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Bone Mineral Density in Postmenopausal Female Patients with Knee Osteoarthritis: A Case-Control Study

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Abstract

Background: The relationship between osteoarthritis and osteoporosis has exhibited contradictory features over the past four decades. Numerous observational and longitudinal studies have shown an inverse association between the two diseases and a protective effect of one against the other. On the other hand, some studies show that patients with OA have impaired bone strength and are more prone to fractures.

Aim of Study: The study's main objective was to determine the correlation between the bone mineral density (BMD) of the spine and hip (femoral neck) of postmenopausal women with radiologically determined OA of the knee.

Patients and Methods: This case-control study included 50 female patients with knee OA diagnosed clinically according to the American College of Rheumatology (ACR) criteria and who had radiographic evidence of grade II,III and IV knee OA as judged by the Kellgren and Lawrence scale (KL) and 50 matched healthy individuals. We evaluated a total of 100 participants aged ≥50 years who underwent knee radiography and dual-energy X-ray absorptiometry. Spearman correlation coefficient was used to test the association of severity of OA knee with BMD.

Results: Compared to the control group, we found statistically significantly lower T-scores of the spine p=0.01, as well as of the hip T-score p<0.0001. The values of T-score of the spine and hip are lower in more severe forms of OA (X-ray stage III and IV, according to KL grade), p=0.009 and p<0.001 respectively. Correlation analyses revealed that KL grades and age were significantly and negatively correlated with hip T-score p<0.0001 not with the spine T-score.

Conclusion: Postmenopausal women with radiographic knee OA had significantly lower T-scores of the hip and spine as compared to the control group without OA. Hip T-scores decrease with severity of OA knee. These data support the fact that the two conditions may be related to each other and primary care physicians must look for these two conditions in co-existence. Primary prevention of either of the two conditions should be advised, if the other condition coexists in the same patient.

Key Words: *Osteoarthritis – Bone mineral density – Osteoporosis.*

Introduction

OSTEOARTHRITIS (OA), the most common aging-related joint pathology is a degenerative disease affecting all the structures of the joints. OA is mainly characterized by articular cartilage destruction along with changes occurring in other joint components including bone, menisci, synovium, ligaments, capsule, and muscles **[1]**. Worldwide estimates that 9.6% of men and 18.0% of women aged over 60 years have symptomatic OA **[2].**

Changes in bone are closely associated with cartilage damage in osteoarthritis (OA). Furthermore, the peri-articular bone appears to have an important function in dissipating peri-articular loads. This suggests that systemic bone health may influence the capacity of peri-articular bone to adapt to stresses and stabilize an osteoarthritic joint. If so, interventions for bone health might influence OA progression **[3].**

Abbreviations:

OA : Osteoarthritis.
OP : Osteoporosis.
BMD : Bone mineral density.
ACR : American College of Rheumatology.
KL : Kellgren and Lawrence.
DXA : Dual-energy X-ray absorptiometry.
BMI : Body mass index.
IL-6 : Interleukin-6.
SPSS : Statistical package for social science.
ANOVA : Analysis of variance test.

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Osteoporosis (OP), the most common bone disease, is characterized by systemic microarchitecture impairment and bone loss, which ultimately lead to fragility fractures. The bone disease is most common in older people, especially in postmenopausal women. It is estimated that approximately 50% of the postmenopausal female population (>50 years old) suffer from osteoporosis [4,5].

OA and OP are the most common skeletal disorders associated with aging. However, any relationship between these conditions remains controversial [6]. Several cross-sectional studies have indicated that knee OA is associated with high BMD [7-11]. Some data show that women with knee and hip radiological OA have less bone loss in the lumbar spine and femoral neck compared to women without OA [8,12]. Conversely, an inverse relationship has been observed between BMD and progression of knee OA [13,14]. A prospective study of 450 patients prior to knee arthroplasty reported that BMD was lower with severe knee OA and biomarkers for bone turnover were higher with worse OA grading [15]. The above-stated facts and contradictory findings in lower limbs make us reconsider whether OA in the elderly is always associated with low bone density [12]. Our study aimed to determine the correlation between the bone mineral density (BMD) of the spine and hip (femoral neck) of postmenopausal women with radiologically determined OA of the knee.

Patients and Methods

Patients were collected from outpatient clinic of El-helmeya physical medicine and rehabilitation center from February 2021 to March 2022.

Inclusion criteria: We included only patients.

- Female sex, age ≥50.
- Postmenopausal status (no menstrual cycle for 12 months).
- Diagnosed with OA knee according to American College of Rheumatology (ACR) criteria (16) using history, physical examination, and radiographic findings.

Exclusion criteria: We excluded patients with

- Presence of comorbidities (metabolic diseases, hyperthyroidism, diabetes mellitus bone metastases, rheumatoid arthritis, kidney and liver insufficiency, malabsorption).
- Premenopausal and perimenopausal status.
- A history of drug use that might affect bone metabolism, such as glucocorticoids, estrogen, thyroid hormone, parathyroid hormone, fluoride, calcitonin, thiazines, barbiturates, antiepileptics, vitamin D or calcium-containing preparations.
- Those with secondary OA knee, local malignancy, history of fracture of pelvis or femur, joint replacement surgery of hip or knee, clinically obvious congenital disorder of lower limb and inability to transfer to the scanning table were excluded from the study.

- Consent was taken from both groups (patients and control group).

Both groups underwent the following measurements:

To assess knee OA, bilateral weight-bearing antero-posterior knee radiographs were taken and graded from 0 to 4 according to Kellgren-Lawrence criteria as follows [17]:

- Grade 0: Normal.
- Grade 1: Possible osteophytes.
- Grade 2: Definite osteophytes and possible narrowing of joint space.
- Grade 3: Multiple moderate osteophytes and definite narrowing of joint space.
- Grade 4: Large osteophytes, marked by joint space narrowing and/or bony sclerosis.

Patients with grade-0 and grade-1 radiographs were considered to not have OA as control group and were compared with the grade-2, grade-3, and grade-4 as patient group.

To assess osteoporosis, the BMDs of the subjects were measured by dual-energy X-ray absorptiometry (DEXANORLAND-1998, USA) on the same day. BMD measurements were obtained for the femoral neck and lumbar vertebrae (L2-L4).

Statistical analysis:

Data were collected, revised, coded and entered to the statistical package for social science (SPSS) version 20. The data were presented as means, standard deviations. The comparison between two independent groups regarding quantitative data with parametric distribution was done by using independent *t*-test, while data with non-parametric distribution was compared using Mann-Whitney test. Analysis of variance test (ANOVA) was used to compare between more than two groups regarding one variable. Spearman correlation coefficients (*r*) were used to assess the correlation between two quantitative parameters in the same group.

Results

Anthropometric characteristics and radiological changes of the experimental and control groups are shown in Table (1). There were no statistical differences in age, height, weight or BMI between the examined groups. There were significant statistical differences in radiological changes between groups (Table 1).

T-score of the spine and hip was significantly lower in OA group compared to controls (Table 2).

The mean values of hip T-score had a tendency to decrease with increasing KL grades. There was no significant difference in spine T-score among the KL grade groups (*p*=0.07). (Table 3).

KL grade II group showed a statistically significant difference in hip (*p*<0.0001) and spine (*p*=0.009) T-score compared to KL grade III and IV groups. (Table 4).

Correlation analyses (Table 5) revealed that KL grades and age were significantly and negatively correlated with hip T-score. There was non-significant correlation between KL grades, age and BMI with spine T-score. (Table 4).

The subjects involved in this study were 50 female patients with knee OA with mean age 57.24±4.611 years, their mean height was 163.58±7.233 cm, their mean weight was 75.6±4.294 kg, and their mean body mass index was 28.378±2.609. In addition to, 50 age and sex matched healthy subjects as a control group. The mean age of the control group was 56.68±4.514 years, their mean height was 162.62±4.853 cm, their mean weight was 77.2 ±4.01 kg, and their mean body mass index was 29.22±2.304.

Table (1): Anthropometric characteristics and radiological median grades of OA severity in the participants.

Variables	OA (Mean ± SD) (N=50)	Control (Mean ± SD) (N=50)	*p*-value
Age	57.24±4.611	56.68±4.514	0.54
Height (cm)	163.58±7.233	162.62±4.853	0.43
Weight (kg)	75.6±4.294	77.2±4.01	0.057
BMI (kg/m)	28.378±2.609	29.22±2.304	0.09
Median grades of OA severity (KL) Median (Min-Max)	2 (2–4)	1 (0–1)	<0.0001

OA : Osteoarthritis.
N : Number.
p-value : Probability value.
SD : Standard deviation.
BMI : Body Mass Index.
kg/m : Kilogram/meter.
KL : Kellgren and Lawrence classification.

Table (2): T-score values of the spine and hip in OA and control groups.

Variables	OA group	Control group	*p*-value
T-score of the spine	-0.8608±0.895	-0.4866±0.469	0.01
T-score of hip	-1.6356±0.690	-0.6236±0.396	<0.0001

Table (3): T-score in various grades of knee OA.

	KL Grade			*p*-value
	II	III	IV	
Number of subjects (%)	20 (40%)	17 (34%)	13 (26%)	
Spinal T-score (Mean ± SD)	-0.9240± 0.5707	-1.2724± 0.4217	-1.2438± 0.4670	0.07
Hip T-score (Mean ± SD)	-1.1095± 0.3570	-1.9188± 0.3961	-2.2331± 0.1051	<0.0001

Table (4): T-score values of the spine and hip in relation to the radiological grades of OA severity (KL) in the experimental group.

Variables	KL grade II (n=20)	KL grade III & IV (n=30)	*p*-value
T-score of the hip	-1.1095±0.3570	-2.055±0.3409	<0.0001
T-score of spine	-0.9240±0.5707	-1.26±0.434	0.009

N : Number.
p-value: Probability value.
KL: Kellgren and Lawrence classification.

Table (5): Spearman Correlation Coefficient (*r*) between patients' OA grading, age, BMI and T-score values of the spine and hip.

Variables	T-score hip		T-score spine	
	r	*p*-value	*r*	*p*-value
KL grades	–0.84	<0.0001	–0.26	0.06
Age	–0.67	<0.0001	–0.24	0.08
BMI	0.22	0.11	-0.11	0.44

r : Spearman Correlation Coefficient.
p-value : Probability value.
BMI : Body Mass Index.
KL : Kellgren and Lawrence classification.

Discussion

Our study aimed to determine the correlation between the bone mineral density (BMD) of the spine and hip (femoral neck) of postmenopausal women with radiologically determined OA of the knee.

We compared spine and hip T-scores in 50 postmenopausal women with ≥2 KL grade knee OA and healthy controls (KL grade 0 and 1). We found that T-score of the spine and hip was significantly lower in OA group compared to controls. These results were in agreement with Stamenkovic et al., who found statistically significant decrease in BMD and T-scores in postmenopausal women with ≥2 KL grade knee OA of the spine (BMD (g/cm^2), *p*=0.014; T-score, *p*=0.007), as well as of the hip

(BMD (g/cm^2), p=0.024; T-score p<0.001) compared to the control group *[12]*. Our results disagreed with previous studies *[8,10,18]* who stated that women with radiographically defined knee OA have a greater BMD than women without knee OA.

There are many pathogenic factors for the comorbidity of knee OA and OP, and the common factors are genetic, hormonal, inflammatory factors and biomechanical factors *[19-21]*. Some genetic factors influences on BMD lead to OA via separate effects on the cartilage. Also, high BMD reflects an underlying tendency towards increased osteoblast activity and bone formation; the same tendency might increase the risk of developing OA as a consequence of greater susceptibility to osteophyte formation. Other genetic variation in the osteoclast enzyme cathepsin K, which is required for bone resorption, was found to relate to the risk of developing OA *[22]*.

Hormonal factors, such as estrogen and leptin, play an important role in bone creation and cartilage homeostasis. Estrogen deficiency can disrupt the differentiation and activation of osteoblasts and osteoclasts, which is very important for the progression of OP *[23]*. Leptin, which has an anabolic effect on chondrocytes, has a negative effect on bone density in patients with knee OA *[24]*. The sympathetic nervous system is also involved in the control of bone activity. Sympathetic nerves release vasoactive intestinal peptide and neuropeptide I, which affect osteoblast and osteoclast activity *[25]*. Finally, inflammatory factors, such as interleukin-6 (IL-6) and highly sensitive Creactive protein, lead to OA progression and bone loss *[26,27]*.

In our study, the mean T score in grade 2 was -1.1095±0.3570, in grade 3 was -1.9188±0.3961, and in grade 4 OA knee it was -2.2331±0.1051. Thus, we observed that as the severity of OA knee increased, the T score at proximal femur decreased. Similar results were noted in the study of Anand et al., *[28]* who examined the relationship between severity of OA and bone mineral density (BMD) by evaluating the bone mineral density in ipsilateral proximal femur and radiographic KL grading of knee OA in 100 Indian patient. There was statistically significant (p<0.0001) association between BMD and severity of OA knee. BMD, T score and Z score decreased as the K L grade of OA knee increased from 1 to 4. Im et al., *[29]* concluded that higher KL grade was associated with lower BMD of proximal femur (p<0.05). Our results disagreed with Sezer et al., who found no correlation between BMD and the grade of knee OA *[30]*. In contrast, there were some observational studies showing that higher femoral neck and lumber spine BMD were associated with an increased knee OA *[31,32]*.

We found that KL grade II group showed a statistically significant difference in hip (p<0.0001) and spine (p=0.009) T-score compared to KL grade III and IV groups. Choi et al., *[33]* did relationship between bone mineral density and different K L grades of OA knee. They compared BMD of the non OA group with mild OA group as well as mild OA with moderate to severe OA group. In their study, they concluded that BMD as well as T score at lumbar spine and total hip are lower in moderate to severe OA group when compared to non OA and mild OA group. Linde et al., *[15]* evaluated 450 patients having knee OA grade 1–4, prior to knee arthroplasty. They reported that T score was lower with grade 3 and 4 in comparison to grade 1 and 2 OA knee patients with p=0.02. They concluded that bone mineral density was lower with severity of knee OA.

In our study, the mean spine T score in grade 2 was -0.9240±0.5707, in grade 3 was -1.2724± 0.4217, and in grade 4 OA knee it was -1.2438± 0.4670. Thus, we observed no significant difference in spine T-score among KL grade groups (p=0.07). Also, we found non-significant correlation between spine T-score and KL grade (r=–0.26, p=0.06). Our results agreed with the result of a previous study that found no significant difference in spine BMD among the KL grade groups (p=0.072) *[29]*. A classic explanation for the lower hip BMD in severe knee OA while spine BMD was relatively unaffected may be that severe OA patients have more pain and disability, leading to immobilization osteopenia *[29,34]*. The presence of osteophytes, vertebral endplate sclerosis, and vascular calcification can increase spine BMD, thus masking bone loss which has developed due to ageing or disease *[12]*. We confirmed this observation as we found significant negative correlation between T-score and age only for the hip (r=–0.67, p<0.0001) not for the spine (r=–0.24, p=0.08). Therefore, lumbar spine BMD is a much less typical and effective measurement than is femoral neck BMD *[29]*.

The relating BMD loss to cartilage loss in knee OA may be explained by the results of animal studies which noticed that OP may impair microstructure of subchondral bone, aggravating knee OA *[35,36]*. OA patients may be more prone to bone loss, due to the pain-induced immobility and lack of exercise *[37]*. The mechanism of association of OA and OP has not yet been established. The hypothesis that uses the phenotype of a person to explain changes in early and advanced OA and determine the association with osteoporosis is 15 years old. A hypertrophic, osteoformative type with increased BMD and slow OA progression has slow bone remodelling and lower fracture incidence. In contrast, a hypotrophic type is related to reduced BMD, accelerated bone remodelling, high fracture incidence, and reduced thickening of joint cartilage *[38]*.

The results of this study point out that radiological OA is connected with bone loss, interventions to improve BMD might provide some benefit in regards to OA structural progression. Bisphosphonates, the most commonly used therapeutic agent for osteoporosis, have been investigated as a potential therapeutic agent in OA **[3]**.

There were several limitations to this study. Only females were included in the study population; hence, it did not accurately reflect the Egyptian population, the relatively small cohort of patients, which requires an investigation of additional cases to reinforce the present conclusions. Also, our study is a case-control observational study; future longitudinal studies are needed to confirm these results. Although we made an effort to adjust for physical variables, we were not able to control for individual lifestyle and physical activity of knee OA patients.

Conclusions: Our research has shown that postmenopausal women with radiological OA of the knee have lower bone mineral density than healthy individuals without OA, which imposes the need for bone mass monitoring in these individuals. A negative correlation was found between KL grade, age and bone mineral density of the hip. These findings point to the need to prevent OA by removing the factors that influence the occurrence of the disease, the need for OA treatment, and the necessity to measure the bone mineral density in these patients with regular monitoring to prevent fractures and preserve the quality of life.

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كثافة المعادن فى العظام لدى المرضى الذين يعانون من خشونة مفصل الركبة

أظهرت العلاقة بين خشونة الركبة وهشاشة العظام سمات متناقضة على مدى العقود الأربعة الماضية. أظهرت العديد من الدراسات الرصدية والطولية وجود علاقة عكسية بين المرضين وتأثير وقائى لأحدهما ضد الآخر. من ناحية أخرى، تظهر بعض الدراسات أن المرضى الذين يعانون من خشونة بالركبة لديهم ضعف فى قوة العظام ويكونون أكثر عرضة للكسور.

تهدف الدراسة هو تحديد العلاقة بين كثافة المعادن في العظام في العمود الفقرى والورك (عنق الفخذ) لدى النساء بعد انقطاع الطمث مع درجة خشونة الركبة المحددة بالأشعة السينية.

شملت هذه الدراسة المقطعية ٥٠ مريضة مصابة بالتهاب المفاصل العظمى في الركبة والتي تم تشخيصها سريريًا وفقًا لمعايير الكلية الأمريكية لأمراض الروماتيزم والذين لديهم دليل في صورة الأشعة السينية على الإصابة بخشونة الركبة من الدرجة الثانية والثالثة والرابعة وفقًا لمقياس كيلجرين ولورنس و٥٠ فردًا يتمتعون بصحة جيدة. قمنا بتقييم ١٠٠ مشارك تتراوح أعمارهم بين ≥ ٥٠ عامًا والذين خضعوا للتصوير الشعاعى للركبة وقياس امتصاص الأشعة السينية مزدوج الطاقة. تم استخدام معامل ارتباط سبيرمان لاختبار ارتباط شدة خشونة الركبة مع كثافة المعادن بالعظام.

نتائج الدراسة: بالمقارنة مع المجموعة الضابطة، وجدنا درجات T للعمود الفقرى أقل بشكل ملحوظ إحصائيًا p = ٠,٠١، بالإضافة إلى نقاط T للورك p < ٠,٠٠٠١. قيم T-score للعمود الفقرى والورك أقل فى الأشكال الأكثر شدة من خشونة الركبة (المرحلة الثالثة والأشعة السينية، وفقًا لدرجة KL)، p = ٠,٠٠٩ و p < ٠,٠٠١ على التوالى. كشفت تحليلات الارتباط أن درجات KL والعمر كانت مرتبطة بشكل كبير وسلبى مع درجة T للورك p < ٠,٠٠٠١ وليس مع درجة T للعمود الفقرى.