


## CLINICAL ARTICLE

# Associations Between Periosteal Reaction of Proximal Tibial and Medial Compartment Knee Osteoarthritis

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**Objective:** To evaluate and analyze the potential relationship between periosteal reaction and medial compartment knee osteoarthritis (KOA), and to assess the independent risk factors for the development of periosteal reaction associated with medial compartment KOA.

**Methods:** This is a retrospective comparative study. From January 2019 to December 2019 at the Third Hospital of Hebei Medical University, a total of 363 patients (726 knees) with medial compartment KOA were enrolled in this study according to our inclusion and exclusion criteria, including 91 males and 272 females, with an mean age of  $57.9 \pm 12.8$  years (range, 18–82 years). Among these patients, 206 patients (412 knees) were allocated to the periosteal reaction group (44 males and 162 females) and 157 patients (314 knees) were allocated to the non-periosteal reaction group (47 males and 110 females). The classification of KOA severity was based on Kellgren and Lawrence (K-L) grading system. The malalignment of the lower extremities in coronal plane was evaluated as medial proximal tibial angle (MPTA), hip-knee-ankle angle (HKA), and lateral distal femoral angle (LDFA). Patients demographics and radiographic parameters were recorded in the two groups. Intra-observer and inter-observer reliabilities of all radiological measurements were analyzed by intraclass correlation coefficients (ICCs). Univariate analyses were conducted for comparison of differences with continuous variables between patients with periosteal reaction and without periosteal reaction. Multivariate logistical regression analysis was performed to determine the independent risk factors of radiographic parameters for periosteal reaction.

**Results:** The overall incidence of periosteal reaction associated with medial compartment KOA was 56.7%. Furthermore, we observed that the incidence of periosteal reaction significantly increased with age and correlated with K-L grade progression ( $P < 0.05$ ). There was a statistically significant difference between the two groups. In the multivariate logistical regression analysis, HKA and JLCA were identified as independent risk factors of the development of periosteal reaction in patients with medial compartment KOA (odds ratio [OR], 0.594; 95% confidence interval [CI] 0.544–0.648;  $P < 0.05$ ; OR, 0.851; 95% confidence interval CI 0.737–0.983;  $P < 0.05$ ; respectively), with other radiographic parameters including MTPA (OR 0.959; 95% CI 0.511–0.648;  $P > 0.05$ ), LDFA (OR 0.990; 95% CI 0.899–1.089;  $P > 0.05$ ), and JSW (OR 1.005; 95% CI 0.865–1.167;  $P > 0.05$ ).

**Conclusions:** In this retrospective study, patients with lower HKA and higher JLCA were identified as independent risk factors for the development of periosteal reaction, which occurred most commonly adjacent to the lateral of proximal

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tibia diaphysis, and thus we concluded that periosteal reaction may be an anatomical adaptation for medial compartment KOA based upon these results.

**Key words:** Knee osteoarthritis; Medial compartment; Periosteal reaction; Proximal tibial shaft

## Introduction

Knee osteoarthritis (KOA) is one of the most common joint disorders arising from multifactorial factors, including genetic component, gender, age, obesity, malalignment of the lower limb, and bone morphology<sup>1-4</sup>, which leads to functional impairment with a decreased physical activity level and often increases the risk of physical disability for patients<sup>5</sup>. Furthermore, KOA was generally regarded as a global public health problem and has the highest incidence rate between the ages of 55–65 years and poses an enormous socioeconomic burden worldwide<sup>6,7</sup>. It is well-known that the medial compartment KOA is considered as the most common subtype of knee osteoarthritis due to the fact that the loading in the medial compartment is about 2.5 times greater than the lateral side in a healthy population<sup>8</sup>. Meanwhile, studies have reported that the incidence rate of medial compartment KOA is approximately 25%, whereas lateral compartment KOA accounts for only 5% in patients with KOA<sup>9</sup>, indicating the medial compartment of the knee are more commonly affected than the lateral compartment. Currently, the common symptoms in patients with medial compartment KOA contains pain and limited knee range of motion, which ultimately result in a decline in patients' quality of life and leads to malalignment of the lower extremities and intra-articular cartilage wear<sup>10-12</sup>. Accordingly, disproportionate loading onto the knee joint with varus malalignment contributes to KOA progression<sup>13</sup>.

Periosteum, located at the interface between the cortex and peri-osseous soft tissues, is a thin but tough peripheral membrane of the bone which contains a fibrous layer and cambial layer, and plays an important role in bone remodeling for adults<sup>14</sup>. Although periosteum exhibit several crucial effects in children and adults, orthopaedists have pay little attention to this dynamic structure. Periosteal reaction in plain radiography can be seen as different thickness lines which may closely parallel the cortex of the bone. Some authors have proven that there could be a wide variety of reasons that induce periosteal bone formation, including trauma, infection, metabolic diseases, inflammatory disorders, systemic diseases, benign and malignant tumors<sup>15-18</sup>. Meanwhile, we found a general phenomenon that the development of periosteal reaction often occurs in lateral of proximal tibia diaphysis in the occurrence and progression of medial compartment KOA according to the standing full-limb anteroposterior (AP) radiographs.

Unfortunately, little is known about the characteristics of the cortical layer of the surface changes associated with medial compartment knee osteoarthritis, nor the radiological measurements of these changes in relationship with coronal malalignment. Since medial compartment KOA with varus knee redistributes the weight-bearing load and realigns the

mechanical axis of the lower limb, the mechanical environment of the proximal tibia would differ from the healthy population. According to our clinical observation and scientific research, we suggest that the theory of “non-uniform” settlement of tibial plateau is in association with the development of periosteal reaction in patients with medial compartment KOA. Given that the theory of “non-uniform” tibial plateau is an initial factor of medial compartment KOA, it may result in the increase of compressive forces on the medial side of proximal tibia shaft while increasing tensile stress on the lateral side of proximal tibia shaft. This may in turn stimulate the periosteum to produce new bone on the cortical layer of the surface of the tibia. Consequently, periosteal reaction in the proximal tibial shaft might be remodeled through a similar mechanism to the theory of “non-uniform” tibial plateau in patients with medial compartment KOA.

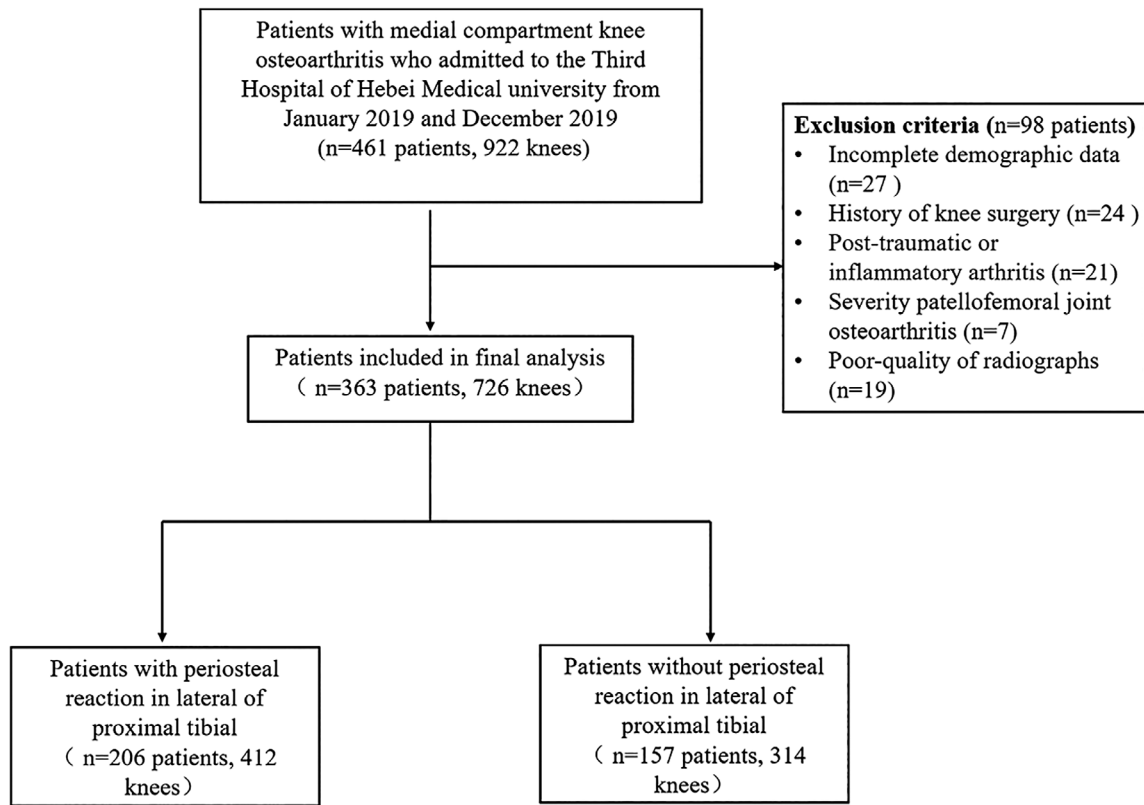
In the present study, we proposed the concept of “adaptive periosteal reaction” (APR) for the first time in response to this phenomenon in patients with medial compartment KOA. Furthermore, this periosteal reaction that occurred in the proximal tibial shaft is non-symmetrical. However, to the best of our knowledge, there have been no reports that investigate the relationship between the periosteal reaction adjacent to the lateral proximal tibia diaphysis and patients with medial compartment KOA. Herein, a consecutive cohort of patients with medial compartment KOA presented in our hospital was retrospectively analyzed. Better understanding the correlation with radiological measurements for the occurrence and development of periosteal reaction may help orthopaedic surgeons develop further insight into the natural history of KOA and the mechanisms of medial compartment KOA.

The purpose of the present study was to: (i) evaluate the potential relationship between the periosteal reaction and medial compartment knee osteoarthritis; (ii) clarify the association between periosteal reaction and age in patients with medial compartment KOA; (iii) and to further explore the measurement of radiographic parameters correlated with periosteal reaction in patients with medial compartment KOA.

## Methods

### Study Design

This study was a single-center retrospective comparative study and was approved by the Ethical Committee of the Third Hospital of Hebei Medical University and was conducted in accordance with the Declaration of Helsinki. All individual participants provided written informed consents to their participation in this study. Weight-bearing in full limb radiographs obtained in our hospital from January 2019



**Fig. 1** Flowchart of patient enrollment.

to December 2019 were reviewed through the picture archiving and communication systems (PACS; Science & Technology General Company of Hebei Medical University, Shijiazhuang, China). As shown in Fig. 1, a total of 476 consecutive patients with long-standing anterior–posterior (AP) radiographs were identified and measured in the PACS system during this time. Out of 476 patients, 98 patients were excluded according to the following exclusion criteria, and 363 patients (726 knees) were enrolled in our study.

Inclusion criteria were as follows: (i) age  $\geq 40$  years; (ii) participants diagnosed with medial compartment KOA based on American Rheumatism Association clinical and radiographic criteria<sup>19</sup>; (iii) patients in standard weight-bearing of long-standing AP views (both the patella and feet facing forwards). Exclusion criteria were as follows: (i) incomplete demographic data; (ii) history of prior knee surgery, including osteotomy, ligament reconstruction, or meniscectomy; (iii) post-traumatic or inflammatory arthritis; (iv) severity patellofemoral joint osteoarthritis; (v) lower extremities with plain radiographs in the position of internal or external rotation.

### Outcome Measurements

#### Evaluation on Severity of KOA

The Kellgren and Lawrence (K-L) classification system was used to evaluate the radiographic severity of KOA<sup>20</sup>. The

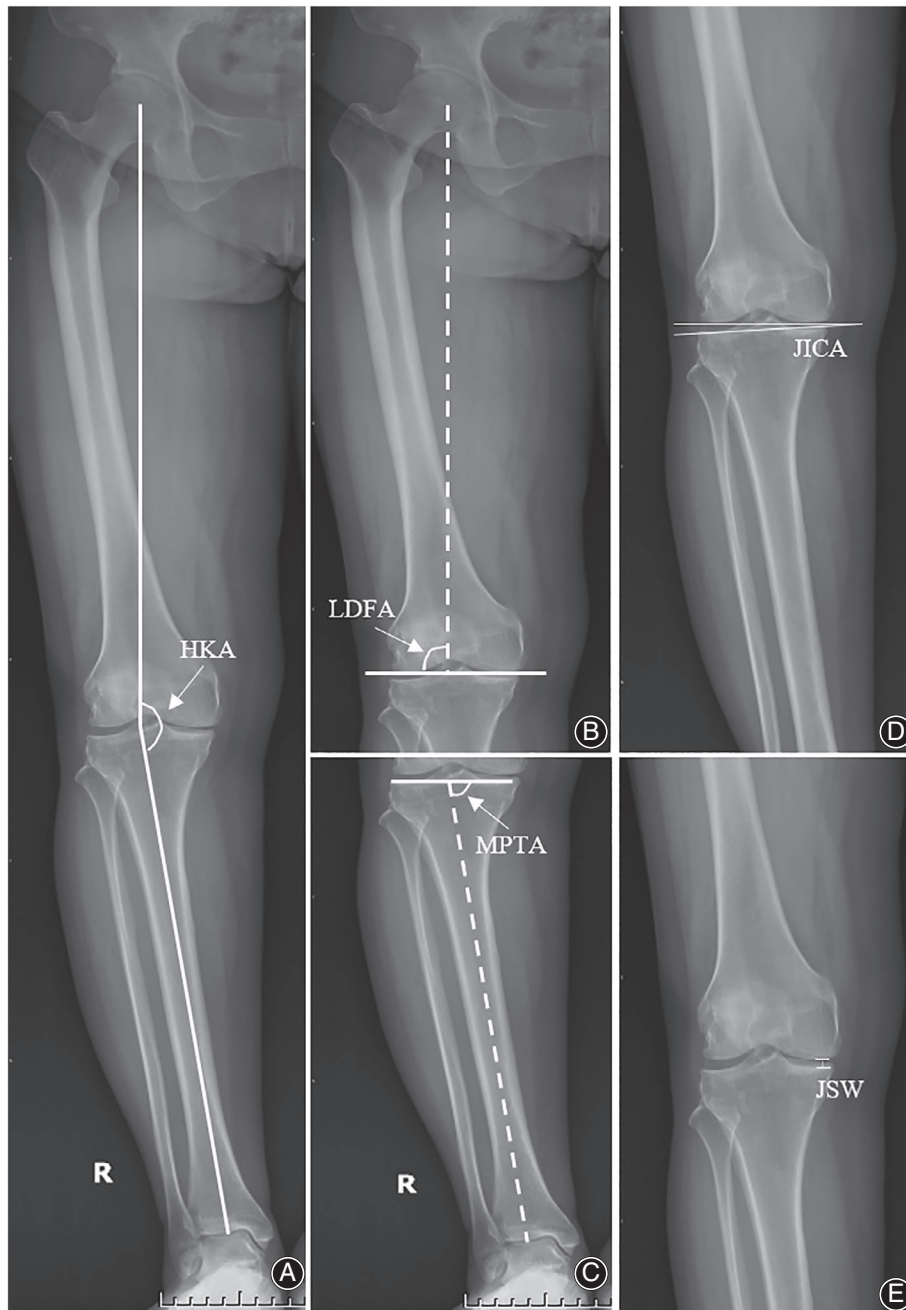
K-L classification system mainly includes five osteoarthritis grades: 0, I, II, III, and IV. K-L grade 0, definitely no osteophyte or joint space narrowing; K-L grade I, possible osteophytes and suspicious joint space narrowing; K-L grade II, definite small osteophytes and slight joint space narrowing; K-L grade III, definite moderate osteophytes, joint space narrowing, and/or slight sub-chondral bone sclerosis; K-L grade IV, definite large osteophytes, severe joint space narrowing, and/or obvious sub-chondral bone sclerosis.

#### Measurements of Medial Proximal Tibial Angle (MPTA)

The medial proximal tibial angle (MPTA) was used to evaluate alignment of tibia on coronal plane, which was defined as the medial angle between the tibial mechanical axis and the tangent line of the medial and lateral edges of the tibial plateau<sup>21</sup>(Fig. 2). The varus alignment was considered as MPTA less than  $85^\circ$ , and the valgus alignment was considered as MPTA greater than  $90^\circ$ .

#### Measurements of Hip-Knee-Ankle Angle (HKA)

The hip-knee-ankle angle (HKA) was used to evaluate the coronal alignment of the lower extremity, which was defined as the angle calculated by intersecting the line between the femoral mechanical axis (from the center of the femoral head to the central point of the knee) and the tibial mechanical



**Fig. 2** Radiological measurements in coronal plane. (A) Hip-knee-ankle (HKA) was the angle calculated by intersecting the line between femoral mechanical axis (from the center of the femoral head to the central point of the tibial spine) and tibial mechanical axis (from the center of the tibial spine to the center of the superior articular surface of the talus); (B) Lateral distal femoral angle (LDFA) was the angle between the tangent to the distal femoral condyle line and the femoral mechanical axis; (C) Medial proximal tibial angle (MPTA); (D) Joint line convergence angle (JICA) was formed by two articular tangential lines of the distal femur and proximal tibia; (E) Joint space width (JSW) was the minimum distance of knee joints.

axis (from the center of the tibial spine to the center of the superior articular surface of the talus)<sup>22</sup> (Fig. 2). Neutral lower-limb alignment was considered if the HKA angle was between  $177^\circ$  and  $183^\circ$ . Varus alignment was defined as HKA less than  $177^\circ$ , and valgus alignment was defined as HKA greater than  $183^\circ$ .

#### Measurements of Lateral Distal Femoral Angle (LDFA)

The lateral distal femoral angle (LDFA) was used to evaluate the coronal alignment of the distal femur, which was defined as the superolateral angle between the tangent line to the

articular surface of the distal femur and the line connecting the center of the femoral head to the center of the knee<sup>23</sup> (Fig. 2). Distal femur varus was defined as LDFA greater than  $87^\circ$ , while the distal femur valgus was defined as LDFA less than  $87^\circ$ .

#### Measurements of Joint Line Convergence Angle (JLCA)

The joint line convergence angle (JLCA) was used to evaluate the intra-articular cartilage loss and soft tissue laxity on the coronal plane, which was measured as the angle between the line connecting the articular surfaces of the distal femur and

**TABLE 1 Comparison of patient demographics and radiographic parameters between the subgroups**

Parameters	APR group	Non-APR group	P value
Number of knees (%)	412 (56.7)	314 (43.3)	N/A
Age (years, %)			<0.001*
<40	32 (7.8)	59 (18.8)	
40–60	142 (34.5)	130 (41.4)	
≥60	238 (57.8)	125 (39.8)	
Sex (male/female)	88/324	94/220	0.008
K-L classification (%)			<0.001*
Grade I	20 (4.9)	80 (25.5)	
Grade II	83 (20.1)	99 (31.5)	
Grade III	208 (50.5)	104 (33.1)	
Grade IV	101 (24.5)	31 (9.9)	
MPTA (°)	82.3° ± 2.6°	84.3° ± 3.8°	<0.001*
HKA (°)	170.8° ± 4.9°	176.7° ± 3.1°	<0.001*
LDFA (°)	88.2° ± 2.8°	88.4° ± 2.7°	>0.05
JICA (°)	4.2° ± 1.9°	3.1° ± 2.2°	<0.001*
Min-JSW (mm)	2.6 ± 1.8	3.8 ± 1.9	<0.001*

Continuous variables were presented as mean ± standard deviation, while categorical variables were presented as number or percentage.; APR, adaptive periosteal reaction; HKA, hip-knee-ankle angle; JICA, joint line convergence angle; K-L, Kellgren and Lawrence score; LDFA, lateral distal femoral angle; min-JSW, minimum joint space width; MPTA, medial proximal tibial angle; N/A, not available.; \* Significant difference between two groups.

proximal tibia<sup>24</sup> (Fig. 2). Varus alignment was defined as JLCA converging medially, and valgus alignment was defined as JLCA converging laterally.

#### Measurements of Joint Space Width (JSW)

The minimum medial joint space width (min-JSW) was used to evaluate the joint space, which was defined as the distance between the centers of the medial femoral condyle and the medial tibial plateau (Fig. 2). A distance smaller than 3 mm is considered to be narrowing joint space.

#### Outcome Evaluation

Figure 2 showed the specific methods of measurement in the above-mentioned radiographic parameters. All patients in radiological parameters were assessed by two senior radiologists (Z.Z.W. and Y.C.W.), independently of each other, to measure the K-L classification, MPTA, HKA, LDFA, JLCA, and min-JSW. The two radiologists (Z.Z.W. and Y.C.W.) repeated the measurements with an interval of 2 weeks. The average of the radiological measurements was recorded and used for analyses.

#### Statistical Analysis

SPSS software (version 25.0, IBM Corp., USA) was performed for statistical analysis. Intraclass correlation coefficients (ICCs) were used to assess intra-observer and inter-observer reliability in evaluating radiological parameters. Univariate analyses were conducted for comparison of differences with continuous variables between patients with periosteal reaction and without periosteal reaction. Chi-squared tests were used to compare the difference for categorical variables. Multivariate binary logistical regression analysis was

performed to determine the independent risk factors of radiographic parameters for periosteal reaction.

## Results

#### Patient Demographics

Three hundred and sixty-three patients (726 knees) were included in the present study, including 91 males and 272 females, with an mean age of 57.9 ± 12.8 years (range, 18–82 years). Of the 726 knees in this series, 206 patients (412 knees, 56.7%) were classified into APR group, and 157 patients (314 knees, 45.3%) were classified as non-APR group. In addition, there are significant differences for gender (male/female, 88/324 vs 94/220) when comparing the APR group with the non-APR group ( $P < 0.05$ , Table 1), which suggests that females have a higher incidence rate of periosteal reaction than males. Patients' demographic data were comparable, as shown in Table 1.

#### Incidence Rate of Periosteal Reaction by Age and K-L Classification

Our results also showed significant differences in the incidence of periosteal reaction among different age groups and K-L grades. Data of patients in medial compartment KOA was divided into three groups according to ages of <40 years, 40–60 years, and >60 years. The patients who were older than 60 years had the highest incidence rate of periosteal reaction, which account for 57.8% of occurrences, and were noted to have a statistically significant difference than the other two groups ( $P < 0.05$ ). It must be noted, the incidence rate of periosteal reaction in this study revealed a significant tendency to increase with age ( $P < 0.05$ , Table 1), indicating

**TABLE 2** Intra-observer and inter-observer reliability assessment of two groups for radiological parameters

Measurements	Intra-observer		Inter-observer	
	ICC	95% CI	ICC	95% CI
K-L classification	0.946	0.912–0.974	0.938	0.907–0.967
MPTA(°)	0.932	0.832–0.968	0.927	0.898–0.954
HKA(°)	0.911	0.847–0.956	0.909	0.854–0.949
LDFA (°)	0.921	0.843–0.961	0.914	0.867–0.948
JICA (°)	0.878	0.768–0.921	0.861	0.752–0.906
Min-JSW (mm)	0.862	0.757–0.919	0.874	0.751–0.901

CI, confidence interval; HKA, hip-knee-ankle angle; ICC, intraclass correlation coefficient; JICA, joint line convergence angle; K-L, Kellgren and Lawrence score; LDFA, lateral distal femoral angle; min-JSW, minimum joint space width; MPTA, medial proximal tibial angle.

higher possibility of periosteal reaction in older patients with medial compartment KOA.

The distribution of the 726 knees based on K-L classification was as follows: K-L grade I were 100 knees (13.8%); K-L grade II were 182 knees (25.1%); K-L grade III were 312 knees (43.0%); K-L grade IV were 132 knees (18.2%). Table 1 demonstrates the specific information regarding incidence rate of periosteal reaction based on each K-L classification, which showed a significant tendency to increase as K-L grade progressed ( $P < 0.05$ ).

#### Comparison of Radiological Evaluation between ARP Group and non-ARP Group

Intra-observer and inter-observer reliability assessment of two groups for radiological parameters are shown in Table 2. All ICC values of radiological measurements for intra-observer and inter-observer reliability exceeded 0.8, indicating excellent agreement. In the APR group, the mean MPTA, HKA, LDFA, JLCA, and min-JSW were  $82.3^\circ \pm 2.6^\circ$ ,  $170.8^\circ \pm 4.9^\circ$ ,  $88.2^\circ \pm 2.8^\circ$ ,  $4.2^\circ \pm 1.9^\circ$ , and  $2.6 \pm 1.8$  mm, respectively. In the non-APR group, the mean MPTA, HKA, LDFA, JLCA, and min-JSW were  $84.3^\circ \pm 3.8^\circ$ ,  $176.7^\circ \pm 3.1^\circ$ ,  $88.4^\circ \pm 2.7^\circ$ ,  $3.1^\circ \pm 2.2^\circ$ , and  $3.8 \pm 1.9$  mm, respectively. The MPTA, HKA, and min-JSW were significantly lower in the APR group compared to the non-APR group ( $P < 0.05$ ), while the JLCA was significantly higher in the APR group compared to the non-APR group ( $P < 0.05$ , Table 1).

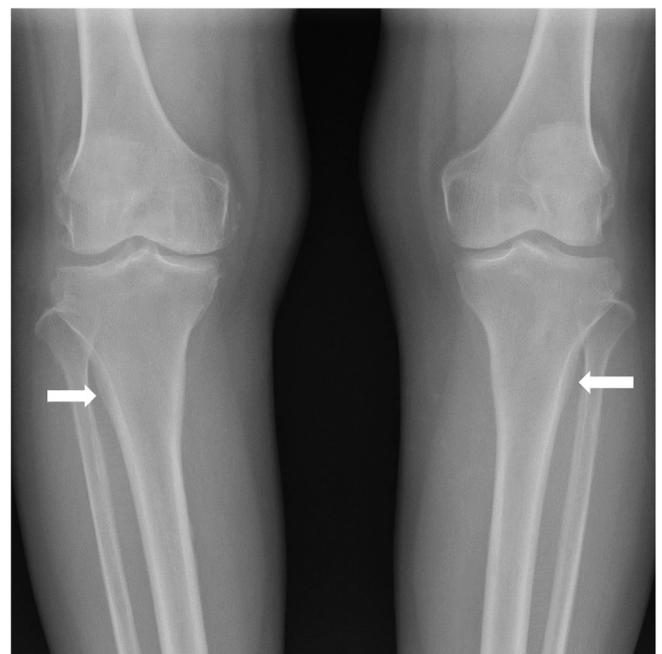
**TABLE 3** Multivariate binary logistic regression analysis

Variables	Odds ratio	95% confidence interval	P value
MPTA (°)	0.959	0.901–1.021	0.193
HKA (°)	0.594	0.544–0.648	0.000*
LDFA (°)	0.990	0.899–1.089	0.831
JICA (°)	0.851	0.737–0.983	0.029*
Min-JSW (mm)	1.005	0.865–1.167	0.951

HKA, hip-knee-ankle angle; JICA, joint line convergence angle; LDFA, lateral distal femoral angle; min-JSW, minimum joint space width; MPTA, medial proximal tibial angle.; \* Significant difference between two groups.

#### Multivariate Binary Logistic Regression Analysis

Radiological parameters including MPTA, HKA, LDFA, JLCA, and JSW were included in multivariate logistic analysis model (Table 3). Multivariate binary logistic regression was performed to analyze the correlation of radiological parameters with APR, indicating that HKA and JLCA were identified as independent risk factors for the development of periosteal reaction (respectively, odds ratio  $OR = 0.594$ , 95%  $CI = 0.544–0.648$ ;  $OR = 0.851$ , 95%  $CI = 0.737–0.983$ ). Meanwhile, JLCA had the highest correlation with the risk of APR, and the differences were statistically significant ( $P < 0.05$ ). These results demonstrated that patients with lower HKA and higher JLCA were susceptible to periosteal reaction. In contrast, MPTA, LDFA, and JSW were not



**Fig. 3** Periosteal reaction in patient with medial compartment KOA in both knees. Weight-bearing knee AP radiographs demonstrated regional periosteal reaction (arrow) in both of the lateral proximal tibia shafts.

identified as independent risk factors for the development of periosteal reaction in the multivariate model analysis (respectively,  $OR = 0.959$ ,  $95\% CI = 0.901-1.021$ ;  $OR = 0.990$ ,  $95\% CI = 0.899-1.089$ ;  $OR = 1.005$ ,  $95\% CI = 0.865-1.167$ ;  $P > 0.05$ ), as shown in Table 3.

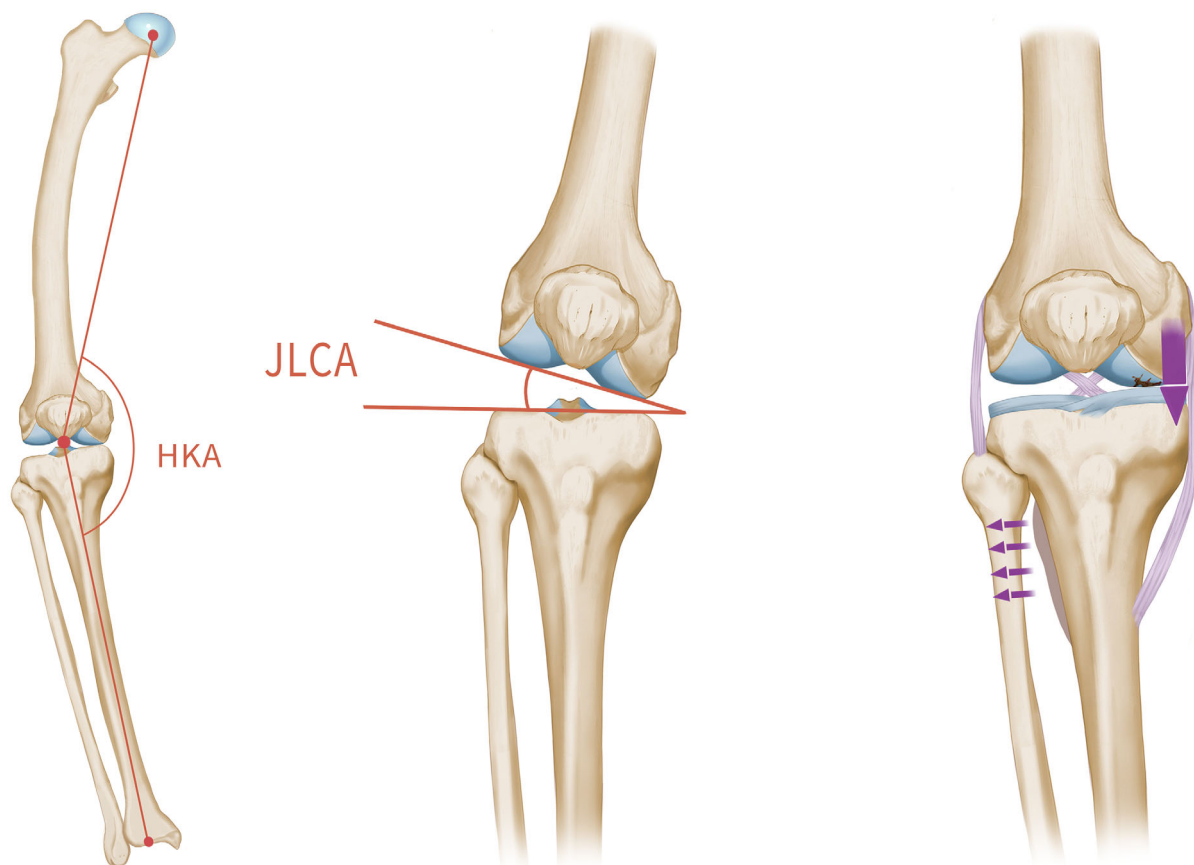
### Discussion

The most important finding of the present study was that the development of periosteal reaction in lateral of proximal tibia diaphysis is a radiographic finding associated with medial compartment KOA, and showed that HKA and JLCA were independent risk factors for the development of periosteal reaction.

#### Association Between Periosteal Reaction and Medial Compartment KOA

The results of this study identified that the incidence rate of periosteal reaction significantly correlated with K-L grades in patients with medial compartment KOA. Our results also showed that with the increased incidence of periosteal

reaction, the medial proximal tibial angle became lower, and the joint line convergence angle became larger, ultimately leading to varus malalignment. This finding of our study was consistent with our hypothesis, showing that the cortical layer changes in the periosteum may be an adaptation to the progression of medial compartment KOA, which could be one of the mechanisms for the development of KOA. Dong *et al.*<sup>25</sup> have shown that “non-uniform” settlement of tibial plateau was closely related to the varus malalignment in medial compartment KOA. Increased joint loading in the medial compartment and occurrence of osteoporosis with age can increase the risk of bone trabecula thinning and bone loss. Meanwhile, it has been reported that the cambial layer situated adjacent to the cortex bone contains periosteum-derived stem cells (PDCs) that are sensitive to inflammatory syndrome and mechanical stimulation<sup>26</sup>. In addition, Moore *et al.*<sup>27</sup> showed that PDCs can be recruited to fibrous layer and modulated by mechanical stress. Therefore, we considered that when the excessive axial load-bearing distributed to the medial side of proximal tibia diaphysis,



**Fig. 4** Schematic illustration showing the possible pathological mechanism of the periosteal reaction in medial compartment knee osteoarthritis. The bold arrows, identified as compressive forces, were used to illustrate the excessive axial loading distribution to the medial side. The thinner arrow was identified as tensile stress, which stimulated the periosteum to produce bone formation on the cortical layer of the surface of the tibia. HKA: hip-knee-ankle angle; JLCA: joint line convergence angle.

distraction osteogenesis of the lateral side of proximal tibia would occur due to the imbalanced mechanical environment of the proximal tibial shaft (Figs 3 and 4).

### **Independent Risk Factors of Radiological Parameters for the Development of APR**

Our study also investigated whether radiological parameters in coronal plane are correlated with APR in patients with medial compartment KOA. Multivariate binary logistic regression analysis identified that HKA and JLCA were independent risk factors for the development of APR ( $OR = 0.594$  and  $0.851$ , respectively). This may be partially explained by the theory of “non-uniform” settlement of tibial plateau<sup>25,28</sup>. Recently, one of our published studies reported that the lateral curvature of the proximal fibular concomitant with aging may be an anatomical adaptation for medial compartment KOA, and these changes in the fibula were in correlation with settlement of the medial plateau<sup>29</sup>. Similarly, based on the findings of this study, we assume that the lateral side of the proximal tibia shaft redistributes the excessive loading to the periosteum, while this increased tensile stress could indirectly affect cortical layer of the surface changes as well. Furthermore, among varus malalignment factors, JLCA was the most significant factor in association with periosteal reaction. Nakayama *et al.*<sup>30</sup> have described that larger JLCA may induce shear stress on articular cartilage. This increased shear stress that transmitted to the proximal tibia may indirectly affect the occurrence of periosteal reaction. Nevertheless, there are no comparable studies reporting on periosteal reaction in association with medial compartment KOA.

### **Radiological Assessment of Lower Extremity**

In this research, we applied MPTA and LDFA to evaluate the coronal malalignment of the lower limb instead of using HKA alone due to both the tibia and femur varus deformities being associated with varus malalignment<sup>31,32</sup>. It has been suggested that periosteal reaction is believed to be the result from certain regional mechanical factors<sup>33</sup>. This anatomical

adaptation of the tibia was in relation with excessive tensile stress in periosteum due to the long-term bearing in lateral side of proximal tibial shaft. Furthermore, based on this background, the adaptive changes of the periosteum in the proximal tibia shaft may further illuminate the theory of “non-uniform” settlement of tibial plateau on medial compartment KOA.

### **Strengths and Limitations**

To date, the present study is the first to evaluate the relationship between the periosteal reaction and medial compartment knee osteoarthritis, and to assess the independent risk factors for the development of periosteal reaction. However, there are some noteworthy limitations to this retrospective comparative study. First, we did not perform the histopathological observation for the development of periosteal reaction in medial compartment KOA. Second, the thickness of the periosteal reaction was not determined quantitatively, and body mass index (BMI) could not be assessed for each patient in this retrospective study. Third, all radiological measurements were evaluated on coronal plane of the lower extremities and did not include sagittal plane. Furthermore, the relatively small sample of patients may present bias in the analysis of our results. Therefore, further large-scale prospective studies are still needed to focus on exploring the underlying mechanisms of periosteal reaction and its role in the development of medial compartment KOA.

### **Conclusions**

In conclusion, this study suggests that periosteal reaction is a radiographic finding related to medial compartment KOA, and the incidence rate of periosteal reaction significantly increases with age and is correlated with the progression of K-L grades. Furthermore, patients with lower HKA and higher JLCA are more likely to develop periosteal reaction, which occurred most commonly adjacent to the lateral of proximal tibia diaphysis.

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