RELATIONSHIP BETWEEN OSTEOARTHRITIS AND OSTEOPOROSIS IN HOMOLOGOUS JOINTS

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ABSTRACT

Introduction: Osteoarthritis and osteoporosis are the two most common musculoskeletal diseases. We investigated whether there is an inverse relationship between osteoarthritis and osteoporosis for the right and left hips.

Material and methods: Sixty-six postmenopausal women were included in this study. The subjects were divided into two groups, the osteoarthritis and control groups (n = 33 each), according to whether they had hip osteoarthritis. In the osteoarthritis group, subjects were blindly graded using the Kellgren–Lawrence system and divided into a right hip osteoarthritis group (n = 29) and a left hip osteoarthritis group (n = 32) according to the affected hip joint. The bone mineral density of both hips was measured using dual-energy X-ray absorptiometry. Physical activity was assessed using the International Physical Activity Questionnaire.

Results: A correlation between the presence of osteoarthritis and bone loss at the femoral neck was observed for the right hip (R = −0.302, p = 0.017), whereas no significant correlation was observed for the left hip. Osteoarthritis in the right hip was associated with older age and higher right femoral neck bone mineral density (R² = 0.368). The odds ratio for the radiographic presence of right hip osteoarthritis was 55.678.5 per unit difference in bone mineral density of the right femoral neck.

Conclusion: Although the right and left hips are homologous joints, the present study revealed an inverse relationship between OA and OP only for the right hip, indicating that the relationship between osteoarthritis and osteoporosis should be assessed using a joint-by-joint approach.

Keywords: Bone mineral density, Coxarthrosis, Osteoporosis.

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Introduction

Osteoarthritis (OA) and osteoporosis (OP) are the two most common musculoskeletal diseases. Both diseases are huge health problems owing to their high prevalence and increasing incidence rates owing to the ageing population(1,2). Although the prevalence of both diseases increases with age, an inverse relationship between OP and OA has been suggested because they rarely coexist(3). This suggestion was partly supported by evidence on the opposite driving mechanisms of bone changes associated with OA and OP(4). OP is characterised by increased bone loss and bone microarchitecture deterioration, leading to reduced bone strength and an increased risk of fragility fractures. However, OA is characterised by progressive degradation of the articular cartilage, increased bone formation, subchondral sclerosis and osteophyte formation(5).

Several studies have provided direct evidence about an inverse relationship between OA and OP(3,6-10), with Foss and Byers publishing the first dramatic study in this area and reporting a lower incidence of osteoporotic femoral fractures in hip OA patients(7). The inverse relationship between OA and OP can be explained by several genetic, systemic (i.e. humoral substances) and local (i.e. biomechanical properties, hip bone geometry) factors(8,11-12). Jiang et al. have suggested that differential levels of bone remodelling markers, leptin, free leptin index and osteoprotegerin...
partly contribute to the proposed inverse relationship\(^{(11)}\). Leptin, which strongly stimulates the anabolic activity of chondrocytes, exerts detrimental effects on BMD of knee OA patients\(^{(12)}\). A study conducted on twins supports the suggestion of an inverse relationship between hip OA and OP. However, this relationship was confined to the OA-affected hip. According to the authors, the generalised and greater increase of BMD in OA patients, as observed in previous studies of unrelated populations could have been partly caused by genetic factors shared by hip OA and high bone mass\(^{(9)}\). Jin et al. showed a differential effect of oestrogen depletion and supplementation on OA and OP\(^{(5)}\).

Some biomechanical properties of the subchondral bone may be locally involved in the inverse relationship between OA and OP, which has been reported mostly for large weight-bearing joints\(^{(8)}\). In this context, a hypothesis was proposed for the association of high BMD with OA, according to which both conditions share common risk factors such as weight-bearing activities\(^{(13)}\). An increase in subchondral bone density increases stiffness, leading to an overload of the overlying cartilage and thereby inducing OA\(^{(1,6,13)}\). In rare, inherited bone diseases such as osteopetrosis, where the skeleton is diffusely sclerotic, there is a high incidence of premature polyarticular OA\(^{(1)}\). However, mechanical loads cannot be efficiently transferred by the osteoporotic subchondral bone\(^{(6)}\), subjecting the cartilage to a lower load and protecting it from the detrimental effects of overload. This interaction between the subchondral bone and cartilage is proposed as a biomechanical explanation for the inverse relationship between OA and OP\(^{(1,6,13)}\). Histomorphometric analysis of femoral head samples supports this explanation in terms of trabecular bone properties, BMD and markers of bone turnover metabolism\(^{(6,14)}\).

The individual contribution of systemic and local mechanisms to the inverse relationship between OA and OP is not clearly understood. If systemic mechanisms are more prominent, it is expected that such an inverse relationship occurs in both right and left extremity homologous joints due to similar structural, anatomic and biomechanical properties. However, if the inverse relationship is not observed for both right and left extremity homologous joints, local mechanisms can be considered more prominent.

Clinical and scientific evidence suggest the existence of an inverse relationship between OA and OP, although it remains controversial. The individual contributions of systemic and local mechanisms to this relationship may help explain the conflicting results of previous studies. In studies reporting inconsistent results, the OA, OP or fragility fracture assessments were not performed in the same joint\(^{(13,15-16)}\). Therefore, a clear confirmation of the existence of an inverse relationship between OA and OP relies on the separate evaluation of OA and OP for each joint.

In the present study, the radiographic and densitometric assessments were separately performed for the right and left hips, aiming to investigate the existence of an inverse relationship between OA and OP.

**Material and methods**

This cross-sectional study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement\(^{(17)}\) and approved by the hospital Local Ethics Committee (Number:2011-3/15). This study was performed between January 2012 and September 2015 on a convenience sample at our institution. Sixty-six postmenopausal females aged 47-81 years were included. The subjects were divided into two groups, the OA and control groups (n = 33 each), according to whether they had OA in the right or left hip. Hip OA was diagnosed following the ACR criteria for the classification of hip OA\(^{(1)}\).

The subjects’ demographic and anthropometric features were recorded. Body mass index (BMI) was calculated as a measure of obesity. Evaluation of secondary hip OA and secondary OP was performed by questioning and examining the subjects.

Anteroposterior pelvic radiographs were taken with the patients in a standing position. Hip OA was graded using the Kellgren-Lawrence system by an investigator blinded to the densitometric findings\(^{(1)}\). Site-specific evaluation of the relationship between OA and OP was performed by dividing OA patients into two subgroups according to the affected hip joint: right hip OA group (n = 29) and left hip OA group (n = 32).

The bone mineral density (BMD) of both the right and left hips was measured using dual energy X-ray absorptiometry (DMS\(^{8}\) Stratos system, DMS, France) according to World Health Organization OP criteria. Bone loss was determined separately for each region of interest (i.e. right femoral neck, total right hip, left femoral neck and total left hip) according to the T-score. A T-score of between -1.0 and -2.5 was indicative of osteopenia, a T-score of -2.5 or less was indicative of osteoporosis\(^{(2)}\).

Physical activity was assessed using the Turkish version of the self-administered International Physi-
cal Activity Questionnaire (IPAQ)\(^{(18)}\). This is a 7-day recall questionnaire that provides information on the time and frequency of walking and moderate and vigorous activity and performing sedentary activities. The responses were converted into Metabolic Equivalent Task minutes per week (METmin/wk), according to the IPAQ scoring protocol. Based on the total MET scores, three physical activity levels were defined: Level 1 (i.e. low level): <600 METmin/wk; Level 2 (i.e. moderate level): 600–3000 METmin/wk; Level 3 (i.e. high level): >3000 METmin/wk.

**Statistical analysis**

Normally distributed data were analysed using the Shapiro-Wilk test. Results are presented as means [standard deviation (SD)] or median [interquartile range (IQR)]. Categorical data were analysed using either the likelihood ratio or the Pearson’s chi-square test. The Mann-Whitney U-test was used to compare the OA and control groups in terms of age and age at menopause. The independent samples t-test was used to compare the OA and control groups in terms of BMI and hip BMDs. The Spearman’s test was used for correlation analysis. A correlation coefficient (R) >0.30 and a level of p<0.05 were considered statistically significant. The odds ratio was calculated with a 95% confidence interval (CI). Multivariate binary logistics regression analysis was performed to identify hip OA-related factors. Factors with a level of p<0.05 in the forward conditional method were included in the regression model. Factors with a level of p<0.1 were excluded. The regression model was considered statistically suitable for a level of p<0.05 in the Hosmer-Lemeshow test. The 95% CIs were calculated for the odds ratios. Wald statistical analysis was conducted to determine the significance of coefficient B. A level of p<0.05 was considered statistically significant. Data were analysed using the PASW statistics software (SPSS Inc., Chicago, IL, USA).

Post-hoc power analysis was performed using the G-Power software (version 3.1.9.2, Franz Paul, Universität Kiel, Germany).

**Results**

No significant differences were observed between the right hip OA and control groups or between the left hip OA and control groups with respect to age, BMI and age at menopause (Table 1). No significant differences were observed among the right hip OA, left hip OA and control groups concerning for better assonance the physical activity level.

<table>
<thead>
<tr>
<th>Group</th>
<th>The left Hip OA (n=32)</th>
<th>The right Hip OA (n=29)</th>
<th>Control (n=33)</th>
<th>P value*</th>
<th>P value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)*</td>
<td>59.0 (12.5)</td>
<td>60.0 (11.3)</td>
<td>58.0 (8.3)</td>
<td>0.251</td>
<td>0.540</td>
</tr>
<tr>
<td>BMI (kg/m²)**</td>
<td>31.9 (4.7)</td>
<td>32.2 (4.7)</td>
<td>30.7 (4.8)</td>
<td>0.321</td>
<td>0.129</td>
</tr>
<tr>
<td>Age at menopause (yrs)</td>
<td>49.0 (7.8)</td>
<td>50.0 (7.5)</td>
<td>47.0 (9.8)</td>
<td>0.787</td>
<td>0.007</td>
</tr>
</tbody>
</table>

**Table 1**: Demographic and anthropometric data of subjects.

* Data were given as median (interquartile range)

** Data were given as mean (standard deviation)

* P value for comparison between left hip OA and Control group

** P value for comparison between right hip OA and Control group

According to the Kellgren-Lawrence grading system, 20 (69.0%) right hips were grade 1, 4 (13.8%) right hips were grade 2, 2 (6.9%) right hips were grade 3 and 3 (10.3%) right hips were grade 4. Furthermore, 20 (62.5%) left hips were grade 1, 7 (21.9%) left hips were grade 2, 3 (9.4%) left hips were grade 3 and 2 (6.3%) left hips were grade 4 (p = 0.784).

A statistically significant difference was found between the right hip OA and control groups regarding the femoral neck BMD and total hip BMD. No such differences were observed between the left hip and control groups (Table 2).

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Right hip OA</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right femoral neck BMD</td>
<td>0.965 (0.135)</td>
<td>0.841 (0.135)</td>
<td>0.001</td>
</tr>
<tr>
<td>Right femoral neck BMD</td>
<td>0.775 (0.153)</td>
<td>0.685 (0.151)</td>
<td>0.120</td>
</tr>
<tr>
<td>Left femoral neck BMD</td>
<td>0.895 (0.161)</td>
<td>0.835 (0.144)</td>
<td>0.274</td>
</tr>
<tr>
<td>Left hip Total BMD</td>
<td>0.951 (0.167)</td>
<td>0.909 (0.137)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2**: The mean BMDs of the right and left hip.

* Data were given as median (interquartile range)

** Data were given as mean (standard deviation)

In the right hip OA group, significant correlations were found between the OA grade and neck BMD and between the OA grade and total hip BMD (R = 0.452, p = 0.0001 and R = 0.305, p = 0.016, respectively). No such correlations were found for the left hip (R = 0.224, p = 0.073 and R = 0.187, p = 0.136, respectively).

The frequency of patients with no bone loss was significantly higher in the right hip OA group (72.4%) than in the control group (42.4%) (P = 0.016) (Table 3).
An inverse relationship was found between the presence of right hip OA and bone loss at the right femoral neck ($R = -0.302$, $p = 0.017$). Among right hip OA patients, the odds ratio (95% CI) for bone loss at the right femoral neck was 0.28 (0.09–0.81). Statistical analysis for the left hip did not yield significant results (Table 4).

The multivariate logistic regression model showed that right hip OA was associated with older age and higher femoral neck BMD (Nagelkerke R square = 0.368, Hosmer-Lemeshow test $p = 0.520$). The odds ratio (95% CI) for the radiographic presence of right hip OA was 55678.5 (120.1-25804661.0) per unit difference in BMD of the right femoral neck (Table 5). Adjustment for potential confounding variables such as BMI, age at menopause, and physical activity level had no significant effect on the results.

Post-Hoc Statistical Power Analysis

The primary outcome measure was the relationship between bone loss and OA. For the determined effect size (0.3) total sample size ($n = 62$) and alpha (0.05, two-tailed), this study had a power of 0.68.

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Bone loss</th>
<th>Hip OA</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right hip</td>
<td>Left hip</td>
<td></td>
</tr>
<tr>
<td>Femoral neck</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>21 (72.4%)</td>
<td>13 (40.6%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Present</td>
<td>8 (27.6%)</td>
<td>19 (59.4%)</td>
<td></td>
</tr>
<tr>
<td>Total hip</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>22 (75.9%)</td>
<td>23 (71.9%)</td>
<td>0.723</td>
</tr>
<tr>
<td>Present</td>
<td>7 (24.1%)</td>
<td>9 (28.1%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Distribution of patients with bone loss between the right and left hip OA group.

"Likelihood ratio"

The main finding of this study was that the relationship between OA and OP depends on the affected joint, even for homologous joints. In the present study, the relationship between OA and OP was investigated for the right and left hips, which are homologous joints. After adjusting for age, BMI, age at menopause and physical activity level, we demonstrated an inverse relationship between OA and OP for the right hip, whereas no such relationship was demonstrated for the left hip.

The relationship between OA and OP has long been a subject of debate. Despite evidence regarding a positive association between systemic BMD and radiographic OA several inconsistencies and areas of controversy remain. Assessing BMD and radiological OA on a joint-by-joint basis may help explain such inconsistencies reported in the literature.

A co-twin control study has confirmed the existence of an inverse relationship between OA and OP for the hip. However, this relationship was confined to the femoral neck and localised to the ipsilateral hip, with no clear association between radiographic hip OA features and BMD in the contralateral hip(9). The authors measured BMD in the non-dominant hip, whereas in the present study, BMD was assessed in both the hips. Similarly, an inverse relationship between OA and OP was found only for one hip.

While OP is determined as a systemic skeletal disease, the relative contribution of mechanical stress and systemic processes to different types of OA remains unclear. The contribution of systemic processes for OA in weight-bearing joints is questionable and difficult to identify because increased mechanical stress and systemic processes frequently occur together in obese individuals(19). The pathogenesis of OA needs to be examined on a joint-by-joint basis(20). Therefore, the site of BMD and radiological assessment is important to identify the exact relationship between OA and OP. Most previous studies have assessed BMD and radiological OA for different body regions and have found no relationship between OA and OP.

Akamatsu et al. have found an inverse relationship for the trabecular bone in the tibial condyles as well as an association between subchondral BMD and OA in the knee joints. They also found an association between lumbar spine BMD and knee OA but not between femoral neck BMD and knee OA(21). Therefore, their results support the view that OA and OP should be assessed on a joint-by-joint basis.
Osteophytes and subchondral sclerosis reflect bone formation, with the metabolic changes that lead to osteophytes favoring bone formation activity\(^{(10)}\). Osteophytosis may, therefore, affect BMD measured at any site. Osteophytes and joint space narrowing may relate to BMD in different ways. Several recent studies using magnetic resonance imaging (MRI) have reported a positive association between BMD and cartilage thickness/volume in the knees of healthy subjects\(^{(22)}\). In the present study, the relationship between OA and OP was determined using osteophytes and joint space narrowing as indicators of OA. Both osteophytes and joint space narrowing were assessed by pelvis radiography, instead of hip MRI. In bone densitometry measurements, if osteophytes and subchondral sclerotic areas remain within the region of interest, bone loss may not be erroneously detected. Accordingly, in the present study, an inverse relationship between OA and OP was found for femoral neck BMD, but not for total hip BMD.

Zhang et al. studied femoral head specimens obtained from 17 postmenopausal women (OA, \(n = 8\); OP, \(n = 9\)) during a hip surgery. They compared the microstructural and mechanical characteristics of the subchondral trabecular bone from postmenopausal women with OA and OP, obtaining specimens from the same area of the femoral head for both groups. They observed differences in the microstructure of bones with OA and OP, confirming the existence of an inverse relationship between the two diseases\(^{(23)}\). Conversely, Tarantino et al. assessed BMD and histomorphometric structure in patients undergoing hip arthroplasty for severe OA- or OP-related femoral fractures. Their preliminary data support the hypothesis that hip OA and OP can coexist. In OA patients, the femoral neck BMD was measured on the hip undergoing surgery, whereas in patients with osteoporotic hip fractures, it was measured in the contralateral, non-fractured hip\(^{(4)}\). As shown in the present study, the right and left hip joints exhibit a different relationship between OA and OP.

Several neuronal, humoral mechanisms may be proposed to explain the inverse relationship between OA and OP. Leptin, which strongly stimulates anabolic activity in chondrocytes, exerts a detrimental effect on knee BMD in OA patients\(^{(11,12)}\). Oestrogen deficiency can alter the differentiation and activity of osteoblasts and osteoclasts, which are of great importance for the development and progression of OP. Oestrogen receptors \(\alpha\) and \(\beta\) are detectable in articular chondrocytes suggesting that oestrogen directly affects the articular cartilage and is therefore involved in OA pathogenesis. It has therefore been suggested that oestrogen depletion and supplementation affects OA and OP differently, although postmenopausal women with OA and OP experience similar hormonal changes\(^{(5)}\).

Bone formation is neuronally regulated. Sympathetic nerves release vasoactive intestinal peptide and neuropeptide Y, which influence bone formation and osteoclast activation for bone resorption\(^{(24)}\). Recent studies have shown that the sympathetic nervous system is involved in the regulation of bone mechanoadaptive responses. The sprouting of sympathetic nerve fibers has been identified in the subchondral bone, inducing the subchondral bone loss at the OA joints\(^{(25)}\). Therefore, sprouting of sympathetic nerve fibers may help explain the coexistence of OA and OP. It is possible that the right and left hip joints differed in terms of sympathetic nerve fiber sprouting throughout OA in our study. Possible differences in sympathetic nerve sprouting between hips may explain our findings of an inverse relationship between OA and OP for the right, but not for the left, hip.

This study has some limitations. The main limitations of the present study were the relatively small cohort and the fact that only females were included. Additional studies should be performed on male patients to support the present conclusions. Another limitation was the cross-sectional and observational nature of the study. Future longitudinal studies are needed to confirm these results.

Several research papers have been published over the past years that debated the relationship between OA and OP. Assessing BMD and radiological joint OA on a joint-by-joint basis may help explain the inconsistencies reported in the literature. To the best of our knowledge, there is no study investigating the relationship between OA and OP in a site-specific way, at homologous joints. We recommend that the presence of the relationship between OA and OP should be assessed on a joint-by-joint basis.

### References


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