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# Correlation between suboptimal vitamin D concentration and secondary hyperparathyroidism in women with low-energy fractures

## Korelacija nedovoljne koncentracije vitamina D i sekundarnog hiperparatireoidizma kod žena sa prelomima na malu traumu

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**Abstract**

**Background/Aim.** Osteoporosis is the most common metabolic bone disorder worldwide characterized by decreased bone strength that predisposes to an increased fracture risk, especially in postmenopausal women. Today, over 25 million people, mainly women, suffer from this metabolic disorder. In addition to genetic predispositions, hormonal disorders, lifestyle, and insufficient vitamin D levels in the blood are significant risk factors for the occurrence of osteoporosis and low-energy fractures. The aim of our study was to analyze the incidence of osteoporosis and the correlation between vitamin D deficiency and secondary hyperparathyroidism in women of different ages with low-energy fractures. **Methods.** This cross-sectional study included 559 women who were not previously treated for osteoporosis. All women were clinically examined and their anamnesis of chronic illnesses, fractures, and therapies was taken. Height and weight were measured, and body mass index (BMI) was calculated. Risk factors for osteoporosis, including the concentration of 25-hydroxyvitamin D [25(OH)D] and parathyroid hormone (PTH), were measured. Vitamin D deficiency was defined as serum level of 25(OH)D less than 30 ng/mL (75 nmol/L). **Results.** The study included a total of 559 women, of which low-energy fractures were identified in 102 women. Women with fractures were older (63.69 ± 13.88 years) compared to women without fractures (54.39 ± 14.10 years) ($p < 0.0005$). Furthermore, BMI was also higher (27.75 kg/m$^2$) in women with fractures compared to the other group (26.49 kg/m$^2$) ($p < 0.025$). Out of 102 women with fractures, 88 were postmenopausal. The most frequent fractures were the humerus and radius fractures, 11.62% (65/559), followed by femoral neck fractures, 7.15% (40/559), and body *vertebrae* fractures, 3.04% (17/559). A significant decrease of the bone mineral density (BMD) in the spinal and the femoral neck sites was observed in women with femoral neck and body *vertebrae* fractures, but not in women with humerus and radius fractures. Vitamin D deficiency did not have a significant impact on fracture incidence. The increased concentration of PTH was statistically significant in women with femoral neck and body *vertebrae* fractures. **Conclusion.** In women with all three types of low-energy fractures, compared to women without fractures, significant risk factors for osteoporosis were age, BMD, and the strength of mechanical force during fall (estimated through BMI).

**Key words:**
**osteoporosis; risk factors; vitamin d; fractures, bone; hyperparathyroidism, secondary; women.**

**Apstrakt**

**Uvod/Cilj.** Osteoporoza je metabolička bolest kostiju koju karakteriše smanjenje koštane čvrstine, posebno kod žena nakon menopauze. Danas, više od 25 miliona ljudi pati od ovog metaboličkog poremećaja. Pored genetske predispozicije, hormonski poremećaj, način života i nedovoljna koncentracija vitamina D u krvi su značajan faktor rizika za pojavu osteoporoze i preloma na malu traumu. Cilj naše studije bio je da ispitamo učestalost osteoporoze, kao i vezu između deficita vitamina D u krvi i hiperparatireoidizma kod žena različite životne dobi koje su imale prelom na malu traumu. **Metode.** U studiju preseka bilo je uključeno 559 žena koje prethodno nisu bile lečene od osteoporoze. Sve žene bile su klinički pregledane i od svih je uzeta anamneza o hroničnim bolestima, prelomima i prethodno uzimanoj terapiji. Svakoj ispitanici izmerene su masa i visina, izračunat je indeks telesne mase (ITM) i uzeta je krv za laboratorijske analize. Analizirani su faktori rizika za osteoporozu, uključujući koncentraciju 25-hidroksi vitamina D [25(OH)D] i paratireoidnog hormona. Snižena koncentracija vitamina D definisana je kao serumska koncentracija 25(OH)D manja od 30 ng/mL (75 nmol/L). **Rezultati.** Studija je

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obuhvatila 559 žena, od kojih su 102 imale prelome na malu traumu. Žene koje su imale prelom bile su starije (63,69 ± 13,88 godina) u poređenju sa ženama bez preloma (54,39 ± 14,10 godina) ($p < 0,0005$). Indeks telesne mase bio je veći kod žena sa prelomima (26,49 kg/m$^2$) u poređenju sa drugom grupom (24,79 kg/m$^2$) ($p < 0,025$). Od 102 žene sa prelomom, 88 je bilo u menopauzi. Ispitanice su najčešće imale prelom distalne podlaktice i proksimalne nadlaktice, 11,62% (65/559), zatim prelom vrata butne kosti, 7,15% (40/559) i prelom tela pršljena, 3,04% (17/559). Značajno niže vrednosti mineralne koštane gustine na kičmi i vratu butne kosti zapažene su kod žena sa prelomom vrata butne kosti i tela pršljena, ali ne i kod žena sa prelomom nadlaktice i podlaktice. Snižene koncentracije vitamina D nisu pokazale statistički podržanu značajnost kod žena sa prelomom. Povišena koncentracija paratireoidnog hormona (> 65 pg/mL) pokazala se statistički značajnom kod žena sa prelomom vrata butne kosti i tela pršljena. **Zaključak.** Kod žena koje su imale prelom kosti na malu traumu, na sve tri lokalizacije, u poređenju sa ženama bez preloma, značajni faktori rizika za osteoporozu su godine života, mineralna koštana gustina i jačina mehaničke snage tokom pada (procenjena preko indeksa telesne mase).

**Ključne reči:**
**osteoporoza; faktori rizika; vitamin d; prelomi; hiperparatireoidizam, sekundarni; žene.**

## Introduction

Osteoporosis is the most common metabolic bone disorder worldwide characterized by decreased bone strength that predisposes especially postmenopausal women to an increased risk of fracture [1]. In addition to genetic predispositions, hormonal disorders, lifestyle, and insufficient vitamin D levels in the blood are significant risk factors for the occurrence of osteoporosis and low-energy fractures. Bone strength is defined by bone mineral density (BMD), which makes 60–80% of bone strength and bone quality. BMD is a measurable category, expressed as grams of mineral *per* area or volume. Bone quality refers to architecture, turnover, and mineralization. Osteoporotic bones are characterized by a reduced trabecular thickness, broken horizontal bonds, and a total reduced bone mass. Osteoporosis is characterized by the imbalance between resorption and deposition in favor of resorption [2].

The association between falls and osteoporosis have been analyzed in several population studies showing that a reduced vitamin D concentration (< 30 ng/mL) is present in 63.9% of people in the general population and the elderly patients older than 60 years of age with a hip fracture in about 97.8% of cases [2].

Today, over 25 million people, mainly women, suffer from this metabolic disorder. Osteoporosis is the cause of 1.5 million fractures annually, including 500,000 body *vertebrae* fractures, more than 250,000 hip fractures, and about 200,000 radius fractures [2, 3]. The highest prevalence of osteoporosis, about 21% of women aged between 50 and 84 years (over 12 million women), has been noted in the European Union (EU) countries (Germany, France, Italy, Spain, and the United Kingdom) [2–8]. It is estimated that about 77% of the population is without diagnosis and therapy, 14% with diagnosis but without treatment, and only 9% with diagnosis and therapy. In the elderly people, 90% of the hip fracture is associated with a fall, while vertebral fractures are most commonly spontaneous and are not associated with a fall. Rarely, a fracture caused by osteoporosis can occur on the pelvis, ribs, and distal part of the tibia and femur. The significance of hip fracture is very important because of the devastating impact on patients: 50% of patients have functional incapacity, 15–25% require long-term care and assistance, while 10–20% die during the first year of fracture [6]. In 2010, there were over 43,000 deaths related to osteoporosis in the EU, of which 50% were caused by hip fractures, 28% by spine fractures, and 22% were caused by other fractures [7]. Less than 20% of patients with low-energy fractures receive therapy in the first year of the fracture [8]. A fall is a significant cause of morbidity and mortality in the older population. About 30% of people over 65 years of age experience falls each year. Aging is one of the factors that increase the incidence of falls, especially in hospital conditions [9, 10]. Based on the previously published data, the total costs of treatment for fractures caused by osteoporosis in the EU were about 39 billion euros in 2010. Moreover, 26 billion was spent on direct costs of fracture treatments, 11 billion on long-term treatments, and 2 billion euros on fracture prevention [7]. A fall is the cause of 90–95% cases of hip fractures, 95% of radius fractures, 75% of proximal humerus fractures, and 25% of *vertebrae* fractures. Vertebral fracture is by far the most prevalent osteoporotic fracture (50%), especially in the spine region of Th 11 to L1, followed by Th 8 [2, 11]. In approximately 2/3 of cases, osteoporotic fractures of body *vertebrae* are asymptomatic. The femoral neck, located near the top of the femur bone, is also susceptible to fracture due to osteoporosis, and it is the next most common complication caused by osteoporosis. The risk of suffering a new femoral neck fracture increases multiple times after the first fracture. Thus, a third of patients with hip fractures have experienced a fracture of the other hip [12]. Moreover, localized fractures caused by osteoporosis can occur in the distal limb.

Among the most commonly used techniques, dual-energy X-ray absorptiometry (DXA) is considered the current “gold standard” for diagnosing osteoporosis. The hip is the most relevant measurement site since this site suffers the most severe fracture. In particular, the World Health Organization (WHO) classifies BMD on the basis of the T-score as normal (≥ -1.0), osteopenia (< -1.0 but > -2.5), osteoporosis (≤ -2.5), and severe osteoporosis (≤ -2.5 with a fragility fracture). The T-score represents the standard deviation (SD) of measured BMD, compared to an average BMD for a female person aged 25 years [13–16]. Osteoporotic fracture of the body *vertebrae* is defined as a reduction in the front of the craniocaudal diameter of the *vertebrae* on lateral

radiography by more than 20% (at least 4 mm), which is a radiological and rather approximate definition of fracture.

The aim of our study was to analyze the incidence of osteoporosis and the correlation between vitamin D deficiency and secondary hyperparathyroidism in women of different ages with low-energy fractures.

## Methods

This cross-sectional study included 559 women not previously treated for osteoporosis. All women were presented to the Military Medical Academy in Belgrade. The study was approved by the Ethics Committee of the Military Medical Academy and informed consents were signed by the patients. All women were clinically examined, and their history of chronic illnesses, fractures, and therapies was taken. Height and weight were measured, and body mass index (BMI) was calculated (kg/m$^2$). Blood samples after 8-hour fasting (8 mL) were collected from all patients for laboratory analyses. Risk factors for osteoporosis, including concentration of 25(OH)D and parathyroid hormone (PTH), were measured. Serum 25(OH)D levels were measured by the competitive binding chemiluminescence immunoassay, IDS Ltd, Boldon, England (reference range 9.3–151.2 nmol/L; intra-assay precision 5.3% at 39 nmol/L, 5.6% at 67.1 nmol/L, and 6.7% at 165 nmol/L, inter-assay precision 4.6% at 40.3 nmol/L, 6.4% at 72.0 nmol/L, and 8.7% at 132 nmol/L, lower limit of sensitivity 5 nmol/L). Serum 25(OH)D concentrations were presented as nmol/L. Serum intact PTH was measured using the commercially available competitive immunoradiometric assay from DiaSorin, Stillwater, Minnesota, USA with detection limit < 0.1 pmol/L. The intra-assay coefficient of variation (CVs) ranged from 2.4% to 3.6%, and the interassay CVs ranged from 3.4% to 4.9%. Vitamin D deficiency was defined as a serum 25(OH)D level less than 30 ng/mL (75 nmol/L); a level of 25(OH)D of 21 to 29 ng *per* milliliter (52 to 72 nmol *per* liter) can be considered to indicate a relative insufficiency of vitamin D.

DXA scans were performed to measure BMD at the spine and hip with the osteodensitometer GE Lunar Prodigy Advance (GE Healthcare Lunar Co, Madison, USA), and the results were expressed as T-scores, Z-scores, and BMD (mg/cm$^2$). The diagnosis of osteoporosis by DXA was made following the WHO definition.

The obtained data were analyzed by appropriate statistical tests, univariate analysis of variance (ANOVA) followed by the Bonferroni test, linear regression tests and correlation. Statistical data analysis was done using the Origin Pro 8.5 program. The *p*-value < 0.05 was considered significant.

## Results

The study engaged a total of 559 women, age range from 18–88 years. Low-energy fractures were identified in 18.24% (102/559) of women included in the study. Women with fractures were older (aged 63.69 ± 13.88 years) compared to those without fractures (aged 54.39 ± 14.10 years) ($p < 0.0005$). Furthermore, BMI was also higher (27.75 kg/m$^2$) in women with fractures compared to the other group (26.49 kg/m$^2$) ($p < 0.025$). Out of 102 women with fractures, 88 were postmenopausal. All subjects included in the study were divided into four groups: three groups of women based on the type of fracture and one group of women without fractures. The first group consisted of women with humerus and radius fractures, followed by the group of women with femoral neck and body *vertebrae* fractures.

In the first studied group of women with humerus and radius fractures, the fractures were identified in 11.62% (65/559) of women, of which 84.61% (55/65) were postmenopausal. Women with fractures were significantly older and had a higher BMI compared to the women without fractures (Table 1). BMD of femoral neck and spine were not statistically lower in women with fractures. We did not find a significant association of 25(OH)D deficiency and secondary hyperparathyroidism in humerus and radius fractures. Osteoporosis was diagnosed in 53.84% (35/65) of women with fractures compared to 39.16% (179/457) of women without fractures ($p < 0.034$). Osteopenia was diagnosed in 38.46% (25/65) of women with fractures compared to 19.3% (87/457) of women without fractures ($p = 0.000$).

The second group consisted of women with femoral neck fractures. The fractures were detected in 7.15% (40/559) of women, of which 90% (36/40) were postmenopausal women. Women with fractures were significantly older and had a higher BMI compared to the

**Table 1**

**Characteristics of women with humerus and radius fractures and without fractures**

| Risk factors | Without fractures (457/559, 81.75%) | Humerus and radius fractures (65/559, 11.62%) | *p*-value |
|---|---|---|---|
| Age (years), mean ± SD | 54.39 ± 14.10 | 64.42 ± 12.91 | 0.008 |
| BMI (kg/m$^2$), mean ± SD | 26.49 ± 5.12 | 30.54 ± 4.20 | 0.003 |
| Spine BMD (mg/cm$^2$), mean ± SD | 966 ± 177 | 926 ± 158 | |
| Femoral neck BMD (mg/cm$^2$), mean ± SD | 833 ± 150 | 790 ± 166 | |
| 25(OH)D < 75 nmol/L, n (%) | 424 (92.77) | 65/65 (100) | 0.049 |
| Increased concentration of PTH (> 65 pg/mL), n (%) | 89 (19.47) | 14 (21.53) | |
| T-score of spine, mean ± SD | -1.6 ± 1.4 | -1.9 ± 1.3 | |
| T-score of femoral neck, mean ± SD | -1.2 ± 1.2 | -1.5 ± 1.4 | |

**BMI – body mass index; BMD – bone mineral density; 25(OH)D – 25-hydroxyvitamin** D; **PTH – parathyroid hormone; SD – standard deviation.**

women without fractures (Table 2). Femoral neck and spine BMD were statistically associated with the incidence of hip fracture. There was no significant difference in 25(OH)D deficiency in these two groups, while the secondary hyperparathyroidism was significantly more frequent in women with fractures. Osteoporosis was diagnosed in 55% (22/40) of women with fractures compared to 39.19% (179/457) of women without fractures ($p$ = 0.074). Osteopenia was diagnosed in 30% (12/40) of women with fractures compared to 19.3% (87/457) of women without fractures ($p$ = 0.145).

In the third studied group, body *vertebrae* fractures were identified in 3.04% (17/559) of women, of which 88.23% (15/17) were postmenopausal. Women with fractures were significantly older, while the BMI was not statistically associated with the incidence of body *vertebrae* fractures (Table 3). BMD of the femoral neck and lumbar spine were statistically lower when fractures are present. There was no significant difference in 25(OH)D deficiency, while the secondary hyperparathyroidism was significantly more frequent in women with fractures. An average vitamin D concentration was statistically lower in the group of women with fractures ($p$ < 0.005). Osteoporosis was diagnosed in 88.23% (15/17) of women with fractures compared to 39.16% (179/457) of women without fractures ($p$ = 0.0007). Osteopenia was diagnosed in 11.76% (2/17) of women with fractures compared to 19.03% (87/457) of women without fractures ($p$ = 0.002).

energy fractures. Women with all three types of fractures were significantly older. We found that women with humerus and radius and hip fractures had statistically higher BMI compared to those without fractures. Furthermore, a significant decrease of the BMD in the spinal and the femoral neck sites was observed in women with femoral neck and body *vertebrae* fractures, but not in women with humerus and radius fractures. However, the suboptimal 25(OH)D concentrations are not the only risk factor for increased incidence of fractures. The increased concentration of PTH was statistically significant in women with femoral neck and body *vertebrae* fractures.

Six studies were included, with a total of 105,129 participants followed from 3 to 19 years. The pooled relative risk (RR ) with 95% confidence interval (CI) for vertebral fracture per each standard deviation increase in BMI was 0.94 (95% CI = 0.80–1.10). Across various studies of women not adjusting for bone mineral density (BMD), there was no significant association between BMI and risk of vertebral fracture (RR = 0.91, 95% CI = 0.80–1.04; $p$ = 0.18; n = 72,755 participants) [17]. A prospective, multinational, observational cohort study of 52,629 postmenopausal women participating in the Global Longitudinal Study of Osteoporosis in Women (GLOW) investigated the relationship between BMI, weight and height and fracture risk at multiple fracture sites. It showed that the relationship between BMI and fracture risk is site-specific. The different

**Table 2**

**Characteristics of women with hip fractures and women without fractures**

| Risk factors | Without fractures (457/559, 81.75%) | Femoral neck fractures (40/559, 7.15%) | *p*-value |
|---|---|---|---|
| Age (years), mean ± SD | 54.39 ± 14.10 | 63.70 ± 14.04 | 0.008 |
| BMI (kg/m$^2$), mean ± SD | 26.49 ± 5.12 | 27.98 ± 4.77 | 0.01 |
| Spine BMD (mg/cm$^2$), | 966 ± 177 | 902 ± 162 | 0.002 |
| Femoral neck BMD (mg/cm$^2$), mean ± SD | 833 ± 150 | 756 ± 149 | 0.00003 |
| 25(OH)D < 75 nmol/L, n (%) | 424 (92.77) | 39 (97.5) | |
| Increased concentration of PTH (> 65 pg/mL), n (%) | 89 (19.47) | 14 (35.00) | 0.034 |
| T-score of spine, mean ± SD | -1.6 ± 1.4 | -2.3 ± 1.3 | 0.0002 |
| T-score of femoral neck, mean ± SD | -1.2 ± 1.2 | -1.8 ± 1.1 | 0.00005 |

**For abbreviations see under Table 1.**

**Table 3**

**Characteristics of women with body *vertebrae* fractures and women without fractures**

| Risk factors | Without fractures (457/559, 81.75%) | Body *vertebrae* fractures (17/559, 3.04%) | *p*-value |
|---|---|---|---|
| Age (years), | 54.39 ± 14.10 | 63.64 ± 13.48 | 0.008 |
| BMI (kg/m$^2$), | 26.49 ± 5.12 | 26.54 ± 4.85 | ns |
| Spine BMD (mg/cm$^2$), | 966 ± 177 | 861 ± 126 | 0.016 |
| Femoral neck BMD (mg/cm$^2$), | 833 ± 150 | 722 ± 138 | 0.003 |
| 25(OH)D < 75nmol/L, n (%) | 424 (92.8) | 17 (100) | 0.507 |
| Increased concentration of PTH (> 65 pg/mL), n (%) | 89/457 (19.47) | 11/17 (64.70) | 0 |
| T-score of spine, mean ± SD | -1.6 ± 1.4 | -2.6 ± 0.7 | 0.009 |
| T-score of femoral neck, mean ± SD | -1.2 ± 1.2 | -2.6 ± 1.0 | 0.001 |

**For abbreviations see under Table 1.**

## Discussion

The present study showed an association between specific risk factors, such as age, BMD, BMI, the concentration of 25(OH)D and PTH, and different low-

associations may be mediated by their effects on BMD, bone structure and geometry, and patterns of falling [18].

In the previous study that included 88 postmenopausal women with osteoporosis, 21 (23.86%) women with fractures had significantly lower 25(OH)D concentration ($p$ < 0.01).

The obtained results implied that vitamin D deficiency in women with osteoporosis is a significant risk factor for fractures [19]. Vitamin D deficiency was also studied in 415 older women, and results showed that it was a contributing factor to different types of fractures of body *vertebrae*. This result highlights the importance of vitamin D insufficiency as a possible risk factor for older women [20]. The results of a meta-analysis of randomized controlled trials showed that vitamin D supplementation, at doses of 700 to 1000 IU per day, reduces the risk of falling in the 65-year-olds by 19%. Doses less than 700 IU in the serum do not reach the serum level of vitamin D of 60 nmol/L and cannot reduce the risk of falling in the elderly women [21, 22]. The association between hypovitaminosis D and the fracture was also studied in postmenopausal women in Tunisia. The first group consisted of 102 women with fractures and the second group of 32 women without fractures. Obtained results showed that all fractures in postmenopausal women were related to BMD and vitamin D deficiency [23]. In the study aimed to analyze the association between concomitant upper limb fractures and both vitamin D status and hip BMD in 549 women with fall-related hip fracture, the concentration of vitamin D was significantly lower in the women with concomitant fractures of both hip and upper limbs compared to the women with hip fractures ($p < 0.001$). However, hip BMD levels were not significantly different between the observed groups [24].

In a case-control study, 105 postmenopausal women with recent distal radial fracture were prospectively engaged. It showed that the mean 25(OH)D levels were similar in the fracture and control groups (44.4 ± 14.6 ng/mL *vs* 41.3 ± ng/mL; $p = 0.08$). The 25(OH)D levels were not associated with distal radial fracture and did not appear to affect the risk assessment for distal radial fracture in the postmenopausal women [25].

In a study that included 1,775 postmenopausal women with osteoporosis, the association between the femoral and total proximal BMD and the incidence of spine and hip fractures was examined. The changes in the femoral neck and total proximal BMD were statistically correlated with the incidence of hip and fragility fractures after 3 years ($p < 0.001$). However, changes in BMD on the spine did not affect the occurrence of *vertebrae* fractures [26].

A recent study has reported that serum levels of PTH > 65 pg/mL and severe vitamin D deficiency were associated with trochanteric fractures and recurrent falls as well. On the other hand, patients without the PTH response to low vitamin D levels were not repeated fallers and suffered mostly from subcapital fractures [27].

Association between fall and fracture of the femur neck was studied in more than 34,000 people who experienced a fall. Obtained results suggested that data on the previous fracture and fall should be taken into consideration during the assessment of risk for osteoporosis [28].

In order to study the relative significance of dietary calcium intake and vitamin D concentration regarding the hip BMD, 4,958 women and 5,003 men ≥ 20 years of age were examined in the United States of America. Among both sexes, BMD increased stepwise and significantly with higher vitamin D concentrations (< 50, 50–74, 75 + nM; women: $p < 0.0001$; men: $p = 0.0001$) [29].

## Conclusion

We concluded that aging and low bone mineral density are important risk factors for all three types of low-energy fractures. Body mass index is an important risk factor for non-vertebral fractures, probably because of the strength of the mechanical force during the fall. The suboptimal concentration of vitamin D did not have a significant impact on the incidence of fractures. The increased concentration of PTH was statistically significant in women with femoral neck fractures and body *vertebrae* fractures.

## Conflict of interest

Authors declare that there is no conflict of interest.

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