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Vitamin K_2 levels in children and adolescents with bone fractures – a pilot study

Ocena stężenia witaminy K_2 u dzieci i nastolatków ze złamaniami kości – badanie pilotażowe

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Abstract

Introduction and objective: In addition to coagulation, vitamin K_2 influences vascular calcification and skeletal mineral balance. Evaluation of its levels and setting reference ranges are mainly relevant for all populations at risk of osteoporosis. However, only few reports have focused on the developmental age population. The aim of this study was to assess vitamin K_2 levels in children with bone fractures. **Materials and methods:** The study group consisted of 145 children aged 5–17 years, hospitalised for suspected metabolic bone diseases. Patients were divided into three groups: healthy children (n = 68), children with osteogenesis imperfecta (n = 29), and children with traumatic fractures (n = 48). All children were assessed for physical development using established methods, and had their vitamin K_2 levels measured with immunoenzymatic assay (ELISA), using a SunRedBio kit (China). **Results:** The evaluated group of children showed normal somatic development. Children with osteogenesis imperfecta showed lower height and body weight compared to the other groups. Vitamin K_2 ranged from 0.90 to 12.46 ng/mL in 80% of healthy children. Low vitamin K_2 levels (2.7 ng/mL for osteogenesis imperfecta and 2.05 ng/mL for fractures) were found in groups 2 and 3, and did not differ statistically significantly between children considered healthy and patients with bone fractures, including those with osteogenesis imperfecta. **Conclusions:** Children with a history of bone fractures have vitamin K_2 levels within the reference ranges for this age group, suggesting that bone fractures in this group are not associated with vitamin K_2 deficiency.

Keywords: vitamin K_2, children, bone fracture

Streszczenie

Wprowadzenie i cel: Poza układem krzepnięcia witamina K_2 wpływa na procesy kalcyfikacji ścian naczyń krwionośnych i gospodarkę mineralną szkieletu. Oznaczanie jej stężenia i wyznaczanie norm referencyjnych dotyczy przede wszystkich populacji zagrożonych osteoporozą, a niewiele badań przeprowadzono z udziałem populacji wieku rozwojowego. Celem pracy była ocena stężenia witaminy K_2 u dzieci i nastolatków ze złamaniami kości. **Materiał i metody:** Grupę badaną stanowiło 145 dzieci w wieku 5–17 lat hospitalizowanych z powodu podejrzenia zaburzeń mineralizacji kośćca. Pacjentów podzielono na trzy grupy: dzieci z wrodzoną łamliwością kości (n = 29), dzieci z co najmniej dwoma złamaniami pourazowymi (n = 48) i dzieci zdrowe (n = 68). U wszystkich badanych przeprowadzono ocenę rozwoju fizycznego zgodnie z przyjętymi metodami i oceniono stężenie witaminy K_2 metodą immunoenzymatyczną (ELISA) z użyciem zestawu firmy SunRedBio (Chiny). **Wyniki:** Rozwój somatyczny ocenianej grupy dzieci był prawidłowy, u dzieci z wrodzoną łamliwością kości wykazano niższy wzrost i mniejszą masę ciała w porównaniu z pozostałymi grupami. Stężenie witaminy K_2 u 80% dzieci zdrowych wynosiło 0,90–12,46 ng/ml. Stężenia witaminy K_2 w grupach II i III były niskie – w grupie z łamliwością kości 2,7 ng/ml, a w grupie ze złamaniami 2,05 ng/ml – i nie różniły się istotnie statystycznie między dziećmi uznanymi za zdrowe a pacjentami ze złamaniami kości, w tym z wrodzoną łamliwością kości. **Wnioski:** Stężenie witaminy K_2 w badanej populacji dzieci i nastolatków ze złamaniami kości w wywiadzie mieściło się w granicach uznanych za referencyjne dla tej grupy wiekowej, co sugeruje, że u badanych złamania nie były związane z niedoborem tej witaminy.

Słowa kluczowe: witamina K_2, dzieci, złamania kości

INTRODUCTION

The involvement of vitamin K in body's mineral metabolism has aroused an increasing interest in the measurement of its various forms in multiple clinical conditions. In addition to coagulation processes, vitamin K_2 influences vascular calcification and skeletal mineral balance. Vitamin K_2 measurements and attempts at setting its reference values are primarily done in populations at risk of osteoporosis, and only few studies have been conducted in children and adolescents.

Many direct and indirect methods have been used for assessing vitamin K levels in the body. However, uniform standards are missing, which makes it difficult to accurately determine its optimal level and compare the results across different studies, which additionally use different measurement units[1].

According to Mager et al., indirect measurements are sensitive to errors and should therefore be used with caution[2,3]. Indirect methods include prothrombin time, serum uncarboxylated osteocalcin, matrix Gla protein and PIVKA-II, i.e. proteins induced by vitamin K deficiency, as well as urinary vitamin K metabolites (7C-aglycone and 5C-aglycone). Direct measurement of vitamin K and its metabolites is currently the preferred approach[4]. Direct methods for determining vitamin K in humans include high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection, HPLC with fluorescence detection, HPLC with electrochemical detectors (ECD), and liquid chromatography atmospheric pressure chemical ionization tandem mass spectrometry (LC-APCI-MS/MS), which shows the highest sensitivity[1].

Although vitamin K levels have been assessed by many authors using direct approaches, most of the studies have been conducted in adults. Tsugawa et al. determined the mean values of MK-4 and MK-7 (menaquinone with 4 and 7 prenyl units) at 0.07–0.1 ng/mL and 4.21–8.42 ng/mL, respectively, using LC-APCI-MS/MS in a group of women >30 years of age[5]. In 2018, Klapkova et al. used HPLC coupled with fluorescence detection (HPLC-FLD) in postmenopausal women, and determined the mean MK-4 and MK-7 at 0.433 ± 0.394 ng/mL and 1.002 ± 1.020 ng/mL, respectively[6]. Volkan et al. (2018), who used the Human Vitamin K_2 Elis immunological kit to determine vitamin K_2 in a group of children aged 8–14 years (with or without celiac disease), found that it was 2.64 ± 2.1 nmol/L[7]. In 2022, Du and Li showed that the median level of vitamin K_2 was 0.1 ng/mL (interquartile range P25, P75 – 0.1, 0.2) in children aged 1–14 years, using high-performance liquid chromatography tandem mass spectrometry[8].

The aim of this study was to assess vitamin K_2 levels in children and adolescents with bone fractures.

MATERIALS AND METHODS

The study was conducted among 145 children aged 5–17 years, who were admitted to the Department of Paediatrics, Neonatal Pathology and Bone Metabolic Diseases due to suspected bone mineralisation disorders after fractures or were considered healthy, with no history of chronic disorders. The participants were allocated into three groups: children with fractures in the course of congenital bone fragility in group 1 (n = 29), children with fractures without metabolic bone disease in group 2 (n = 48), and children considered healthy in group 3 (controls; n = 68). None of the children were supplemented with vitamin K prior to the study.

All patients had their medical history taken and underwent anthropometric measurements (height and weight, body mass index – BMI). Serum vitamin K_2 was also determined by enzyme-linked immunosorbent assay (ELISA) using a kit from SunRedBio (China). The sensitivity of the kit was 2.225 ng/mL.

R version 4.0.1. was used for statistical analysis. The study was approved by the Bioethics Committee at the Medical University of Lodz (no. RNN/116/17/KE).

RESULTS

No statistically significant differences were found between the three study groups in terms of age, BMI, BMI Z-score or body mass. For body height, it was shown that the groups differed significantly both in absolute and Z-score values. In the case of body weight, the difference between the groups was statistically significant only for the Z-score. Post-hoc analysis showed that group 1 was characterised by a significantly lower mean height and body mass than groups 2 and 3 (Tab. 1).

The analysis of vitamin K_2 levels across the groups is presented in Tab. 2.

Based on the mean and *SD* values for vitamin K_2 levels in group 3, a distribution curve was drawn and an asymmetric, right-sided distribution was obtained (Fig. 1). No extremely low vitamin K_2 levels were observed in this group. This was confirmed by the Shapiro–Wilk test for vitamin K_2 levels in this group ($p < 0.001$) (Fig. 1).

Data distribution other than normal distribution can be presented using deciles, which are a reference point for a given result against the background of the entire group. For this purpose, Tab. 3 presents a decile division for vitamin K_2 in group 3. It was found on its basis that after excluding 20% of children with extreme vitamin K_2 levels, the level ranged between 0.90 and 12.46 ng/mL in the remaining 80% of children.

Then, the levels of vitamin K_2 were assessed across the study groups. The median vitamin K_2 level was 2.05 ng/mL in group 2 and 2.30 ng/mL in group 3. No statistically significant difference in vitamin K_2 levels was confirmed between the two groups (median – MD = −0.25; 95% CI: −0.80, 0.40; p = 0.575) (Tab. 4).

The median vitamin K_2 level was 2.70 ng/mL in group 1 and 2.30 ng/mL in group 3. No statistically significant difference in vitamin K_2 levels was shown between the two groups (MD = 0.40; 95% CI: −0.50, 1.30, p = 0.424) (Tab. 5).

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Variable	Total	Group 1	Group 2	Group 3	*p*
Age [years]	9.98 ± 2.70	9.90 ± 3.72	10.48 ± 2.20	9.66 ± 2.50	0.488
Height [cm]	143.00 (127.25; 157.00)	127.00[a,b] (109.00; 146.00)	144.50[a] (132.38; 160.00)	144.75[b] (129.63; 157.00)	0.006
Height Z-score	0.29 (−0.74; 1.01)	−1.14[c,d] (−3.92; −0.27)	0.35[c,e] (−0.41; 0.86)	0.65[d,e] (−0.11; 1.64)	<0.001
Body weight [kg]	36.00 (25.50; 43.50)	29.00 (17.00; 43.50)	37.50 (30.30; 45.75)	35.75 (26.33; 40.75)	0.155
Body weight Z-score	−0.03 (−0.97; 0.66)	−1.07[f,g] (−2.07; 0.27)	0.20[f] (−0.58; 0.86)	−0.07[g] (−0.69; 0.88)	0.021
BMI	17.23 (14.86; 20.14)	18.11 (14.72; 21.97)	17.89 (15.47; 20.13)	16.38 (14.54; 18.44)	0.072
BMI Z-score	−0.13 (−1.17; 0.78)	0.12 (−1.38; 1.23)	0.14 (−0.81; 0.93)	−0.41 (−1.19; 0.23)	0.157

Data presented as arithmetic mean ± *SD* or as median (Q1; Q3), depending on the normality of distribution. Groups were compared using ANOVA or Kruskal–Wallis test with Dunn's post-hoc test. a–h – statistically significant differences for Dunn's post-hoc test (a: $p = 0.001$, b: $p = 0.002$, c, d: $p < 0.001$, e: $p = 0.048$, f: $p = 0.004$, g: $p = 0.011$).
BMI – body mass index.

Tab. 1. Anthropometric data for the study population by groups

Vitamin K_2 [ng/mL]	*N*	*M*	*SD*	*MD*	Q1	Q3	Min	Max
Total	145	3.85	3.88	2.40	1.30	4.80	0.40	18.10
Group 1	29	4.22	3.86	2.70	1.70	4.90	0.80	15.30
Group 2	48	3.48	3.55	2.05	1.10	4.80	0.60	16.00
Group 1 + 2	77	3.76	3.66	2.40	1.30	4.80	0.60	16.00
Group 3	68	3.94	4.13	2.30	1.28	5.23	0.40	18.10

N – number; ***M*** – arithmetic mean; ***SD*** – standard deviation; ***MD*** – median; **Q1** – first quartile; **Q3** – third quartile; **Min** – minimum; **Max** – maximum.

Tab. 2. Vitamin K_2 levels in the study population by groups

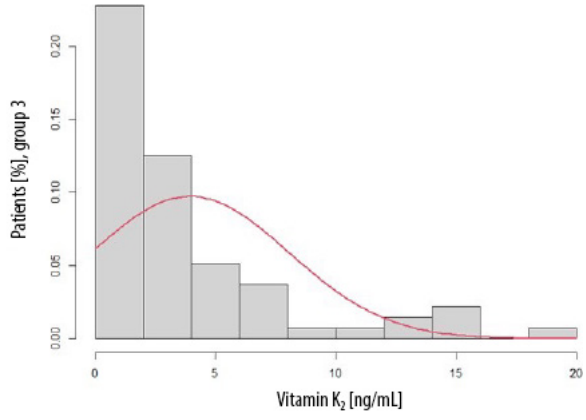

Fig. 1. Histogram for vitamin K2 levels in group 3

After combining groups 1 and 2 into one group and comparing it with group 3 for vitamin K_2 levels, no statistically significant difference was found (*MD* = 0.10; 95% CI: −0.60, 0.60; $p = 0.997$) (Tab. 6).

Decile	Vitamin K_2 [ng/mL]
1st	0.90
2nd	1.00
3rd	1.37
4th	1.70
5th	2.30
6th	3.10
7th	4.08
8th	6.06
9th	10.75

Tab. 3. Decile distribution of vitamin K_2 levels in group 3

	Group 2	Group 3	*MD* (95% CI)	*p*
n	48	68		
Vitamin K_2 [ng/mL]	2.05 (1.10; 4.80)	2.30 (1.28; 5.23)	−0.25 (−0.80; 0.40)	0.575

Data presented as median (Q1; Q3). ***MD*** – difference in medians between both groups with 95% confidence level. Mann–Whitney *U* test.

Tab. 4. Mean vitamin K_2 levels in patients with vs. without bone fractures

	Group 1	Group 3	*MD* (95% CI)	*p*
n	29	68		
Vitamin K_2 [ng/mL]	2.70 (1.70; 4.90)	2.30 (1.28; 5.23)	0.40 (−0.50; 1.30)	0.424

Data presented as median (Q1; Q3). ***MD*** – difference in medians between two groups with 95% confidence level. Mann–Whitney *U* test.

Tab. 5. Comparison of the mean vitamin K_2 levels between groups 1 and 3

	Groups 1 + 2	Group 3	*MD* (95% CI)	*p*
n	77	68		
Vitamin K_2 [ng/mL]	2.40 (1.30; 4.80)	2.30 (1.28; 5.23)	0.10 (−0.60; 0.60)	0.997

Data presented as median (Q1; Q3). ***MD*** – difference in medians between both groups with 95% confidence level. Mann–Whitney *U* test.

Tab. 6. Mean vitamin K2 level in patients with bone fractures (combined groups 1 and 2) vs. group 3

This indicates no relationship between vitamin K_2 levels and bone fractures in the study group of children and adolescents (Tab. 6).

DISCUSSION

Vitamin K plays a major role in coagulation, bone metabolism and vascular calcification. Many methods have been developed to measure vitamin K levels in the body. Vitamin K_1 levels are used to determine vitamin K status, with a level of <0.15 μg/L indicating a deficiency. Factors that increase the risk of deficiency include lipid absorption disorders, malnutrition, renal dysfunction and cancer, as well as neonatal and involutional periods[9].
Children considered healthy and those with fractures without significant bone mineralisation disorders were included

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in the study to assess vitamin K_2 levels in the developmental age population. Since eating habits or diet were not assessed, anthropometric measurements were performed in all patients to rule out malnutrition. This allowed to exclude risk factors for vitamin K_2 deficiency in the study population.

Based on the research by van Summeren et al., who were among the first to assess vitamin K in children and found that vitamin K_2 (menaquinones) is more effective than K_1 in the context of bone health[10,11], a decision was made to determine vitamin K_2 levels in this study. We used the immunoenzymatic ELISA method for this purpose. No reference values for this method were found for the developmental age population in either Polish or foreign literature. Therefore, we created our own reference group, with levels of 0.90–12.46 ng/mL considered normal.

Various indirect and direct methods for determining vitamin K levels have been described in the literature. Their diversity makes it difficult to obtain uniform norms and reference values[5–9,13–16], which arises from the multiple roles of vitamin K in the pathophysiology of the assessed disorders. In this study, we made an attempt to determine vitamin K_2 levels in children and adolescents with bone fractures since the vast majority of available literature refers to adults with osteoporosis. Since vitamin D preparations and selected forms of vitamin K are used in the prevention of osteoporotic fractures in adults, it seemed reasonable to enquire whether vitamin K should also be used to reduce the risk of bone fractures in children.

Attempts to determine serum vitamin K in adults were undertaken by, among others, Fusaro et al., who assessed data from 387 dialysis patients treated or not with sevelamer. The authors reported mean levels of MK-4 and MK-7 of 0.45 ng/mL (interquartile range 0.15, 0.67) and 1.15 ng/mL (interquartile range 0.53, 1.22), respectively[17]. Klapkova et al. measured vitamin K_2 in 350 postmenopausal women (with or without osteoporosis) and found that osteoporotic women had mean levels of 0.890 ± 0.291 ng/mL for MK-4 and 1.002 ± 1.020 ng/mL for MK-7, whereas the mean levels in non-osteoporotic patients were 0.825 ± 0.266 ng/mL and 1.186 ± 1.076 ng/mL, respectively[5]. Vitamin K_2 (menaquinone) occurs in multiple forms. Menaquinones contain an unsaturated side chain with a variable number of prenyl units, which indicates the type of menaquinone, e.g. MK-4 and MK-7 contain four and seven prenyl units, respectively[23]. These two forms are most commonly used in the treatment of adult osteoporosis.

Much higher levels of vitamin K were shown by Japanese researchers, which is a consequence of high natto intake in this region. Suhara et al., who assessed osteoporotic and healthy adults, reported MK-7 levels of 6.37 ± 7.45 ng/mL[18]. Similar high values, i.e. 3.82 ± 3.11 ng/mL and 16.27 ± 20.58 ng/mL, were also reported by other researchers[19,20]. These discrepancies, which may arise from diverse dietary habits and geographical or cultural differences, generate significant challenges in establishing uniform reference values.

There have been only few studies on the direct determination of vitamin K in children and adolescents.

Kürşat et al. measured vitamin K_2 in healthy Turkish children aged 6 months to 6 years who experienced febrile seizures. Although the researchers used the same method to measure vitamin K_2 levels as we did (ELISA), they obtained significantly higher mean values, i.e. 675.6 ng/mL[14]. This may be due to the age difference between the study groups, with a larger proportion of children ≤17 years in our study.

The largest group of 1,732 patients aged 1–14 years was assessed by Du and Li, who measured vitamin K_2 levels using HPLC (median level was 0.1 and decreased with age from 0.11 in 1–3-year-olds to 0.08 in 6–14-year-olds). Additionally, these researchers showed a minor negative correlation between age and vitamin K_2 levels ($p = 0.031$, $r = -0.18$)[8], which was not found in our study.

In one of the latest reports (2024), Chen et al. measured vitamin K using the HPLC method in 807 healthy children aged 0–14 years. The researchers determined reference values for vitamin K_1 for age groups 0–3 years (0.10–1.73 μg/L) and 4–14 years (0.09–4.54 μg/L). The reference range for MK-4 for all children was 0–0.42 μg/L[21].

Popko et al. conducted their research in a population similar to the one described in our paper, i.e. children from northeastern Poland who had suffered bone fractures. However, they indirectly measured vitamin K and described its role in the pathophysiology of bone fractures by assessing two forms of osteocalcin using the ELISA approach[22].

The cited research shows that the assessment of vitamin K levels is a difficult and complex process that depends on multiple factors, including the measurement technique and purpose, as well as the study group. Additionally, Fusaro et al. emphasised that the measurement of vitamin K may be challenging due to lipid interference and its low serum levels, as well as its nonpolar properties, especially in the case of some forms of MK[1].

CONCLUSIONS

Vitamin K_2 levels in the study population of children and adolescents with a history of bone fractures were within the reference range for this age group, which suggests that bone fractures were not associated with a deficiency of this vitamin.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

Author contributions

Original concept of study: MP, EJP. Collection, recording and/or compilation of data: MP, EW. Analysis and interpretation of data; writing of manuscript: MP. Critical review of manuscript; final approval of manuscript: EJP.

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