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〔 Original Article 〕

Osteophyte formation at the posterior notch of the femur serves as an early sign of osteoarthritic change of the knee joint

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Abstract

We previously reported that osteophytes formed at the posterior condylar notch of the femur could serve as a predictive imaging biomarker for osteoarthritis of the knee joint（KOA）development using magnetic resonance imaging（MRI）. Considering the location in the knee joint, we named the osteophyte as hidden osteophyte formation on plain x-ray（HOPOX）. To apply the findings to general clinical usage, x-rays that are less costly than MRI are a preferred imaging modality. In this study, we examined the feasibility of using the x-ray tunnel view to detect HOPOX. First, the diagnostic ability of the tunnel view was examined in 30 cases using computed tomography（CT）as a standard reference. Then, in a longitudinal study, the timing of HOPOX formation was examined retrospectively with a radiographic follow-up of 28 meniscectomized knees. The tunnel view showed greater diagnostic ability; the sensitivity, specificity, positive predictive value, and negative predictive value were 0.73, 0.93, 0.92, and 0.78 respectively. The longitudinal study revealed that HOPOX was the earliest osteophyte in those cases in which osteophytes formed. In conclusion, the x-ray tunnel view was effective in detecting HOPOX, thus feasible way to predict early KOA.

***Key words*: Osteophytes, imaging biomarker, osteoarthritis, radiography, knee**

Ⅰ. Introduction

A growing number of older people worldwide suffer from osteoarthritis of the knee joint（KOA）that impairs activities of daily living（ADL）[1,2]. Preventing disease development and progression has been sought but remains unsuccessful[3]. One plausible strategy to achieve prevention would be to detect KOA as early as possible, or even to detect changes prior to overt disease when symptoms are absent, because cartilage is difficult to restore once it begins to degenerate. Many biomarkers have been proposed to detect early stage disease status using serum or urine biomarkers but they

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are not specific to the knee joints[4]. Thus, imaging of the knee joint has been regarded as an ideal biomarker where only the affected joint is assessed[5].

The initial pathology associated with KOA can be attributed to cartilage but many tissues in the knee joint are affected as KOA progresses. Magnetic resonance imaging (MRI) has revealed many pathological changes in the knee joint: joint effusion, synovitis, bone marrow lesion (BML), loss and degeneration of cartilage, subluxation and degenerative tears of the meniscus, bone attrition, free body formation, and osteophyte formation [6]. Changes observable from MRI that emerge in the early stage of KOA and constantly increase or decrease over the course of KOA progression could serve as a clinically useful biomarker[7]. Osteophyte formation is one of those that increases both in size and in number and can be detected not only by MRI but also using x-ray or computed tomography (CT).

In our previous study using publicly available MRI data from the osteoarthritis initiative (OAI), we showed that osteophytes at the posterior condylar notch of the femur were frequently observed prior to radiographic evidence of KOA[8]. Considering the location, the osteophytes cannot be detected with antero-posterior, lateral, or skyline x-ray projections that are commonly used clinically. Thus, we named the osteophyte as hidden osteophyte formation on plain x-ray (HOPOX). However, we hypothesized that detection of HOPOX would be possible by modification of the x-ray projection. Considering the femoral notch location of osteophytes in the knee, we proposed that the radiographic tunnel view would best facilitate visual detection of HOPOX.

In the present paper, we first examined the feasibility of the tunnel view x-ray to detect HOPOX using CT as a standard reference. Then, we examined whether HOPOX could be detected at an earlier stage of KOA than other osteophytes when radiography was used as the imaging modality. For this purpose, a retrospective longitudinal x-ray follow-up of meniscectomized knees was performed.

Our hypothesis was that the radiographic tunnel view could detect HOPOX and serve as a biomarker to identify early stage KOA.

Ⅱ. Materials and methods

1) *Tunnel view to detect the HOPOX*

Patients were selected from among those who underwent surgical treatment of the knee at our institution. Patients were eligible when a pre-operative radiographic series comprising anteroposterior (AP), lateral, skyline, and tunnel views were available, and when a CT examination of the affected knee for operative planning or diagnosis had been performed within one month of the radiographic examination. Excluded were patients assessed with Kellgren and Lawrence (K/L) grade >2[9], inflammatory disease such as rheumatoid arthritis, or a history of surgical treatment on the affected knee prior to the study. CT scans were obtained at a voxel size of 0.68 mm in plane, in 1.0 mm sections, and at 0.8 mm increments using a 64-slice scanner (Aquilion 64, Toshiba, Japan).

Two orthopedic surgeons served as examiners and assessed the knees on the 0-3 scale reported by Altman and Gold[10] in 2007 for the existence of HOPOX from a tunnel view x-ray, which was taken with knees flexed at 55 degrees in our institution. A score of 1 or more was regarded as positive for osteophytes. When both examiners assigned a score of 1 or more, a knee was classified as positive for HOPOX (Fig. 1a). CT images were utilized as a reference for the presence of HOPOX (Fig. 1b) and the results of the tunnel

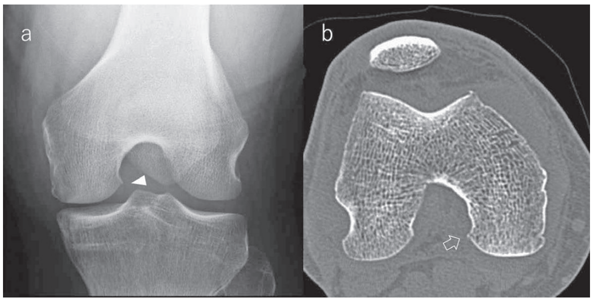

Fig. 1 Representative CT and tunnel view to detect HOPOX

The right knee of a sixty-five year-old male was examined using x-rays (a) and CT (b). The tunnel view revealed HOPOX formation (1a, arrowhead) on the medial side that was confirmed by CT (1b, open arrow).

view were compared with a CT image for consistency. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the tunnel view for the detection of HOPOX were calculated.

2) *Time of HOPOX formation through longitudinal x-ray follow-up study*

Another set of patients was identified for longitudinal study. Included were 1) those who had pre-operative four-directional x-rays of the knee (AP, lateral, skyline, and tunnel views); 2) those who received arthroscopic meniscectomy due to symptomatic meniscal injuries; 3) no osteophyte formation observable on the x-rays at the time of surgery; 4) follow-up x-rays comprising four-directional x-rays available on a regular basis (every 6 months or every year); and 5) availability of more than three-year follow-up x-rays. Knees from these patients were followed-up by four-directional x-rays including tunnel view to check whether osteochondritis dissecans (OCD) might develop. In some post-meniscectomy patients, especially young patients, the possibility of OCD is a concern for surgeons[11], and the tunnel view is most beneficial for detecting OCD in the femoral condyle[12].

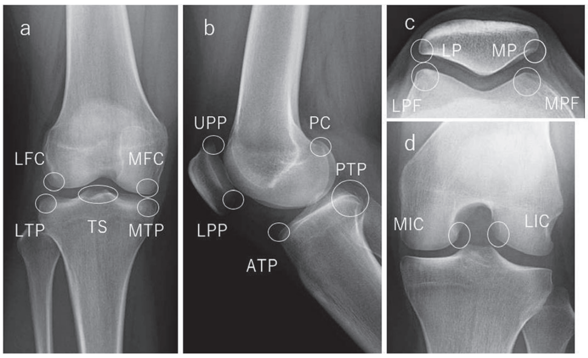

Fig. 2 Evaluation of osteophyte formation

A total of 16 sites indicated with circles were assessed for osteophyte formation through 4 directional x-rays [(a) anteroposterior, (b) lateral, (c) skyline, (d) tunnel view].

(a) LFC = lateral femoral condyle; LTP = lateral tibia plateau; MFC = medial femoral condyle; MTP = medial tibia plateau; TS = tibial spine

(b) UPP = upper pole of patella; LPP = lower pole of patella; PC = posterior condyle; ATP = anterior tibia plateau; PTP = posterior tibia plateau

(c) LP = lateral patella; MP = medial patella; LPF = lateral facet of the patellofemoral joint; MPF = medial facet of the patellofemoral joint

(d) MIC = medial intra-condylar notch of the femur; LIC = lateral intra-condylar notch of the femur

Two orthopaedic surgeons served as examiners and 16 locations of the knee joint were evaluated for osteophyte formation including HOPOX (Fig. 2). The existence of osteophytes was counted only when the two examiners both scored more than 1.

Informed consent for each individual was waived for the first part of the study by posting the study design and purpose on a notice board at our institution. Written informed consent was obtained from each individual for the latter part of the study.

This research protocol of this study was following the Helsinki Declaration, approved by the Institutional Review Boards. (Research Ethics Committees of Graduate School of Medicine, Chiba University; the reference number #2558)

Ⅲ. Results

1) Tunnel view to detect HOPOX

Demography

A total of 218 patients met the inclusion criteria. Some subjects were excluded due to a KL score of III or IV (n = 109), systemic inflammatory joint disease (n = 17), or they were post-operative (n = 63). This left 24 females and 5 male patients with 30 knees (a single bilateral case was included). Eight knees had early KOA, anterior cruciate ligament (ACL) ruptures in 4, OCD in 3, meniscal lesions in 3, tibial spine fractures in 3, osteonecrosis in 2, free bodies in 2, patellar fractures in 2, synovial chondromatosis in 2, and there was a single case of intra-articular tumor. The mean (SD) age of subjects was 45.8 (19.5) years (age range; 23-80 years). As for KL grade, 8, 15, and 7 patients were grade 0, I, and II, respectively.

Ability to detect HOPOX with a tunnel view X-ray

CT revealed 12 knees with isolated medial side HOPOX, 2 with isolated lateral HOPOX, 8 with both medial and lateral HOPOX, and 8 without HOPOX. Thus, a total of 30 HOPOXs existed either medially or laterally on the posterior femoral condyle. Sensitivity, specificity, PPV, and NPV for HOPOX detection with the tunnel view at 55° of knee flexion were 0.73, 0.93, 0.92, and 0.78, respectively.

2） Identification of HOPOX in longitudinal study

Demography

For the longitudinal study, 28 knees from 22 patients met the inclusion criteria including 6 bilateral cases. The mean（SD）age of subjects at the time of surgery was 12.6（0.7）years（age range; 3-19 years）. Preoperative diagnoses included 22 torn discoid lateral menisci, a single lateral meniscal injury, and 5 torn medial menisci. The average follow-up period was 5.4 years（3-15 years）.

Eighteen knees showed osteophytes at an average of 36.2 months after surgery. Sixteen of the 18 knees showed HOPOX formation at an average of 34.5 months after arthroscopic surgery. Twelve were medial HOPOX and 4 were lateral HOPOX. There was no combined medial and lateral case. In 13 knees, at the time HOPOX was detected, no other osteophytes were detected（Fig. 3）. Three knees had another site osteophyte when HOPOX was detected（Fig. 3）. This indicated that HOPOX was one of the earliest osteophytes, or even the first osteophyte in many cases, to form in the knee joint. Fig. 4 presents a representative case that medial HOPOX was the first and only osteophyte in the knee joint 10 years postoperatively.

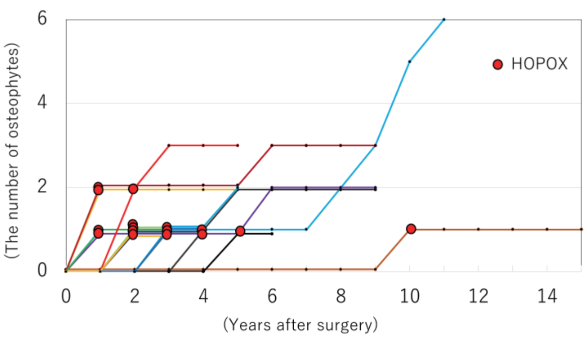

Fig. 3　Time of HOPX formation and other osteophytes

The total number of osteophytes in the knee joint after arthroscopic surgery in cases with HOPOX-positive knees（n＝16）. The circles indicate HOPOX. In 13 knees, HOPOX was the first and only osteophyte when a single osteophyte was observed, whereas in the other three knees, HOPOX was co-observed with osteophytes at other sites.

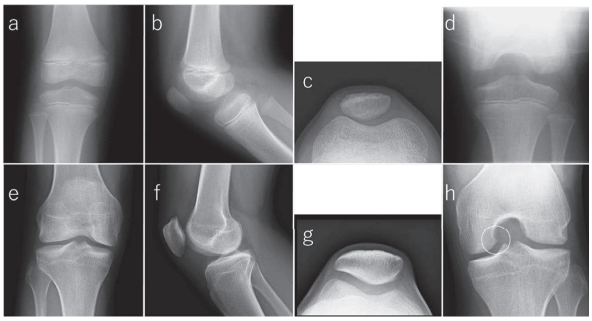

Fig. 4　Representative case of HOPOX in longitudinal study

Four sets of x-rays at the time of surgery showed no osteophytes（a-d）. Ten years post-operatively（e-h）, the only osteophyte detected was on a tunnel view（open circle）.

［(a, e) anteroposterior,（b, f）lateral,（c, g）skyline,（d, h）tunnel view］

Ⅳ. Discussion

We have shown through a longitudinal study that the tunnel view with knees flexed at 55^0 can detect HOPOX effectively and that HOPOX is formed in the early stages of KOA. This shows the feasibility of the tunnel view to detect pre-radiographic KOA through HOPOX detection. We examined post-meniscectomized knees longitudinally because radiographic osteoarthritic changes are known to accelerate after meniscectomy [13].

In our previous study employing MRI data from the OAI, we showed that knees with no sign of KOA at baseline, but with HOPOX, tended to develop radiographic KOA within 4 years, but those without HOPOX did not[8]Therefore, we concluded that HOPOX could be used as a predictive imaging biomarker for KOA. That study was based on MRI but the present study used x-rays. Because x-rays are less costly and less time consuming than MRI, the x-ray tunnel view can be utilized for mass screening of early KOA or pre-KOA subjects.

Primary KOA and post meniscectomized knee

Although our goal was to detect early or pre-KOA occurring in the 5^{th} or 6^{th} decades of life, we included much younger patients in the longitudinal part of this study. One reason for this was that meniscectomy accelerates osteoarthritic changes, allowing us to examine early KOA changes in a relatively short period of time. As a result, we observed HOPOX formation at an average of 34.5 months post-operatively, including two cases as early as 1 year. Roemer et al. reported KOA related cartilage damage in meniscectomized knees within one year post-surgery[14]and Eichinger et al. reported a similar result within 6 months after meniscectomy[15]. It would have been better to use older subjects, but we identified a group with an average age of 12.6-years for the practical reason that they were followed up with 4 sets of x-rays on a regular basis. In 2017, Yamasaki et al. reported about 50% of meniscectomized knees showed KOA changes after an average of 39.6 months in subjects with an average age of 12.0 years[16]. Thus, our subjects were in an acceptable age range for our study purpose.

Cartilage specific MRI technique or osteophyte formation

As an imaging biomarker for early KOA, cartilage specific MRI has been shown to detect early pathological changes[17]. T2 mapping, T1 rho mapping, and dGEMRIC are representative of those and they enable quantitative measurement of cartilage, but their clinical role has yet to be proven. In our previous study we compared T2 mapping and T1 rho mapping to discriminate early cartilage degeneration, referencing histological examination of specimens with a macroscopically intact or nearly intact cartilage surface retrieved at the time of total knee arthroplasty[18]. As a result, we reported that T1 rho mapping was superior to discriminate early degeneration of cartilage and that T1 rho relaxation time and T2 relaxation time varied from site to site even when the histological grades were the same. Thus, it was not accurate to determine the status of cartilage simply by the value of T1 rho or T2 relaxation time without considering the location of the cartilage[18]. As for dGEMRIC, the requirement to administer an intra-venous contrast agent makes it difficult to screen for early KOA. Compared to quantitative MRI techniques, the x-ray tunnel view appears to have greater benefits in terms of ease of interpretation.

Importance of early KOA detection

One of the most frequent causes of disability in the elderly population is KOA[19,20], making early detection of KOA an important clinical priority. The first step toward prevention is to detect very early stage disease and to identify a population at risk before KOA becomes radiographically evident (K/L II or more). In the wake of this, the definition of early KOA was proposed by Luyten et al. in 2012 but this definition is not useful for arthroscopic diagnosis or MRI examination[21]because these methods are time consuming, costly and invasive. On the other hand, a consensus meeting to discuss the criteria for early KOA held in Tokyo in 2014[22]incorporated KL 0 or 1 as imaging criteria. KL 0 or 1 are associated with the absence of definite x-ray findings. Our study suggests that positive findings such as HOPOX would be better used as an imaging criterion for early KOA.

Limitations

The present paper has a few limitations. First, in our previous study, HOPOX was detected from MRI using OAI data, but in the present study CT was used as a reference for the presence of osteophyte formation. A comparison of CT and MRI data might be valuable, but we decided CT would be sufficient to examine osteophyte formation. Second, only retrospectively reviewed meniscectomized cases were employed in the longitudinal part of the study. A prospective study dealing with the middle-aged general population would be ideal but the requirement of an unpredictably longer time period for the development of KOA made this untenable as a pilot study. We chose to test our hypothesis using only retrospective evaluation of a limited number of cases. The rarity of the tunnel view in daily clinical settings prevented us from gathering a large number of cases. Verifying the usefulness of HOPOX detection in a prospective cohort study will be the next subject of a study. Third, only 55^0 degrees of knee flexion was studied and there may be a more suitable flexion angle.

Ⅴ. Conclusion

The feasibility of the x-ray tunnel view to determine early or pre-radiographic KOA was demonstrated. This can be performed in many facilities that are not equipped with MRI or CT.

Contributors

Guarantor of integrity of the entire study: SO, TS. Study concepts and design: All authors. Clinical studies: YO, RN, TS. Manuscript preparations: YO, TS. Manuscript editing: TS.

Conflict of interest

The authors declare that they have no conflicts of interest, either financial or non-financial, with the contents of this article.

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