Association between platelet count and osteoarthritis in women older than 50 years

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Abstract

Background: Osteoarthritis (OA) is a multifactorial disease involving inflammatory processes. Platelets play important roles in both hemostasis and the inflammatory response; however, the relationship between platelet count and OA is unclear. Our aim was to evaluate the association between platelet count and knee and hip OA in Korean women.

Methods: In this cross-sectional designed study, we included a total of 6011 women aged ≥50 years from the 2010–2013 Korea National Health and Nutrition Examination Survey. Knee and hip OA were defined as Kellgren–Lawrence grade ≥2 and presence of knee or hip pain, respectively. Platelet counts were divided into quartiles as follows: Q1, 150–212 (10^3/µl); Q2, 213–246 (10^3/µl); Q3, 247–283 (10^3/µl); and Q4, 284–450 (10^3/µl). Multiple logistic-regression analysis was conducted to calculate odds ratios and 95% confidence intervals. Receiver operating characteristic analysis was performed to determine the optimal platelet count cut-off with which to discriminate participants with knee and/hip OA versus those without OA.

Results: Of the 6011 participants, 1141 (18.1%) had knee or hip OA. The mean age of participants without OA was 60.6 years, and that of participants with OA was 68.0 years. Compared with the lowest quartile, odds ratios (95% confidence intervals) for OA were 1.08 (0.84–1.39) for Q2, 0.94 (0.73–1.23) for Q3, and 1.35 (1.08–1.69) for Q4 after adjusting for confounders. The prevalence of OA was significantly higher with platelet counts ≥288 × 10^3/µl, compared with platelet counts <288 × 10^3/µl.

Conclusion: High platelet counts within the normal range are significantly associated with knee and hip OA.

Keywords: knee osteoarthritis, KNHANES, hip osteoarthritis, platelet count, women

Received: 22 September 2019; revised manuscript accepted: 24 February 2020.

Introduction

Osteoarthritis (OA) is a degenerative joint disease that causes extensive deformity and damage to bone, synovium, soft tissue, and cartilage due to a pathologic process involving both inflammatory mediators and mechanical wear.1,2 Globally, hip and knee OA is the 11th most common cause of global disability out of 291 conditions across 187 countries.3 With worldwide increases in aging and obesity, OA prevalence is anticipated to continuously increase and become a major public health concern.4 OA on large joints, such as the knee and hip, can result in disability and loss of independence that lead to increased economic burden.5

OA is more common in women than in men and occurs after 40–50 years of age.6 Sex differences in the severity, pain, hormonal modulation, and biomechanics of OA have also been noted.7 Comorbidities, genetic predisposition, and joint-level risk factors are important risk factors of OA.8 Although the primary treatment strategies for OA are nonpharmacological interventions, such as education, weight loss, and exercise, pharmacological treatment with acetaminophen/paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) are also important modalities for patients with symptomatic OA.9 OA has been recognized as a local, irreversible disease; however, a recent meta-analysis reported that OA is closely...
associated with cardiovascular disease and cerebrovascular accidents.\textsuperscript{10,11} In light of this, OA has increasingly been regarded as a systemic musculoskeletal disorder with metabolic components not limited to articular cartilage.

Platelets derived from megakaryocyte cytoplasm are important to maintaining hemostasis and managing vascular integrity.\textsuperscript{12} Emerging evidence has indicated that platelets play considerable roles in inflammatory processes, range from infectious disease to atherosclerosis.\textsuperscript{13} Platelets directly and indirectly interact with white blood cells (WBCs) and vascular endothelial cells.\textsuperscript{14} Platelet counts are also known to be affected by estrogen.\textsuperscript{15,16} Therefore, we hypothesized that chronic inflammation and disrupted vascular function linked to elevated platelet counts could be related to the presence of OA in Korean women over 50 years old.

A previous study reported that mean platelet volume and platelet–lymphocyte ratio are independent predictors of severe hip OA.\textsuperscript{17} However, the association between platelet count and OA is still unclear. Therefore, we aimed to investigate the relationship between platelet count and OA in Korean women over 50 years old using data from the 2010 to 2013 Korea National Health and Nutrition Examination Survey (KNHANES).

**Methods**

**Study population**

KNHANES, a population-based study, has been used to assess health risk factors and the prevalence rates of major chronic diseases among Korean people since 1998. All data are publicly available through the KNHANES website (http://knhanes.cdc.go.kr). We used data from 2010 to 2013 that included knee and hip-joint X-rays. We included a total 7498 women aged ≥50 years. We excluded cases with missing platelet counts (n = 1053) or missing radiological findings (n = 258). We also excluded women with a platelet count <150 × 10³/µl or >450 × 10³/µl, both of which are outside the normal range (n = 176). Finally, 6011 participants were included in the final analysis. The process of study population selection is shown in Supplementary Figure 1. The study protocol was approved by the Institutional Review Board of Korea Centers for Disease Control and Prevention, and all participants provided written informed consent to participate in the KNHANES. The Institutional Review Board of Yongin Severance Hospital approved this study (IRB Number: 9-2019-0010).

**Definition of knee and hip osteoarthritis**

During the KNHANES, knee and hip radiography (DigiRAD-PG) was assessed for all participants. Plain anterior-posterior and lateral radiographs of the knee and pelvis anterior-posterior and hip-joint oblique of the hip were taken according to a standard protocol. The radiographs were evaluated by two well-trained radiologists based on the Kellgren–Lawrence (KL) grading system.\textsuperscript{18} The KNHANES conducted academic meetings with experts who categorized radiological levels of OA in the knee into five grades (grade 0 to grade 4) and those in the hip into four grades (grade 0 to grade 3) based on the KL grades (available at https://knhanes.cdc.go.kr/knhanes/sub04). Unfortunately, they did not mention the exact reasons for these classifications in the guideline for KNHANES examination.

KL grading of the knee was as follows: Grade 1, possible osteophytes; Grade 2, definite osteophytes; Grade 3, moderate joint space narrowing and definite osteophytes; and Grade 4, severe joint space narrowing with subchondral sclerosis. Based on these scores, knee OA was classified into five groups: K0, no abnormal finding (normal); K1, mild degenerative changes in both knees (KL grade 1); K2, degenerative OA in both knees (KL grade 2); K3, degenerative OA in both knees (KL grade 3); and K4, degenerative OA in both knees (KL grade 4). Both sides of the knee were graded, and the higher grade was determined as the KL grade of each participant.
KL grading of the hip was as follows: Grade 1, osteophyte; Grade 2, joint space narrowing; and Grade 3, definite subchondral sclerosis with joint space narrowing. Hip OA was classified in four groups: H0, no abnormal findings (normal); H1, mild degenerative changes in both hips (KL grade 1); H2, degenerative OA in both hips (KL grade 2); and H3, degenerative OA in both hips (KL grade 3). The interrater agreements of two different radiologists were Kappa = 0.7407 and Kappa = 0.4674 for knee and hip OA, respectively. Knee and hip pain were assessed by a questionnaire. Participants were asked the following questions: ‘Have you ever experienced knee pain for more than 30 days during the last 3 months?’ and ‘Have you ever experienced hip pain for more than 30 days during the last 3 months?’ Knee OA was defined as KL grade ≥2 and the presence of knee pain. Hip OA was defined as KL grade ≥2 and the presence of hip pain. Presence of OA was defined when participants had knee OA or hip OA.

Statistical analysis
The sampling plan was a multistage clustered probability design based on primary sampling units. All statistics were calculated using sample weights assigned to sample participants. More detailed information was published in a previous study. All statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Data are presented as mean ± standard error (SE) or percentage ± SE. Clinical characteristics were compared with weighted, two-sample, and independent Student’s t tests for continuous variables or weighted Chi-square test for categorical variables. We used a weighted Chi-square test to compare radiologic findings of knee/hip OA and presence of pain according to OA.

Results
Table 1 shows the clinical characteristics of the study population according to the presence of OA. Of the 6011 participants, 1141 (18.1%) had knee or hip OA. The mean age of the participants without OA was 60.6 ± 0.2 years, and that for participants with OA was 68.0 ± 0.3 years. BMI was significantly higher in participants with
OA than those without OA (25.4 kg/m² versus 24.1 kg/m², \( p < 0.001 \)). Participants with OA had significantly higher SBP, fasting glucose, and WBC counts than those without OA. The proportions of current smokers, regular exercisers, and alcohol consumption were not significantly different between subject with and without OA \( (p = 0.626, p = 0.091 \text{ and } p = 0.270, \text{ respectively}) \). The participants with OA had more chronic diseases \( (p = 0.005) \). The mean platelet count was significantly higher in participants with OA than in those without OA \[ 264.4 \text{ versus } 259.5 \text{ (10}^3/\mu l), \quad p = 0.022 \].

Table 2 presents the radiological findings and presence of pain according to the presence of OA: 28.8% of participants with hip OA and 99.6% of participants with knee OA had symptomatic pain.

Figure 1 shows the probability of the presence of OA according to platelet counts (with 95% CIs) as predicted by the unadjusted logistic-regression model. We found a linear relationship between platelet counts and presence of OA (insert Figure 1).

The ORs and 95% CIs of OA are presented in Table 3. Compared with the lowest quartile, ORs (95% CIs) for the presence of OA were 1.09 (0.85–1.39) for Q2, 0.95 (0.74–1.22) for Q3, and 1.34 (1.07–1.68) for Q4 after adjusting for age and BMI. Compared with the lowest quartile,
ORs (95% CIs) for the presence of OA were 1.08 (0.84–1.39) for Q2, 0.94 (0.73–1.23) for Q3, and 1.35 (1.08–1.69) for Q4 after adjusting for age, BMI, smoking, alcohol intake, and regular exercise. Significant associations were noted between platelet counts and OA after additionally adjusting for WBC count and the number of chronic diseases.

In addition, we performed tests for interactions for age grouping. There were no effects of interaction for age (p = 0.425). However, we wanted to
identify the characteristics of age groups, as age is a well-known risk factor of OA. Subgroup analysis of age identified significantly higher OR values for OA in the highest-platelet quartile group, compared with the lowest-platelet quartile group, in the older age group (≥65 years). There was no significant association between platelet count quartiles and OA in the 50–64-year age group. The results are shown in Supplementary Table 1.

In ROC analysis, a platelet count of 288 (10^3/μl) was used as a cut-off point to maximize the Youden index. The prevalence of OA was significantly higher in participants with platelet counts ≥288 × 10^3/μl, compared with platelet counts <288 × 10^3/μl (21.6% and 16.8%, p < 0.001).

Discussion
We found that an elevated platelet count within the normal range is associated with the presence of symptomatic knee and hip OA confirmed on radiography in Korean women. Specifically, a platelet count ≥288 × 10^3/μl showed discriminatory power for the presence of knee and hip OA.

Previous studies have shown that individuals with knee or hip OA are likely to have increased risks of hypertension, acute coronary syndrome, and stroke. Impaired physical function due to OA has been attributed to a limited range of motion and joint pain, and this could partly be a reason for increased risks of cardiovascular disease and cerebrovascular accidents. However, a Framingham heart study still found a significant association between symptomatic hand OA and coronary heart disease after additional adjustment for physical activity score. In the current study, physical activity levels were not significantly different between participants without OA and with OA (p = 0.091). We considered participants who walk more than 30 min and more than 5 days per week as regular exercisers, regardless of intensity.

OA was traditionally considered a local disease of hyaline cartilage with associated bone and ligament caused by 'wear and tear’. This concept has been reconsidered since OA pathophysiology is multifactorial, and chronic low-grade inflammation is a crucial underlying mechanism of OA development. The proposed relationship between platelet count and OA is bidirectional. In our study, individuals with knee and hip OA had more chronic diseases and higher age, BMI, SBP, fasting blood glucose, and WBC count. These results could suggest that metabolic-triggered inflammation is associated with knee and hip OA. We also found a significant association between platelet count and OA after adjusting for these confounders. This suggests that platelet count itself is still likely an important factor affecting the presence of OA. Also, in the current study, the difference in BMI between participants with OA and those without OA was relatively small; however, previous studies have reported that the risk of knee OA increases 15% for each 1 unit increase in BMI, and an increase in 1 unit of BMI at baseline has been found to be associated with a 10.5% increased risk in total knee arthroplasty (p = 0.017).

Chronic inflammation is a potential mechanism linking elevated platelet counts and OA. Platelets release cytokines and chemokines, which attract leukocytes and promote adhesion to damaged vascular endothelium during the inflammatory response. Platelets regulate this process through the action of thrombopoietin and interleukin (IL)-6 when the protoplasm of megakaryocytes formed in the bone marrow divides into many pieces and is released into the blood. A 2.9-year longitudinal study found that circulating IL-6 was associated with cartilage loss in knee OA. Systemic and local IL-6 stimulate osteoclast activation, leading to synovial cell and chondrocyte production of matrix metalloproteinases that induce cartilage destruction. IL-6 has also been implicated in increasing platelet counts and activity and initiating the coagulation cascade, while increasing C-reactive protein levels.

Increased oxidative stress could be a link between higher platelet counts and OA. Both platelets and chondrocytes produce reactive oxygen species (ROS), and high ROS levels lead to platelet activation, thrombus formation, and OA development due to both cartilage destruction and inhibition of new cartilage synthesis. The ROS scavenger α-lipoic acid was shown to protect articular cartilage against OA progression in a rat model of the disease.

Finally, vascular dysfunction could lead to both elevated platelet counts and OA progression. Several population-based studies have reported a significant association between atherosclerosis and OA in women. Hoeven and colleagues showed that blood levels of CD40L and vascular cell adhesion molecule 1 were higher in women
with knee OA than those without knee OA. The prospective Rotterdam study demonstrated that carotid intima media thickness is significantly associated with OA in women.36 Platelets interact with the endothelium to regulate vascular integrity.37 Disturbed endothelial cell function has been attributed to prolonged exposure to cardiovascular risk factors leads to platelet aggregation, adhesion to the endothelium, and the release of platelet-derived growth factors.38

In age-specific analysis, there was some discrepancy between platelet counts and OA across the age groups. An independent association between platelet count and OA was only significant in women over 65 years. Although the reason for this discrepancy is unclear, the lack of statistical significance for the association between platelet counts and OA for the middle-aged group (50–64 years) might be attributable to the relatively small prevalence of OA therein, compared with prevalence of OA in groups over 65 years.

Our study has several limitations. First, despite the significant relationship observed between elevated platelet counts and OA, we cannot conclude whether platelet count is a risk factor for OA development or a consequence of OA. Because this study had a cross-sectional design, the results should be cautiously interpreted, and further prospective studies are needed. Second, as we used secondary data from the 2010 to 2013 KNHANES, we were not able to assess possible associations between OA and other platelet indices, such as mean platelet volume or platelet distribution width. Also, we also did not consider other inflammatory markers, such as C-reactive protein or IL-6, in this study. Third, since the inclusion rate was 80.2%, there was a possibility of having selection bias in the participation rate. However, we applied sampling weights to all analyses to accurately represent the study population using representative data. Thus, our findings can be generalized to all Korean women ≥50 years old. Fourth, the Kappa value for diagnosis of radiological hip OA was moderate. Also, the prevalence of hip OA in the KNHANES was too small, making it difficult to identify the relationship between platelet counts, knee OA, and hip OA after distinguishing between knee OA and hip OA. Finally, we had limited information on the use of medications that affect platelet function (e.g. NSAIDs). Even though NSAIDs can inhibit platelet cyclooxygenase, platelet counts in patients with OA were significantly higher than those without OA. We also found that a significant association between platelet count and OA remained after adjusting for treatment of stroke, angina, and myocardial infarction. Despite these limitations, our study has several strengths. To the best of our knowledge, this is the first investigation of a possible association between platelet count and OA in women. Knee and hip OA were radiographically confirmed. We used platelet counts as an easy and economic parameter with which to discriminate the presence of OA in clinical settings.

Conclusion
High platelet counts within the normal range are significantly associated with knee and hip OA in Korean women over 50 years. Further studies to elucidate the biological mechanisms between platelet count and OA are warranted. Strategies to reduce chronic inflammation, such as weight reduction and lifestyle modification, could help prevent OA development and progression.

Acknowledgments
Y-JK and I-HK contributed to the conception and design of the work; the acquisition, analysis, and interpretation of data; manuscript drafting; and gave final approval of the version to be published. K-HC contributed to the acquisition, analysis, and interpretation of data and gave final approval of the version to be published. Y-JL contributed to the interpretation of data, revised critically for important intellectual content and approved the version to be published in the revision process. H-SK contributed to the conception and design of the work, data analysis and interpretation, revision for important intellectual content, and gave final approval of the version to be published.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: this study was supported by a 2018 Faculty Research Grant from Yonsei University College of Medicine (6-2018-0090) to Y-JK.

Conflict of interest statement
The authors declare that there is no conflict of interest.
Supplemental material
Supplemental material for this article is available online.

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