o	
	Correlation Coefficient (r)	P-value	Correlation Coefficient (r)	P-value
Serum Calcium	0.28	0.40	0.20	0.62
Serum Phosphorus	−0.29	0.38	−0.12	0.76
Phenylalanine	0.51	0.10	−0.18	0.65
Alkaline Phosphatase	0.72	0.01*	−0.30	0.46
25-hydroxyvitamin D_3	0.12	0.70	−0.17	0.67

those with normal bone mineral density (32). However, Al-Qadreh's study did not find a significant correlation between bone density and phosphorus levels (31). Our analysis found no significant connections between phosphorus levels and bone densitometry results (*P*-value = 0.27).

Al-Qadreh's study revealed a significant correlation between bone density and phenylalanine levels (31). In contrast, Lage's study could not find any association between phenylalanine and bone mineral densitometry (36). De Groot's study also could not find a significant correlation between average phenylalanine levels or phenylalanine fluctuations and *Z*-scores for bone mineral density (32). Our analysis did not reveal any significant correlations between phenylalanine and bone densitometry results (*P*-value = 0.57).

Koura's study found a negative correlation between alkaline phosphatase levels and bone mineral density (37). But, Al-Qadreh's research did not identify a significant relationship between bone density and alkaline phosphatase levels (31). Our analysis found no significant correlations between alkaline phosphatase levels and bone densitometry results (*P*-value = 0.86). However, a significant relationship was found between bone densitometry and alkaline phosphatase levels in the age group below 8 years with a correlation of 0.720 (P-value = 0.01).

Al-Qadreh's study found no significant correlation between bone density and levels of 25-hydroxyvitamin D3 (31). Lage's research revealed no association between 25-hydroxyvitamin D levels and bone mineral density (36). We also discovered no significant correlations between 25-hydroxyvitamin D3 and bone densitometry data in our study (*P*-value = 0.95).

5. Conclusion

Phenylketonuria is an inherited disorder that arises due to a deficiency in the enzyme phenylalanine hydroxylase, leading to impaired phenylalanine metabolism. Effective management of PKU necessitates the implementation of dietary measures to regulate phenylalanine levels and prevent complications. However, these treatments can lead to long-lasting negative consequences, such as impacts on bone health. The objective of this study is to investigate the correlation between biochemical factors and bone mineral density in patients with PKU. Although there is a lack of substantial correlations between bone densitometry and the majority of commonly used laboratory indices, further investigation using larger sample sizes and more rigorous criteria is necessary to further our understanding of the relationship between PKU, biochemical factors, and bone health. The investigation of improving the management of PKU and optimizing bone health in individuals affected by this condition is a crucial area of scholarly inquiry.

5.1. Study limitations

A limitation in our investigation was the small sample size, which was connected to the specific characteristics of the condition being investigated. One potential solution to this constraint is to widen the scope of data collection to include a larger and more diverse cohort of participants from various geographical regions. Furthermore, future research projects should include multicenter trials to improve the findings' generalizability.

Furthermore, due to the study's retrospective character, the available laboratory data for analysis were limited because certain biochemical indicators are not regularly tested in clinical practice. A prospective study with dedicated funding for the collection specific non-routine laboratory tests would yield more thorough and solid results.

Furthermore, there was little information available about the patients' diets or nutritional intake, which could have a major impact on both bone mineral density and biochemical indicators. Future research should collect specific dietary and nutritional data in order to better examine the potential impact on study findings.

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Ethics approval and consent to participate

The Ethics Committee of Urmia University of Medical Sciences approved the study (Approval Number IR.UMSU.REC.1402.221), which was performed under the principles outlined in the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study. Informed consent was obtained from all individual participants included in the study. Additionally, informed written consent was obtained from parents or guardians of patients who were under 16 years old if they were included.

Consent for publication

The authors affirm that human research participants provided informed consent for publication.

CRediT authorship contribution statement

Akram Ehsasat Vatan: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Amin Mottaghizade Gargari:** Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Arian Haghtalab:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Formal analysis. **Nima Ebrahimpour:** Writing – review & editing, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that support the findings of this study are available from Urmia University of Medical Sciences and Motahari Hospital of Urmia but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Urmia University of Medical Sciences and Motahari Hospital of Urmia.

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