

Original Article

Association of vitamin D, BMD and knee osteoarthritis in postmenopausal women

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Abstract

Objectives: The aim of this study was to analyze the association of knee OA with bone mineral density (BMD) and vitamin D serum levels in postmenopausal women. **Methods:** A cross-sectional study including 240 postmenopausal women with knee OA was conducted. Demographic data were recorded along with balance and functionality scores. Knee OA severity was assessed by the radiological Kellgren & Lawrence scale. BMD and T-scores were calculated in hips and lumbar spine. Serum levels of vitamin D were also measured. **Results:** High BMI ($p < 0.005$), high number of children ($p = 0.022$) and family history of hip fracture ($p = 0.011$) are significantly associated with knee OA severity. Lumbar spine OP is negatively associated with knee OA ($p < 0.005$). A significant difference was detected between vitamin D deficiency and severe knee OA, adjusted for BMD [OR (95%CI); 3.1 (1.6-6.1), $p = 0.001$]. BMD does not affect the relationship of vitamin D levels in relation to OA and vitamin D levels do not affect the relationship of BMD with OA. **Conclusions:** Low BMD has a protective role against knee OA while vitamin D deficiency contributes significantly to knee OA severity. However, the association between OA and OP is not affected by vitamin D deficiency and the association of OA and vitamin D serum levels is not affected by BMD.

Keywords: Bone Mineral Density, Hypovitaminosis D, Osteoarthritis, Osteoporosis, Vitamin D

Introduction

Osteoarthritis (OA) is a chronic degenerative joint disease, affecting millions of patients worldwide. The main characteristics of OA are the gradual cartilage degradation, the formation of subchondral cysts, the sclerosis of the adjacent subchondral bone, the development of osteophytes and synovial inflammation. Damage of articular cartilage is caused by a complex interaction of genetic, metabolic, biochemical, inflammatory and biomechanical factors¹. The main risk factors for

osteoarthritis include age, gender, genetic predisposition, mechanical stress, trauma and obesity^{2,3}.

Osteoporosis (OP) is a systemic metabolic bone disease characterized by low bone mineral density (BMD) and disruption of the bone microarchitecture, resulting in increased bone fragility and fracture risk. The basic pathophysiologic mechanism of OP is increased bone resorption caused by osteoclast activity and decreased bone production caused by osteoblast activity. The main risk factors for OP are decreased peak bone mass and increased rate of bone loss or a combination of both⁴. Postmenopausal is the most common form of OP, occurring in postmenopausal women and is associated with decreased estrogen production, which is normally seen in women of this age^{5,6}.

Vitamin D is a steroid hormone with many different biological effects on a number of target tissues. The main function of vitamin D is the regulation of calcium homeostasis by increasing intestinal calcium absorption, renal calcium resorption and stimulating osteoclastic activity⁷. Vitamin D deficiency (hypovitaminosis D), defined as a decrease in serum 25(OH)D₃ levels below 20 ng/ml, is caused by

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Table 1. Demographic and clinical parameters of the study population.

| Variables | Mean | SD | Min | Max |
|---|-------|-------|-------|-------|
| Age (years) | 68.92 | 9.39 | 47 | 90 |
| Menopause age (years) | 49.33 | 3.73 | 38 | 55 |
| Height (m) | 1.55 | 0.06 | 1.43 | 1.74 |
| Weight (kg) | 68.50 | 10.66 | 49 | 102 |
| BMI (kg / m ²) | 28.51 | 4.28 | 20.7 | 38.9 |
| Number of children | 1.58 | 0.81 | 0 | 3 |
| Falls during last year | 0.58 | 0.7 | 0 | 3 |
| % risk of osteoporotic fracture | 20.27 | 13.71 | 4.5 | 69.7 |
| % risk of hip fracture | 9.75 | 15.36 | 0.4 | 70 |
| Berg Balance Scale | 55.29 | 1.34 | 48 | 56 |
| Sit To Stand Test | 12.12 | 3.99 | 4 | 34 |
| TUG test | 7.21 | 2.27 | 4.5 | 14.9 |
| T-score femoral neck (L) | -1.94 | 0.79 | -3.8 | 0 |
| T-score femoral neck (R) | -1.94 | 0.87 | -3.2 | 1.6 |
| BMD femoral neck (L) | 0.75 | 0.10 | 0.528 | 0.979 |
| BMD femoral neck (R) | 0.74 | 0.09 | 0.6 | 0.986 |
| T-score hip (L) | -1.37 | 0.97 | -4 | 1.4 |
| T-score hip (R) | -1.4 | 0.92 | -3.1 | 1.2 |
| BMD hip (L) | 0.82 | 0.11 | 0.515 | 1.09 |
| BMD hip (R) | 0.83 | 0.10 | 0.633 | 1.1 |
| T-score L ₂ - L ₄ | -1.81 | 1.30 | -4.4 | 1.6 |
| BMD L ₂ - L ₄ | 0.95 | 0.19 | 0.08 | 1.29 |
| Kellgren – Lawrence Score | 2.75 | 0.99 | 0 | 4 |
| 25(OH) Vit D ₃ | 24.48 | 10.20 | 2.7 | 47.6 |

SD: Standard deviation. (L): Left. (R): Right. BMD: Bone Mineral Density.

inadequate dietary intake, sunlight exposure and metabolic diseases⁸. The result is incomplete mineralization of the osteoid in both the cortical and cancellous bones leading to the onset of OP and osteomalacia, which very often remains undiagnosed for a long time⁹. Low serum levels of vitamin D have been also observed in older patients with OA and have been associated with increased cartilage destruction in knee OA¹⁰.

In literature, there is a strong scientific interest in recognizing the coexistence and association of OP with OA and vitamin D deficiency. Current studies have shown conflicting results and have failed to draw safe conclusions¹¹⁻¹⁴. The aim of this study was to analyze the association of knee OA with BMD and vitamin D serum levels in postmenopausal women.

Materials and Methods

This is an observational cross-sectional study that took place between January and July 2017. The study has been approved by the local ethical committee and informed consent was signed by all participants.

The study included postmenopausal women, over the age of 50, who were diagnosed with OP or osteopenia and

complained for knee pain at the time of clinical evaluation. Women suffering from secondary OA, secondary OP or other systematic disease affecting bone metabolism were excluded from the study.

Demographic data (gender, age, weight, height) were recorded in all patients and bone mass index (BMI) was calculated. Clinical data including history of falls, menopausal age, number of children, alcohol and tobacco use, previous surgeries, medications and comorbidities, and a family history of hip fracture were recorded.

All patients were subjected to anteroposterior and lateral knee x-rays, and the radiological severity of knee OA was assessed by Kellgren & Lawrence (K-L) Scale¹⁶. Dual - energy X-ray absorptiometry (DEXA) was used to measure BMD and calculate T-score in both hips and lumbar spine. The T-score was defined as the standard deviation of the mean peak BMD of a young Caucasian standard population of similar sex, irrespective of the patient's age¹⁷. Based on T-score, osteopenia was defined as a T-score from -1 to -2.5 and osteoporosis was defined as a T-score <-2.5¹⁸. Computer-based FRAX algorithm was used to calculate the 10-year risk of osteoporotic fracture and hip fracture in all patients¹⁵.

Blood samples were taken, serum levels of 25(OH)D₃ were

Table 2. Association of demographic, clinical and laboratory parameters with knee OA severity.

| | Knee OA | | p-value |
|--|---------------------|-------------------|------------------|
| | K-L \leq 2 (N=80) | K-L>2 (N=80) | |
| Age (years) | 66.13 \pm 9.19 | 70.31 \pm 9.21 | 0.001 |
| Menopause age (years) | 50 \pm 3.50 | 49 \pm 3.81 | 0.06 |
| Height (m) | 1.56 \pm 0.06 | 1.55 \pm 0.06 | 0.078 |
| Weight (kg) | 62.31 \pm 6.5 | 71.59 \pm 11 | 0.005 |
| BMI (kg / m ²) | 25.58 \pm 2.36 | 29.98 \pm 4.27 | <0.005 |
| Number of children | 1.38 \pm 0.79 | 1.69 \pm 0.81 | 0.005 |
| % risk of osteoporotic fracture ¹ | 17.95(20.8) | 14.90(12.63) | 0.554 |
| % risk of hip fracture ¹ | 5.95(7.93) | 3.5 (7) | 0.348 |
| Berg Balance Scale | 55.75 \pm 0.44 | 55.06 \pm 1.56 | 0.105 |
| Sit To Stand Test | 13.43 \pm 5.66 | 11.47 \pm 2.61 | 0.004 |
| TUG test | 6.80 \pm 2.48 | 7.42 \pm 2.14 | 0.045 |
| T-score femoral neck (L) | -2.17 \pm 0.67 | -1.83 \pm 0.83 | 0.003 |
| T-score femoral neck (R) | -2.28 \pm 0.49 | -1.78 \pm 0.96 | <0.005 |
| T-score hip (L) | -1.61 \pm 1.11 | -1.26 \pm 0.88 | 0.012 |
| T-score hip (R) | -1.75 \pm 1.01 | -1.25 \pm 0.84 | <0.005 |
| T-score L ₂ - L ₄ | -2.36 \pm 1.18 | -1.55 \pm 1.28 | <0.005 |
| BMD femoral neck (L) | 0.715 \pm 0.076 | 0.769 \pm 0.101 | <0.005 |
| BMD femoral neck (R) | 0.706 \pm 0.058 | 0.759 \pm 0.092 | <0.005 |
| BMD hip (L) | 0.776 \pm 0.082 | 0.846 \pm 0.107 | <0.005 |
| BMD hip (R) | 0.78 \pm 0.082 | 0.85 \pm 0.101 | <0.005 |
| BMD L ₂ - L ₄ | 0.9 \pm 0.144 | 0.967 \pm 0.21 | <0.005 |
| 25(OH) Vit D ₃ ¹ | 26 (11.7) | 24.7(16.2) | 0.033 |

All values are presented as mean \pm SD, ¹ median (IQR). OA: Osteoarthritis. K-L: Kellgren & Lawrence Scale. SD: Standard deviation. (L): Left. (R): Right. BMD: Bone Mineral Density.

measured in all patients and vitamin D deficiency was defined as serum levels less than 20 ng/ml. Clinical evaluation of knee OA was performed by Lequesne Index¹⁹. The Berg Balance Scale was used to assess the risk of fall in all patients²⁰. Functionality of patients was evaluated by the Sit-To-Stand test and the Timed Up & Go (TUG) test^{21,22}.

Statistical analysis

The quantitative and qualitative variables are presented by the mean, standard deviation (SD) or median, interquartile range (in case of violation of normality), and the frequencies, percentages respectively. The Kolmogorov - Smirnov test was utilized for normality analysis of the quantitative variables. Univariate analyses were made by using the Student t-test or Mann-Whitney in case of violation of normality and Fisher exact test to analyze the relation between the OA severity, (K-L \leq 2 vs K-L>2), and the quantitative and qualitative demographic and clinical variables respectively. Demographic and clinical variables were assessed in multivariate binary logistic regression model with enter method (all variables are entered at the same time in the model) to identify independent demographic and clinical predictors of OA severity (K-L>2).

ORs and 95% CIs were reported for all variables in the multivariable model.

The impact of BMD (osteopenia-osteoporosis) to the relation between vitamin D deficiency and OA severity was examined by using the Mantel-Haenszel test. Two-way analysis of variance (ANOVA) model was used to examine the interaction between BMD and vitamin D deficiency factors in relation to OA estimated by Kellgren-Lawrence scale. All tests are two-sided, statistical significance was set at p<0.05. All analyses were carried out using the statistical package SPSS v19.00 (IBM Corporation, Somers, NY, USA).

Results

The study included 240 postmenopausal women (mean age 68.9 \pm 9.4 years). 80 patients suffered from mild knee OA (K-L \leq 2) while 160 patients suffered from severe knee OA (K-L>2). Demographic and clinical data of the studied population are presented in Table 1.

47.9% of patients had a history of fracture, while 18.7% of participants had a family history of hip fracture. The 10-year risk of osteoporotic fracture was more than 20% in 41.7% of patients, while the 10-year risk of hip fracture was

Table 3. Multivariate analysis of the association of demographic, clinical and laboratory variables with knee OA.

| | OR | 95% CI | | p-value |
|--------------------------------|------|--------|-------|---------|
| Age | 0.96 | 0.9 | 1.03 | 0.234 |
| BMI | 1.57 | 1.34 | 1.84 | <0.005 |
| Number of children | 1.94 | 1.1 | 3.42 | 0.022 |
| History of falls | 1.49 | 0.63 | 3.51 | 0.366 |
| Family history of hip fracture | 4.08 | 1.37 | 12.14 | 0.011 |
| History of fracture | 0.8 | 0.34 | 1.9 | 0.613 |
| TUG test score | 1.24 | 0.97 | 1.59 | 0.088 |
| Sit to Stand test score | 0.91 | 0.82 | 1.02 | 0.116 |
| Vitamin D deficiency | 2.96 | 1.1 | 7.96 | 0.032 |
| Lumbar osteoporosis | 0.15 | 0.06 | 0.37 | <0.005 |

OR: Odds Ratio. CI: Confidence Interval.

Table 4. The influence of BMD to the relationship between vitamin D serum levels and OA severity.

| | | | OA | | OR (95% CI) | p-value |
|-----------------------------|------------------------------|---|-----------|-----------|---------------|---------|
| | | | K - L ≤ 2 | K - L > 2 | | |
| Osteopenia | VitD ≥ 20 ng/ml (normal) | N | 25 | 72 | 3 (1.1-8.4) | 0.048 |
| | | % | 25.8% | 74.2% | | |
| | VitD ≤ 20 ng/ml (deficiency) | N | 5 | 43 | | |
| | | % | 10.4% | 89.6% | | |
| Osteoporosis | VitD ≥ 20 ng/ml (normal) | N | 37 | 25 | 3.7 (1.4-9.7) | 0.012 |
| | | % | 59.7% | 40.3% | | |
| | VitD ≤ 20 ng/ml (deficiency) | N | 8 | 20 | | |
| | | % | 28.6% | 71.4% | | |
| Independently of BMD status | VitD ≥ 20 ng/ml (normal) | N | 62 | 97 | 3.1 (1.6-6.1) | 0.001 |
| | | % | 39% | 61% | | |
| | VitD ≤ 20 ng/ml (deficiency) | N | 13 | 63 | | |
| | | % | 17.1% | 82.9% | | |

OR: Odds Ratio. CI: Confidence Interval. VitD: Vitamin D. OA: Osteoarthritis. K-L: Kellgren & Lawrence Scale. BMD: Bone Mineral Density. OR: Odds Ratio. CI: Confidence Interval.

more than 6% in 43.8% of patients. The T-score was below -2.5 in 17.7% of patients for the left femoral neck, 21.8% for the right femoral neck, 6.7% for the left hip, 9.5% for the right hip and 38.3% for the L₂-L₄ area. 32.5% of the patients had vitamin D deficiency. 43% of the patients had osteopenia and normal vitamin D serum levels. 18.7% had osteopenia and vitamin D deficiency. 26.4% had OP and normal vitamin D serum levels and 11.9% had OP and vitamin D deficiency. The prevalence of the combination of vitamin D deficiency, OP and severe OA was 8.5%.

Univariate analysis (Table 2) showed that patients with severe OA (K-L>2) had older age (p=0.001), higher weight (p=0.005), higher BMI (p<0.005), higher number of children (p=0.005), lower SIT TO STAND test scores (p=0.004)

and higher TUG test scores (p=0.045) than patients with K-L≤2. T-scores and BMD in both hips and lumbar spine were significantly lower (p<0.005) in patients with severe OA in comparison with patients with K-L≤2. Severe OA was also associated with lower vitamin D serum levels (p=0.033). Lequesne index was strongly associated with K-L score (r=0.592, p<0.0005).

As shown in Table 3, multivariate analysis demonstrated that high BMI [1.57(1.34-1.84) p<0.005], high number of children [1.94(1.10-3.2) p=0.022], family history of hip fracture 4.08(1.37-12.14) p=0.011 and vitamin D deficiency [2.96(1.1-7.96) p=0.032] were significantly associated with knee OA severity. Moreover the role of Lumbar OP was protective against knee OA [0.15(0.06-0.37) p<0.005].

Table 5. Correlation between risk of OP or Hip fracture with severity OA.

| | | | OA | | OR (95% CI) | p-value |
|----------------------|-----------------|---|-----------|-----------|---------------|---------|
| | | | K - L ≤ 2 | K - L > 2 | | |
| Risk of OP fracture | Negative (<20%) | N | 45 | 95 | 0.9 (0.5-1.5) | 0.678 |
| | | % | 32.1% | 67.9% | | |
| | Positive (>20%) | N | 35 | 65 | | |
| | | % | 35% | 65% | | |
| Risk of Hip fracture | Negative (<6%) | N | 45 | 90 | 1 (0.6-1.7) | 1 |
| | | % | 33.3% | 66.7% | | |
| | Positive (>6%) | N | 35 | 70 | | |
| | | % | 33.3% | 66.7% | | |

OA: Osteoarthritis. K-L: Kellgren & Lawrence Scale. OR: Odds Ratio. CI: Confidence Interval.

Table 6. Comparison of K-L score in relation to BMD and Vitamin D levels.

| | | Mean K-L score | SE | p-value |
|-----------------------------|--------------------------------|----------------|------|---------|
| Independently of VitD | Osteopenia | 3.08 | 0.08 | <0.005 |
| | Osteoporosis | 2.54 | 0.1 | |
| Independently of BMD status | VitD ≥ 20 ng / ml (normal) | 2.57 | 0.07 | <0.005 |
| | VitD ≤ 20 ng / ml (deficiency) | 3.05 | 0.11 | |

K-L: Kellgren & Lawrence score. SE: Standard Error. VitD: Vitamin D.

The people with vitamin D deficiency presented statistically significant higher risk of severe OA compared with those with D adequacy for people with osteopenia [OR (95% CI); 3 (1.1-8.4), $p=0.048$] and OP [OR (95% CI); 3.7(1.4-9.7), $p=0.012$] (Table 4). We examined the influence of BMD to the relationship between vitamin D serum levels and OA severity. There is homogeneity of the odds ratio of the vitamin D levels in relation to OA severity (Breslow-Day test, $p=0.765$) something that showed that BMD does not affect the association of vitamin D serum levels with OA severity. The people with vitamin D deficiency presented statistically significant higher risk of severe OA compared with those with D adequacy adjusted for BMD [OR (95% CI); 3.1 (1.6-6.1), $p=0.001$] (Table 4).

The risk of osteoporotic fracture [OR (95% CI); 0.9(0.5-1.5), $p=0.678$] or hip fracture [OR (95% CI); 1 (0.6-1.7), $p=1$] did not affect the severe OA (Table 5). Two-way ANOVA model was used to examine the interaction between BMD factor and vitamin D factor in relation to OA estimated by K-L score. No statistically significant interaction was observed between BMD and VitD [F(1.231)=0.012; $p=0.914$] something that allows us to compare the difference of Kellgren Lawrence in relation to bone density regardless of the level of vitamin D and the difference of Kellgren Lawrence in relation to vitamin D independently of bone. As shown in Table 6, there is a statistically significant difference in the value of the K-L score between patients with osteopenia and OP independently of

vitamin D levels (3.08±0.08 vs 2.54±0.1; $p<0.005$) and between people with vitamin D adequacy and deficiency independently of BMD (2.57±0.07 vs 3.05±0.11 $p<0.005$). Conclusively, BMD does not affect the relationship of vitamin D levels in relation to OA and vitamin D levels do not affect the relationship of BMD with OA.

Discussion

As the average life expectancy gradually increases, musculoskeletal disorders become more important, as they represent the most common cause of disability and chronic pain in the elderly population. OA and OP are two of the most widespread age-related diseases, with a huge demographic and socioeconomic burden²³. Vitamin D deficiency is a common feature in elderly people, affecting bone health and contributing to muscle weakness and falls^{24,25}. Taking all these facts into consideration, the present study investigated the complex interaction between OA, OP and serum levels of vitamin D in postmenopausal women.

The results of this study have confirmed that advanced age and higher BMI are predisposing factors to knee OA. Recent meta-analyses have identified the contribution of advanced age in OA progression²⁶. In literature, obesity has been correlated with a more than 2-fold increase of knee OA risk and this increase seems to be dose-dependent, as mechanical overload in weight-bearing joints activates chondrocytes

and accelerates cartilage degeneration²⁷. Framingham study estimated that weight loss by 5 kg reduced the risk of developing knee OA by 50%²⁸. Functionality, depicted by the Sit-to-Stand and TUG tests, was also impaired in cases of severe OA. In agreement with previous studies, OA severity has been positively correlated with the number of births, a fact that may be attributed to increased cartilage damage or hormonal changes during pregnancies²⁹⁻³¹. Positive family history of hip fracture increases the rate of OA by 4 times, a finding that suggests genetic contribution and needs further investigation.

The negative correlation between OA and OP has been traditionally observed in many studies, especially in Caucasian populations^{17,32,33}. As they are both age-related disorders, it is generally assumed that as the age increases, the incidence of OA also increases, while BMD decreases. Women with OP tend to have a low BMI and low BMD, while women with OA are usually obese and have normal or high BMD, leading to the assumption that the presence of OA is a protective factor against OP and osteoporotic fractures^{13,34}. Moreover, OA patients tend to have bigger bone size in comparison to healthy controls³⁵. Reduced BMD is also associated with the loss of articular cartilage in knee OA^{17,36}. However, there are studies, mainly in Asian populations, where an association between OA and OP could not be established³⁷⁻³⁹, while in other studies, BMD has been reported to be decreased in OA-affected joint¹⁴. Animal studies have noticed that OP may impair microstructure of subchondral bone, aggravating knee OA^{40,41}. OA patients may be more prone to bone loss, due to the pain-induced immobility and lack of exercise⁴². In agreement with the majority of clinical studies in literature, in the present study, T-scores and BMD of both hips, femoral necks and lumbar spine were higher in patients with K-L>2. Similar were the results of the cross-sectional study by Multanen et al. (2015), which found that increased hip BMD is related to knee OA severity⁴³. Osteoporosis in lumbar spine has been correlated with an 85% decrease in rate of severe knee OA.

Accordingly, we observed that risk of hip fracture was significantly lower in patients with severe OA in comparison to patients with mild OA ($p=0.048$), while severe OA does not affect the risk of osteoporotic fracture. While one could infer that hip fracture risk is lower in knee OA patients due to increased hip BMD, cohort studies have not found any association and some studies have recorded increased rates of hip fractures in knee OA patients, perhaps due to pain, disturbed balance and pronation to falls^{44,45}. A large prospective cohort study, including more than 20000 knee OA patients, found that the risk of hip fracture is slightly lower in OA patients compared with controls, but this risk increases significantly for 1 year after total knee arthroplasty⁴⁶.

The role of vitamin D deficiency in OA pathogenesis has remained controversial. Studies have shown contradictory results; however, there appears to be some association between low vitamin D levels in OA patients^{47,48}. Veronese et al. (2015) noticed that low vitamin D serum levels were associated with OA of the hip and the hand⁴⁹. Heidari et al.

(2011) detected a significant association between vitamin D deficiency and knee OA in patients aged <60 years⁵⁰. Vitamin D deficiency may exacerbate pain and compromise quality of life in OA patients⁵¹. Serum levels of $25(\text{OH})\text{D}_3 < 15 \text{ ng/ml}$ have a more than 2-fold elevated risk of knee OA progression compared with patients with serum levels of $25(\text{OH})\text{D}_3 > 15 \text{ ng/ml}$ ⁵². On the other hand, the aforementioned association has not been confirmed by other studies, indicating that vitamin D deficiency is not a predictor of knee and hip OA^{53,54}. Subchondral bone sclerosis is a typical feature of OA, but there is insufficient data on the exact action of vitamin D and the way it is expressed in different tissues. In the present study, vitamin D deficiency has been correlated with a 3-fold higher risk of severe knee OA, after adjustment for BMD. Therefore, vitamin D supplementation may prevent OA progression and reduce fracture risk by increasing BMD.

The plethora of literature studies have investigated the relationship between OA and OP, OA and vitamin D and OP and vitamin D, but no study has evaluated the complex interaction among OA, OP and vitamin D deficiency. The main findings of the present study were that BMD does not affect the association of vitamin D levels with knee OA severity and that vitamin D does not affect the association of BMD and OA. Severe OA was higher in patients with vitamin D deficiency in patients with either osteopenia or OP. Most severe form of OA was found in patients with osteopenia and vitamin D deficiency. Change in OA severity is independent to BMD and vitamin D levels ($p=0.914$). A recent study investigated the prevalence of OP and hypovitaminosis D in knee OA patients, highlighting the correlation of vitamin D deficiency with OP and OA, but no further analysis of the complex interaction was made⁵⁵.

Our study has certain limitations. First the sample size was relatively low, weakening the power of the drawn conclusions. Second, we did not record data for patients' lifestyle and physical activity, which contribute to OA and OP pathogenesis. Moreover, only patients with symptomatic knee OA were included in the study; therefore the relationship between BMD and radiographic knee OA in healthy participants could not be investigated.

Conclusions

The results of the present study have confirmed that low BMD has a protective role against knee OA while vitamin D deficiency contributes significantly to knee OA severity. However, the association between OA and OP is not affected by vitamin D deficiency and the association of OA and vitamin D serum levels is not affected by BMD. Further studies are needed in order to fully elucidate the interaction of BMD and vitamin D in OA pathogenesis.

References

1. Appleton CT. Osteoarthritis year in review 2017: biology. *Osteoarthritis Cartilage* 2018;26(3):296-303.

2. Berenbaum F, Eymard F, Houard X. Osteoarthritis, inflammation and obesity. *Curr Opin Rheumatol* 2013; 25(1):114-8.
3. Brandt KD, Dieppe P, Radin EL. Etiopathogenesis of osteoarthritis. *Rheum Dis Clin North Am* 2008; 34(3):531-59.
4. Armas LA, Recker RR. Pathophysiology of osteoporosis: new mechanistic insights. *Endocrinol Metab Clin North Am* 2012;41(3):475-86.
5. Aspray TJ, Hill TR. Osteoporosis and the Ageing Skeleton. *Subcell Biochem* 2019;91:453-76.
6. Black DM, Rosen CJ. Clinical Practice. Postmenopausal Osteoporosis. *N Engl J Med* 2016;374(3):254-62.
7. Fleet JC. The role of vitamin D in the endocrinology controlling calcium homeostasis. *Mol Cell Endocrinol* 2017;453:36-45.
8. Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA, et al. Global vitamin D status and determinants of hypovitaminosis D. *Osteoporos Int* 2009;20(11):1807-20.
9. Holick MF. Optimal vitamin D status for the prevention and treatment of osteoporosis. *Drugs Aging* 2007; 24(12):1017-29.
10. Felson DT, Niu J, Clancy M, Aliabadi P, Sack B, Guermazi A, et al. Low levels of vitamin D and worsening of knee osteoarthritis: results of two longitudinal studies. *Arthritis Rheum* 2007;56(1):129-36.
11. Avci D, Bachmann GA. Osteoarthritis and osteoporosis in postmenopausal women: clinical similarities and differences. *Menopause* 2004;11(6 Pt 1):615-21.
12. Bultink IE, Lems WF. Osteoarthritis and osteoporosis: what is the overlap? *Curr Rheumatol Rep* 2013; 15(5):328.
13. Geusens PP, van den Bergh JP. Osteoporosis and osteoarthritis: shared mechanisms and epidemiology. *Curr Opin Rheumatol* 2016;28(2):97-103.
14. Im GI, Kim MK. The relationship between osteoarthritis and osteoporosis. *J Bone Miner Metab* 2014; 32(2):101-9.
15. www.sheffield.ac.uk.FRAX/tool.jsp, Accessed on: 5 August 2021.
16. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthritis. *Ann Rheum Dis* 1957;16(4):494-502.
17. Zhang Y, Hannan MT, Chaisson CE, McAlindon TE, Evans SR, Aliabadi P, et al. Bone mineral density and risk of incident and progressive radiographic knee osteoarthritis in women: the Framingham Study. *J Rheumatol* 2000;27(4):1032-7.
18. Kanis JA, Cooper C, Rizzoli R, Reginster JY. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 2019;30(1):3-44.
19. Lecorney J, Verhoeven F, Chouk M, Guillot X, Prati C, Wendling D. Correlation between catastrophizing and Lequesne index in case of osteoarthritis of the knee: A prospective study. *Joint Bone Spine* 2018;85(5):605-7.
20. Berg KO, Maki BE, Williams JI, Holliday PJ, Wood-Dauphinee SL. Clinical and laboratory measures of postural balance in an elderly population. *Arch Phys Med Rehabil* 1992;73(11):1073-80.
21. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. *Res Q Exerc Sport* 1999;70(2):113-9.
22. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991;39(2):142-8.
23. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. *Bull World Health Organ* 2003;81(9):646-56.
24. Dhaliwal R, Aloia JF. Effect of Vitamin D on Falls and Physical Performance. *Endocrinol Metab Clin North Am* 2017;46(4):919-33.
25. Ringe JD. The effect of Vitamin D on falls and fractures. *Scand J Clin Lab Invest Suppl* 2012;243:73-8.
26. Silverwood V, Blagojevic-Bucknall M, Jinks C, Jordan JL, Protheroe J, Jordan KP. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 2015;23(4):507-15.
27. Jiang L, Tian W, Wang Y, Rong J, Bao C, Liu Y, et al. Body mass index and susceptibility to knee osteoarthritis: a systematic review and meta-analysis. *Joint Bone Spine* 2012;79(3):291-7.
28. Christensen R, Bartels EM, Astrup A, Bliddal H. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2007;66(4):433-9.
29. Wise BL, Niu J, Zhang Y, Felson DT, Bradley LA, Segal N, et al. The association of parity with osteoarthritis and knee replacement in the multicenter osteoarthritis study. *Osteoarthritis Cartilage* 2013;21(12):1849-54.
30. Wei S, Venn A, Ding C, Martel-Pelletier J, Pelletier JP, Abram F, et al. The associations between parity, other reproductive factors and cartilage in women aged 50-80 years. *Osteoarthritis Cartilage* 2011;19(11):1307-13.
31. Liu B, Balkwill A, Cooper C, Roddam A, Brown A, Beral V. Reproductive history, hormonal factors and the incidence of hip and knee replacement for osteoarthritis in middle-aged women. *Ann Rheum Dis* 2009;68(7):1165-70.
32. Dequeker J, Aerssens J, Luyten FP. Osteoarthritis and osteoporosis: clinical and research evidence of inverse relationship. *Aging Clin Exp Res* 2003;15(5):426-39.
33. Nevitt MC, Lane NE, Scott JC, Hochberg MC, Pressman AR, Genant HK, et al. Radiographic osteoarthritis of the hip and bone mineral density. The Study of Osteoporotic Fractures Research Group. *Arthritis Rheum* 1995;38(7):907-16.
34. Karlsson MK, Magnusson H, Cöster M, Karlsson C, Rosengren BE. Patients with knee osteoarthritis have a phenotype with higher bone mass, higher fat mass, and lower lean body mass. *Clin Orthop Relat Res* 2015; 473(1):258-64.
35. Arokoski JP, Arokoski MH, Jurvelin JS, Helminen HJ, Niemitukia LH, Kroger H. Increased bone mineral content and bone size in the femoral neck of men with

- hip osteoarthritis. *Ann Rheum Dis* 2002;61(2):145-50.
36. Masuyama R, Stockmans I, Torrekens S, Van Looveren R, Maes C, Carmeliet P, et al. Vitamin D receptor in chondrocytes promotes osteoclastogenesis and regulates FGF23 production in osteoblasts. *J Clin Invest* 2006;116(12):3150-9.
37. Bae KJ, Gong HS, Kim KW, Kim TK, Chang CB, Jang HC, et al. Evaluation of femoral neck bone mineral density and radiographic hand and knee osteoarthritis in a Korean elderly population. *Clin Orthop Surg* 2014;6(3):343-9.
38. Im GI, Kwon OJ, Kim CH. The relationship between osteoarthritis of the knee and bone mineral density of proximal femur: a cross-sectional study from a Korean population in women. *Clin Orthop Surg* 2014;6(4):420-5.
39. Chang CB, Kim TK, Kang YG, Seong SC, Kang SB. Prevalence of osteoporosis in female patients with advanced knee osteoarthritis undergoing total knee arthroplasty. *J Korean Med Sci* 2014;29(10):1425-31.
40. Bellido M, Lugo L, Roman-Blas JA, Castañeda S, Caeiro JR, Dapia S, et al. Subchondral bone microstructural damage by increased remodeling aggravates experimental osteoarthritis preceded by osteoporosis. *Arthritis Res Ther* 2010;12(4):R152.
41. Zhang J, Chen S, Chen W, Huang Y, Lin R, Huang M, et al. Ultrastructural change of the subchondral bone increases the severity of cartilage damage in osteoporotic osteoarthritis of the knee in rabbits. *Pathol Res Pract* 2018;214(1):38-43.
42. Ding C, Cicuttini F, Boon C, Boon P, Srikanth V, Cooley H, et al. Knee and hip radiographic osteoarthritis predict total hip bone loss in older adults: a prospective study. *J Bone Miner Res* 2010;25(4):858-65.
43. Multanen J, Heinonen A, Hakkinen A, Kautiainen H, Kujala UM, Lammentausta E, et al. Bone and cartilage characteristics in postmenopausal women with mild knee radiographic osteoarthritis and those without radiographic osteoarthritis. *J Musculoskelet Neuronal Interact* 2015;15(1):69-77.
44. Arden NK, Nevitt MC, Lane NE, Gore LR, Hochberg MC, Scott JC, et al. Osteoarthritis and risk of falls, rates of bone loss, and osteoporotic fractures. Study of Osteoporotic Fractures Research Group. *Arthritis Rheum* 1999;42(7):1378-85.
45. Bergink AP, van der Klift M, Hofman A, Verhaar JA, van Leeuwen JP, Uitterlinden AG, et al. Osteoarthritis of the knee is associated with vertebral and non vertebral fractures in the elderly: the Rotterdam Study. *Arthritis Rheum* 2003;49(5):648-57.
46. Prieto-Alhambra D, Javaid MK, Maskell J, Judge A, Nevitt M, Cooper C, et al. Changes in hip fracture rate before and after total knee replacement due to osteoarthritis: a population-based cohort study. *Ann Rheum Dis* 2011; 70(1):134-8.
47. Park H, Park CY. Risk of Osteoarthritis is Positively Associated with Vitamin D Status, but Not Bone Mineral Density, in Older Adults in the United States. *J Am Coll Nutr* 2021;25:1-9.
48. Yoshimura N, Muraki S, Oka H, Nakamura K, Kawaguchi H, Tanaka S, et al. Serum levels of 25-hydroxyvitamin D and the occurrence of musculoskeletal diseases: a 3-year follow-up to the road study. *Osteoporos Int* 2015;26(1):151-61.
49. Veronese N, Maggi S, Noale M, De Rui M, Bolzetta F, Zambon S, et al. Serum 25-Hydroxyvitamin D and Osteoarthritis in Older People: The Progetto Veneto Anziani Study. *Rejuvenation Res* 2015;18(6):543-53.
50. Heidari B, Heidari P, Hajian-Tilaki K. Association between serum vitamin D deficiency and knee osteoarthritis. *Int Orthop* 2011;35(11):1627-31.
51. Alkan G, Akgol G. Do vitamin D levels affect the clinical prognoses of patients with knee osteoarthritis? *J Back Musculoskelet Rehabil* 2017;30(4):897-901.
52. Zhang FF, Driban JB, Lo GH, Price LL, Booth S, Eaton CB, et al. Vitamin D deficiency is associated with progression of knee osteoarthritis. *J Nutr* 2014;144(12):2002-8.
53. Muraki S, Dennison E, Jameson K, Boucher BJ, Akune T, Yoshimura N, et al. Association of vitamin D status with knee pain and radiographic knee osteoarthritis. *Osteoarthritis Cartilage*. 2011 Nov;19(11):1301-6.
54. Konstari S, Kaila-Kangas L, Jääskeläinen T, Heliövaara M, Rissanen H, Marniemi J, et al. Serum 25-hydroxyvitamin D and the risk of knee and hip osteoarthritis leading to hospitalization: a cohort study of 5274 Finns. *Rheumatology (Oxford)* 2014;53(10):1778-82.
55. Ghosh B, Pal T, Ganguly S, Ghosh A. A study of the prevalence of osteoporosis and hypovitaminosis D in patients with primary knee osteoarthritis. *J Clin Orthop Trauma* 2014;5(4):199-202.