Associations between MRI-detected early osteophytes and knee pain and structure in older adults: a population-based cohort study

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ABSTRACT

Objectives: To describe prevalence of osteophytes (OPs) detected only by magnetic resonance imaging (MRI) but not by standard X-ray in older adults and to evaluate longitudinal associations with knee pain and structural changes.

Methods: 837 participants (mean age 62 years, 50% female) were randomly selected from the local community at baseline. T1- or T2-weighted fat suppressed MRI was used to assess knee OPs, cartilage volume, cartilage defects and bone marrow lesions (BMLs) at baseline and after 2.6 years. OPs detected only by MRI but not by standard X-ray were defined as MRI-detected early OPs (MRI-OPs for short). OPs detected by both MRI and X-ray were defined as established-OPs. Knees without MRI- or X-ray-detected OPs were defined as no-OPs.

Results: The prevalence of MRI-OPs was 75% while the prevalence of established-OPs was 10% and no-OPs was 15% in total knee at baseline. Compared with no-OPs, participants with MRI-OPs and/or established-OPs had greater cartilage volume loss, increased cartilage defects and increased BMLs over 2.6 year. Participants with no-OPs, MRI- early OPs and established-OPs showed dose-response relationships with OA structural progression (p for trend <0.01). Surprisingly, presence of medial tibiofemoral MRI-OPs predicted a decrease in knee pain over 5 years, while established-OPs predicted an increase in total knee pain, after adjustment for relevant covariates.

Conclusion: MRI-detected early OPs are associated with knee structural changes in a dose response manner. Unexpectedly, they have opposite associations with pain suggesting MRI-detected early OPs prior to knee pain development.

Introduction

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Knee osteoarthritis (OA) is a leading cause of pain and disability [1]. Symptomatic knee OA is estimated to occur in 10% of men and 13% of women aged 60 years or older [2]. Although osteophytes (OPs) have long been viewed as a defining structural feature of knee OA [3] and a fundamental sign of disease incidence and progression [4], correlation between OPs and clinical features is weak at best [5, 6], and change in symptoms is poorly predicted by baseline radiographic OPs [7].

In an observational study, knee pain was reported by 1004 subjects, only 15% of whom had radiographic grade 2 to 4 changes of OA [8]. The discrepancy between clinical and radiographic OA may be due to the inherent limitations of conventional radiography as an imaging tool [9]. Many OA features cannot be detected using radiography and some pre-radiographic OA features are missed using radiographic assessment. A recent study revealed that about 90% of radiographically normal knees had one or more OA-related features on MRI, and MRI-detected OP is the most common abnormality among these features[10]. An obeservational study has reported that prevalence of MRI-detected OPs is 72% among middle-aged women [11] and another study reports 74% MRI-detected OPs in 710 knees without radiographic evidence of OA [10]. In contrast, the prevalence of radiographic OPs was approximately 10% in a generally older population (mean age 61 years) [12].

Given that radiography fails to detect a large proportion of OPs which can only be detected on MRI, there would be a large number of OA patients who have MRI-detected early OPs (MRI-OPs) are misclassified as normal. Moreover, they represent different stages of OA process. To date, the relevance of MRI-OPs for the development of structural and clinical abnormalities is uncertain. We hypothesized that MRI-OPs that are detected only by MRI can serve as a biomarker in identifying patients at a high risk of osteoarthritic progression. The

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aim of this population-based cohort study, therefore, was to describe the prevalence of MRI-OPs in older adults and the longitudinal associations with knee pain and structural abnormalities.

Materials and Methods

Subjects

These analyse suse data from the Tasmania Older Adult Cohort (TASOAC) Study, a population-based, ongoing, prospective longitudinal cohort study which was designed to identify the environmental, genetic, biochemical factors associated with the development and progression of OA at multiple sites. Participants between 50 and 80 years old were randomly selected from the electoral roll in Southern Tasmania (population 229, 000) using sex-stratified random sampling (response rate 57%). Participants were excluded if they were institutionalised or had contraindications to MRI. The Southern Tasmania Health and Medical Human Research Ethics Committee approved the study, and written informed consent was obtained from all participants. Baseline examinations were taken between February 2002 and September 2004, and follow-up measures were taken at approximately 2.6 and 5.1 years later. This study consisted of 837 participants who had knee MRI and radiographic scans at baseline.

Magnetic Resonance Imaging

MRI scans of the right knees were performed on two occasions and imaged in the sagittal plane on a 1.5-T whole body magnetic resonance unit (Picker, Cleveland, OH) using a commercial transmit-receive extremity coil. The image sequences used are listed as follows: (1) a T1-weighted fat saturation 3D gradient recall acquisition in the steady state; flip angle 30°; repetition time 31 ms; echo time 6.71 ms; field of view 16 cm; 60 partitions; 512×512 matrix; acquisition time 11

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min 56 s; one acquisition. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31×0.31 (512×512 pixels). (2) a T2-weighted fat saturation 3-D fast spin echo, flip angle 90, repetition time 3067 ms, echo time 112 ms, field of view 16 cm, 15 partitions, 228x256-pixel matrix; sagittal images were obtained at a partition thickness of 4 mm with a between-slices gap of 0.5 to 1.0 mm. The image database was transferred to an independent computer workstation using the software program Osirix (University of Geneva, Geneva, Switzerland) as previously described [13, 14].

MRI-detected osteophytes

MRI-detected OPs were measured by ZZ according to the Knee Osteoarthritis Scoring System (KOSS) [15] where OPs are defined as focal bony excrescences, seen on sagittal, axial or coronal images, extending from a cortical surface. OPs were measured using the following scale: grade 0, absent; grade 1, minimal (<3mm); grade 2, moderate (3-5 mm); grade 3, severe (>5 mm) [15]. Size was measured from the base (distinguished from that of adjacent articular cartilage with a normal MRI appearance) to the tip of the OP [16] at each of the following 14 sites: the anterior (a), central weight bearing (c) and posterior (p) margins of the femoral condyles (medial and lateral) and tibial plateaus (medial and lateral), and the medial (M) and lateral (L) margins of the patella [17]. The highest score of each individual site in the relevant compartment (or whole knee) was regarded as the OP score in that compartment (or whole knee). MRI-detected OP score of ≥1 was considered as OP present. MRI-detected OPs were remeasured in 40 randomly selected participants with four weeks interval by ZZ and WH to calculate intra-observer and inter-observer reliabilities. Intra-observer reliability (expressed as intraclass correlation coefficients, ICCs) was 0.94-0.97 and inter-observer reliability was 0.90-0.96.

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Cartilage defects

Cartilage defects were graded by CD at medial tibial, lateral tibial, medial femoral, lateral femoral and patellar regions as previously described [18-21] as follows: grade 0, normal cartilage; grade 1, focal blistering and low-signal intensity change with an intact surface and bottom; grade 2, irregularities on the surface or bottom and loss of thickness of less than 50%; grade 3, deep ulceration with loss of thickness of more than 50%; grade 4, full thickness cartilage loss with exposure of subchondral bone [18]. The highest score of each individual site in the relevant compartment (or whole knee) was regarded as the cartilage defect score in that compartment (or whole knee). The presence of cartilage defects was defined as a cartilage defect score of ≥2 at any site. An increase in cartilage defects was defined as a change in cartilage defects of ≥1. Intra-observer reliability was 0.89-0.94 and inter-observer reliability was 0.85-0.93 [18].

Cartilage volume

Knee cartilage volume was measured on T1-weighted images by a single trained observer at baseline as previously described [22, 23]. The volumes of individual cartilage plates (medial tibial, lateral tibial, medial femoral, lateral femoral and patellar) were isolated from the total volume by manually drawing disarticulation contours around the cartilage boundaries on a section by section basis. These data were resampled by means of bilinear and cubic interpolation (area of 312×312) μm and 1.5 mm thickness, continuous sections) for the final 3-dimensional rendering. Changes in cartilage volume were calculated as: percentage change per annum= [(follow-up volume – baseline volume)/baseline cartilage volume]/time between 2 scans in years × 100. The coefficients of variation (CVs) for cartilage volume measures were 2.1% to 2.6% [22, 23].

Bone marrow lesions

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Subchondral bone marrow lesions (BMLs) were defined as discrete areas of increased signal adjacent to the subcortical bone on T2-weighted MRI and scored at medial tibial, lateral tibial, medial femoral, lateral femoral, medial patellar and lateral patellar regions using a modified version of Whole-Organ Magnetic Resonance Imaging Score (WORMS): grade 0, absence of BML; grade 1, area smaller than 25% of the region; grade 2, area between 25% to 50% of the region; grade 3, area larger than 50% of the region [17]. The highest score of each individual site in the relevant compartment (or whole knee) was regarded as the BML score in that compartment (or whole knee). An increase in BMLs was defined as a change in BMLs of ≥1. The intraclass correlation coefficients (ICCs) for intra-observer reliability were 0.89-0.96 [24]. The inter-observer reliability of this BML scoring system was assessed by randomly selecting 40 subjects with BMLs and having their MRI scans re-read by another observer. The ICCs for inter-observer reliability were also excellent (0.73-0.95).

X-ray assessment

A standing anteroposterior semiflexed view of the right knee with 15° of fixed knee flexion was performed in all subject at baseline. Joint space narrowing (JSN) and radiographic osteophytes (OPs) were scored at each site of medial tibia, medial femur, lateral tibia and lateral femur on a scale of 0-3 (0=normal, 3= severe) according to the Osteoarthritis Research Society International (OARSI) atlas developed by Altman et al [25]. Medial tibiofemoral (femoral and tibial combined) X-ray-detected OP and lateral tibiofemoral X-ray-detected OP were the highest scores of all the regions. The total X-ray-detected OP score was the highest score of the four sites (medial tibia, medial femur, lateral tibia and lateral femur). The presence of X-ray-detected OP was defined as X-ray-detected OP scores of ≥ 1 in the specific compartment. The presence of radiographic OA (ROA) was defined as any score of ≥ 1 (JSN or OP). Each score was determined

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by two readers who simultaneously assessed the radiograph with immediate reference to the atlas. Intraobserver repeatability was tested in 40 subjects one month apart with ICCs of 0.65-0.85 [26].

WOMAC pain assessment

Knee pain was assessed using the Western Ontario McMaster University Osteoarthritis Index (WOMAC) [27] at baseline and 5 years later using a 10-point scale from 0 (no pain) to 9 (severe pain). The 5 subscales (walking on flat surface, going up/down stairs, at night, sitting/lying and standing upright) were assessed separately and summed to create a total pain score (0 to 45). Change in knee pain score was calculated as follow-up value - baseline value. The presence of knee pain was defined as total WOMAC pain score of 1 or greater. Worsening knee pain was defined as a change in WOMAC pain score of 1 or greater. Regular nonsteroridal anti-inflammatory drugs (NSAIDs) use in most days (>15 days) of the last month at baseline were recorded by questionnaire.

Anthropometrics

Height was measured to the nearest 0.1 cm (with shoes, and headgear removed) using a stadiometer. Weight was measured to the nearest 0.1 kg (with shoes, socks, and bulky clothing removed) by using a single pair of electronic scales (Delta Model 707, Seca, Hamburg, Germany) that were calibrated using a known weight at the beginning of each clinic. Body mass index (BMI, weight (kg)/height (m^2)) was also calculated.

Data analysis

One-way analysis of variance or χ^2 tests were used to compare means or proportions among participants with no-OPs (no X-ray or MRI OPs), MRI-OPs (only MRI OPs, not detected by X-ray) and established-OPs (both X-ray and MRI

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OPs). Multivariable linear regression analyses were used to examine the associations between different phenotypes of OP (independent variables) and knee cartilage volume change (dependent variable), with age, sex, BMI, cartilage defects and BMLs as covariates. Multivariable log binominal regression analyses were used to assess associations between different phenotypes of OP (independent variables) and increases in cartilage defects /BMLs (dependent variables); multivariable linear regression analyses were also used to evaluate longitudinal associations between OP phenotypes and change of total WOMAC knee pain over 5 years, both after adjustment for potential confounders. All statistical analyses were performed on Stata version 12.0 for Windows (StataCorp, College Station, TX, USA)

A *p*-value < 0.05 (2-tailed) or a 95% confidence interval (CI) not including the null point (for linear regression) or 1 (for log binominal regression) was considered statistically significant.

Results

Characteristics of study sample

Of the 837 participants, 628 (75%) had MRI-OPs, 127 (15%) had no-OPs and 80 (9.6%) had definie-OPs in the whole knee. In medial tibiofemoral compartment, 205 (24%) had MRI-OPs, and in lateral tibiofemoral compartment, 446 (53%) had MRI-OPs (Table 1). 2 cases had OPs only seen on radiographs. We ignored this group as the sample was too small to do any proper analyses. Due to lack of skyline view of radiographs, patellofemoral compartment was not investigated in current study. Follow-up MRI scans were only available in 395 out of 837 participants. However there were no significant differences in baseline demographics, cartilage defects, BMLs, or cartilage volume between the subjects

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who were included in the present study and the those who did not have follow-up MRI scans (data not shown). The baseline characteristics of the participants are shown in Table 2. Over the observational period 83%, 69%, 77%, and 53% of participants had persistent MRI-detected OP scores and 17%, 30%, 23%, and 46% of subjects had increased MRI-detected OP scores in the medial tibiofemoral compartment, lateral tibiofemoral compartment, patellar compartment, and total knee compartment, respectively. Change in MRI-detected OP scores were significant associated with increases in cartilage defects, BMLs before and after adjusted for age, sex, BMI and baseline structural abnormalities (data not shown). At baseline, subjects with no-OPs, establishedestablished-OPs and MRI-OPs were significant different in terms of age ($p<0.01$), body weight ($p<0.01$), BMI ($p<0.01$), female proportion ($p=0.03$), tibial bone area ($p<0.01$), prevalence of JSN ($p<0.01$), cartilage defects and BMLs ($p<0.01$), and total cartilage defect and BML scores($p<0.01$). Subjects with no, MRI-, and established-OPs were similar in terms of baseline cartilage volume.

Associations with cartilage defects

Figure 1a shows a dose-response relationships between baseline OP phenotypes and increases in knee cartilage defects in different knee compartments. Compared to knees with no-OPs, knees with MRI-OPs were associated with a greater risk of increased cartilage defect scores in medial (RR 1.26, 95%CI 1.08-1.48) and lateral tibiofemoral (RR 1.28, 95%CI 1.08-1.51), but not in total, compartments, after adjustment for age, sex, BMI, baseline cartilage volume and BMLs in the same compartments (Table 3). Similarly, knees with established-OPs had greater risk of increased cartilage defect scores in total knee (RR 1.50, 95%CI 1.13-2.00) and medial tibiofemoral (RR 1.44, 95%CI 1.05-1.97), but not in lateral tibiofemoral, compartment, after adjustment for relevant covariates and the effect sizes were larger than MRI-OPs group (Table 3).

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Associations with cartilage volume

Figure 1b shows significant associations of baseline OP phenotypes with changes of total cartilage volume in different compartments. Compared to subjects with no-OPs, knees with MRI-OPs had significantly greater loss of total knee cartilage volume over 2.6 years in medial tibiofemoral compartment (β -0.55, 95%CI -1.10, -0.01), after adjustments for age, sex and BMI, and remained significant after further adjustment for cartilage defects and BMLs in the same compartments (Table 3). Associations between MRI-OPs and cartilage loss in total and lateral tibiofemoral compartment were not significant. Established-OPs were associated with loss of knee cartilage volume over 2.6 years in total and lateral compartments, after adjustment for age, sex and BMI (β -5.41, 95%CI -9.68, -1.13), but significant association in total compartment did not persist after further adjustment for cartilage defects and BMLs in the same compartments. No significant associations were found between established-OPs and cartilage volume loss in medial compartments (Table 3).

Associations with BMLs

Figure 1c showed significant associations between baseline OP phenotypes and increases in total knee BMLs in different compartments. Comparing with no-OPs knees, knees with MRI-OPs had higher risks of having increased medial tibiofemoral BMLs over 2.6 years, after adjustment for age, sex and BMI, and remained significant after further adjustment for cartilage volume and cartilage defects (RR 1.51, 95%CI 1.08-2.11). MRI-OPs were not significantly associated with increases in BMLs in the total and lateral tibiofemoral compartments. Knees with established-OPs had significantly higher risks of increased knee BMLs over 2.6 years in both total knee (RR 1.76, 95%CI 1.03-3.01) and tibiofemoral compartments (RR 2.16, 95%CI 1.36-3.45 for medial; RR 1.88, 95%CI 1.18-3.00

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for lateral) after adjustment for age, sex and BMI. These significant associations remained, after further adjustment for cartilage volume and cartilage defects in the same compartments (Table 3).

Associations with knee pain

Figure 2 showed the associations between baseline OP phenotypes and increases in total WOMAC knee pain in different compartments. Established-OPs in total knee compartment were positively associated with change in knee pain over 5 years (β 1.96, 95%CI 0.17, 3.76), after adjustment for age, sex, BMI, BMLs and cartilage defects (Table 4). Similar significant associations were found for established-OPs in medial tibiofemoral compartment (β 2.54, 95%CI 0.74, 4.35). In contrast, there was a significantly negative association between MRI-OPs in medial tibiofemoral compartment and change in total knee pain over 5 years (β -1.51, 95%CI -2.50, -0.52), and this association remained significant after adjustment for age, sex, BMI, BMLs and cartilage defects in the same compartments (Table 4). MRI-OPs in total knee compartment were also negatively associated with knee pain change, but this did not reach statistical significance. All associations remained largely unchanged after further adjustment for NSAIDs usage and baseline WOMAC pain score (data not shown). No statistically significant associations were found for OPs in lateral tibiofemoral compartment (Table 4).

Discussion

In this population-based cohort study, MRI-detected early OPs (MRI-OPs) were highly prevalent, affecting 75% of older adults; in contrast, the prevalence of established-OPs was only 10%. Only 0.2% (2 case in this sample) had x-ray only OPs. Both categories of OP predicted progression of knee structural abnormalities

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in a dose-response manner. In contrast, medial tibiofemoral MRI-OPs were associated with decreases in total knee pain over 5 years while established-OPs were associated with worsening knee pain. This association is unexpected but suggests MRI-OPs may alleviate pain to a limited extent but lead to OA progression over time.

Our current study confirmed that MRI-detected early OPs were highly prevalent in an older population-based sample which highlights the need for an understanding of clinical relevance of these common findings. OPs are considered to be the hallmark of knee OA [28] and their size and extent are used for defining OA [29]. Despite the development and widespread use of MRI in recent decades, conventional radiography remains the most commonly used imaging tool to detect OPs in research and clinical practice [5, 30]. The discrepancies of using MRI and radiography in detecting OPs have been reported previously [31]. MRI-defined OPs were present in 60% of older persons without radiographic OA [11], and were the most common abnormality that was found in 74% of all participants without radiographic evidence of OA [10].

Our study found that MRI-detected early OPs and established-OPs are associated with knee structural changes in a dose response manner. Cross-sectional studies suggested that greater size of MRI-defined OPs correlated with higher Kellgren-Lawrence score, and increasing size and presence of MRI-defined OPs was associated with severity of knee OA [32, 33]. Another study reported that patients with central OPs detected by MRI had higher likelihood of full thickness or near-full thickness cartilage defects than patients without central OPs [16]. To the best of our knowledge, there are only two longitudinal studies examining the associations of MRI-defined OPs with knee structural changes so far. While one did not find any significant associations between MRI-defined OPs and knee structural progression [11], another reported that MRI-defined OP was an

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important factor in determining future total knee arthroplasty [34]. Our findings from the current longitudinal study were consistent, with OPs detected only by MRI but not by X-ray (MRI-detected early OPs) being associated with increases in cartilage defects/loss and subchondral bone abnormalities over time. Our results are largely in line with findings from a previous case-control study which reported that hidden OPs on plain x-ray at femoral inter-condylar notch were at risk for the development of radiographic OA after 48 months [35], indicating MRI-detected early OPs can serve as a biomarker for knee osteoarthritic structural progression before radiographic changes become evident.

Although knee OPs are associated with pain and predict pain weakly but more accurately than joint space narrowing, the longitudinal associations are inconsistent [36-39]. In one prior study, increasing x-ray-detected OP size at baseline was reported to be associated with increasing WOMAC pain severity score [11]. In contrast, Link et al [33] reported that MRI-defined OPs were not associated with clinical findings as assessed with the WOMAC scores in patients with varying degree of OA. Neogi et al estimated the relationship of radiographic features with knee pain and found that JSN was more strongly associated with knee pain than OPs [40]. A recent systematic review concluded that there was a lack of evidence on the association between OPs and knee pain [41], and it is still debatable if OPs are detrimental or beneficial for pain [39, 42]. Our data showed that while OPs detected only by MRI predicted a decrease of WOMAC knee pain over 5 years, established-OPs (both on MRI and x-ray) predicted an increase in knee pain over time. This is unexpected. It suggests that MRI-OPs, which would largely represent early subchondral bone overgrowth, may alleviate pain to a limited extent compared to larger OPs. Pain medication usage and baseline WOMAC pain score may be potential factors that affect our results; however, the

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significant associations remained largely unchanged after further adjustment for NSAIDs usage and baseline WOMAC pain score, suggesting this is unlikely.

A previous study reported that removal of OPs from the arthritic compartment significantly increased the varus-valgus motion [43]. OPs have been considered an adaptive reaction of the joint to cope with instability and may play a compensatory role in the redistribution of forces to provide articular cartilage protection [42]. However, our data do not support this as both categories of OP were associated with worse structural change, although MRI-OPs are associated with reduced knee pain over time.

We employed a combination of WORMS and KOSS for the measurement of OPs in current study. WORMS and KOSS scoring systems are two validated instruments which have good reliability to assess OPs semi-quantitatively on MR imagines [15, 17]. In our study, WORMS was used to divide the whole knee into 14 different subregions as it has one of the most complex differentiation of OP in terms of number of locations, and KOSS was used to score OP at each site. The reason for making this choice is because WORMS grading system has advantage of subdividing whole knee into different subregions which includes both marginal and central OPs, but its OP grading scale is more subjective . On the other hand, KOSS grading system has the advantage of quantitative OP grading scale for each subregion. The reliability of our measures were excellent.

There were several potential limitations in our study. One limitation was lack of skyline view to assess patellofemoral radiographic OPs, so we were unable to comment on the associations of patellofemoral OPs with OA progression. The patellofemoral joint is a common site of knee pain and contribute to functional limitation among OA patients [44, 45]. Future study are needed to investigate whether MRI-OPs in patellofemoral compartment have similar relationships with

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knee pain change as those in tibiofemoral knee compartments. Second, using higher field strength magnet than 1.5 T might be marginally more sensitive in detecting OPs; however, as reported previously [46], the results would not be markedly different as this benefit is modest. Third, follow-up MRI scans were only available in 395 out of 837 participants; However, there were no significant differences in demographic factors, ROA, baseline cartilage volume, defects and BMLs between the current study sample and the rest of cohort (data not shown). Last, the WOMAC knee pain questionnaire was not asked specifically for the right knee, while MRI scans were taken at right knee. Thus, the associations found between MRI-OPs and WOMAC knee pain change needs to be interpreted with caution.

Conclusion

MRI-detected early OPs are associated with knee structural changes in a dose response manner. Unexpectedly, they have opposite associations with pain suggesting MRI-detected early OPs may prior to knee pain development.

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Contributors

ZZ had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study design: CD, FC and GJ. Acquisition of data: ZZ, CD, XJ and FP. Analysis and interpretation of

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Competing interests

The authors declare that they have no competing interests.

Patient consent: Obtainded.

Ethics approval

This study was approved by the Southern Tasmania Health and Medical Human Research Ethics Committee, and written informed consent was obtained from all participants.

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Table 1. Frequencies of OP types detected by x-ray and MRI in the studied sample

	Total knee			MTF			LTF		
	x-ray OPs	MRI OPs	n	x-ray OPs	MRI OPs	n	x-rays OP	MRI OPs	n
No-OPs	N	N	127	N	N	571	N	N	358

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MRI-OPs	N	Y	628	N	Y	205	N	Y	446
	Y	N	2	Y	N	2	Y	N	0
Established-OPs	Y	Y	80	Y	Y	59	Y	Y	33
Total			837			837			837

OP: osteophytes; MTF: medial tibiofemoral; LTF: lateral tibiofemoral; Y means with x-ray OP or MRI OP, N means without x-ray OP or MRI OP.

Table 2. Baseline characteristics of participants

	No-OP N=127	MRI-OPs N=628	Established-OPs N=80		Total Sample N=837
Age (year)	**60.5±6.5**	**62.4±7.5**	**65.2±7.5**		62.4 7.4
Female sex (%)	**61**	**48**	**46**		50
Weight (kg)	**72.1±12.0**	**77.9±14.5**	**85.4±15.1**		77.7 14.8
BMI (kg/m²)	**26.4±3.7**	**27.7±4.4**	**30.4±6.2**		27.7 4.7
Total tibial bone area (cm²)	**3.2±1.5**	**3.3±0.5**	**3.5±0.6**		3.3 0.8
Any joint space narrowing (%)	**51**	**56**	**95**		59
Joint space narrowing score (n)					
0	62	276	4		342
1	51	273	18		342
2	13	66	35		114
3	1	13	23		37
Total cartilage defects score (0-20)	**4.3±1.4**	**5.7±1.9**	**9.5±3.2**		5.8 2.4
Total BML score (0-5)	**0.38±0.63**	**0.65±0.90**	**1.3±1.2**		0.47 0.71
Total tibial cartilage volume (ml)	4.9±1.2	5.1±1.2	4.9±1.3		5.1 1.2
Any cartilage defects (%)	**18**	**54**	**90**		53
Any BMLs present (%)	**22**	**33**	**64**		34
Knee pain present (%)	**42**	**50**	**73**		51
Total WOMAC score (0-45)	**2.8** ± **5.7**	**3.3** ± **6.0**	**6.4** ± **7.4**	**<0.01**	3.5 ± 6.1
Total radigraphic OP score (n)					
0	127	628	0		755
1	0	0	46		46
2	0	0	25		27

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	3	0	0	9	9

One-way analysis of variance was used for differences between three subgroups, and $\chi 2$ tests were used for proportions (percentages). Mean ± SD except for percentages. Significant differences are shown in bold. OPs: osteophytes; BMI: body mass index; BML: bone marrow lesions.

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Table 3. Longitudinal associations of OP phenotype status and changes/increases in total knee structure in 2.6 years

	Increases in Cartilage Defects		**Cartilage Volume changes (p.a)**		**Increases in BMLs**	
	Adjusted*	**Adjusted****	**Adjusted***	**Adjusted****	**Adjusted***	**Adjusted****
	RR (95% CI)	RR (95% CI)	β (95% CI)	β (95% CI)	RR (95% CI)	RR (95% CI)
OP phenotypes n=395						
Total knee						
No-OPs (n=53)	*Ref.*	*Ref.*	*Ref.*	*Ref.*	*Ref.*	*Ref.*
MRI-OPs (n=310)	1.16 (0.89, 1.50)	1.14 (0.88, 1.47)	-0.49 (-1.25, 0.26)	-0.24 (-0.99, 0.51)	0.83 (0.53, 1.30)	0.71 (0.46, 1.11)
Established-OPs (n=32)	**1.63 (1.23, 2.17)**	**1.50 (1.13, 2.00)**	**-1.21 (-2.37, -0.06)**	-0.42 (-1.61, 0.78)	**1.94 (1.17, 3.23)**	**1.76 (1.03, 3.01)**
p for trend		**p<0.01**		**p=0.03**		**p<0.01**
Medial tibiofemoral						
No-OPs (n=259)	*Ref.*	*Ref.*	*Ref.*	*Ref.*	*Ref.*	*Ref.*
MRI-OPs (n=111)	**1.31 (1.12, 1.53)**	**1.26 (1.08, 1.48)**	**-0.56(-1.09, -0.04)**	**-0.55 (-1.10, -0.01)**	**1.52 (1.10, 2.11)**	**1.51 (1.08, 2.11)**
Established-OPs (n=24)	**1.64 (1.41, 1.90)**	**1.49 (1.26, 1.75)**	-0.79 (-1.83, 0.26)	-0.47 (-1.57, 0.63)	**2.29 (1.48, 3.56)**	**2.16 (1.36, 3.45)**
p for trend		**p<0.01**		**p<0.01**		**p<0.01**
Lateral tibiofemoral						
No-OPs (n=165)	*Ref.*	*Ref.*	*Ref.*	*Ref.*	*Ref.*	*Ref.*
MRI-OPs (n=219)	**1.33 (1.13, 1.57)**	**1.28 (1.08, 1.51)**	-0.01 (-1.12, 1.14)	-0.14 (-0.64, 0.37)	1.23 (0.88, 1.71)	0.97 (0.63, 1.50)
Established-OPs (n=11)	**1.50 (1.08, 2.09)**	**1.44 (1.05, 1.97)**	**-5.93 (-10.2, -1.70)**	**-5.41 (-9.68, -1.13)**	**2.60 (1.59, 4.26)**	**1.88 (1.18, 3.00)**
p for trend		**p=0.01**		p=0.08		**p<0.01**

OP: osteophytes; p.a, percentage per annual; Results of this table are generated from a linear regression or log binominal regression model. *Adjusted for age, sex and BMI; ** Further adjusted for cartilage volume, cartilage defects and BMLs in the same compartments (excluded the outcome structures); Significant differences are showed in bold.

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Table 4. Longitudinal associations of OP phenotype status and WOMAC knee pain changes in 5 years

	Total knee Pain	
	Adjusted *	Adjusted **
	β (95% CI)	β (95% CI)
OP phenotypes n=646		
Total		
No-OPs (n=103)	*Ref.*	*Ref.*
MRI-OPs (n=481)	-0.23 (-1.33, 0.88)	-0.28 (-1.40, 0.84)
Established-OPs (n=62)	**2.20 (0.51, 3.89)**	**1.96 (0.17, 3.76)**
Medial tibiofemoral		
No-OPs (n=447)	*Ref.*	*Ref.*
MRI-OPs (n=155)	**-1.25 (-2.2, -0.30)**	**-1.51 (-2.50, -0.52)**
Established-OPs (n=43)	**2.91 (1.21, 4.60)**	**2.54 (0.74, 4.35)**
Lateral tibiofemoral		
No-OPs (n=287)	*Ref.*	*Ref.*
MRI-OPs (n=332)	0.12 (-0.70, 0.94)	-0.05 (-0.91, 0.81)
Established-OPs (n=27)	1.08 (-1.11, 3.27)	0.35 (-1.95, 2.66)

OP: osteophytes; Significant differences are shown in bold. Results of this table are generated from a linear regression model. * Adjusted for age, sex and BMI, ** Further adjusted for BMLs and cartilage defects in the same compartments.

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Figure Legends:

Figure 1. Associations of baseline osteophytes phenotypes with increases in total knee cartilage defects (a), change in cartilage volume (b), and increases in BMLs (c). OP: osteophytes; MTF: medial tibiofemoral; LTF: lateral tibiofemoral.

Figure 2. Associations of baseline osteophytes phenotypes with increases in total WOMAC knee pain. OP: osteophytes; MTF: medial tibiofemoral; LTF: lateral tibiofemoral.

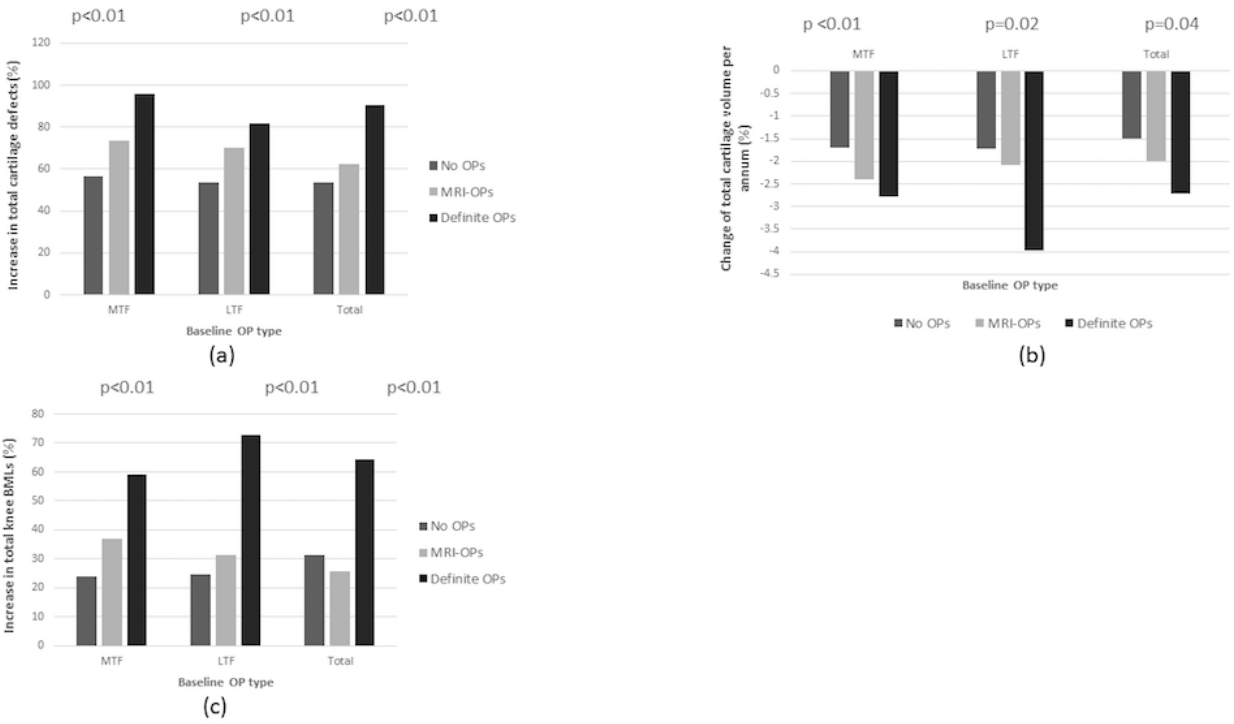

Figure 1

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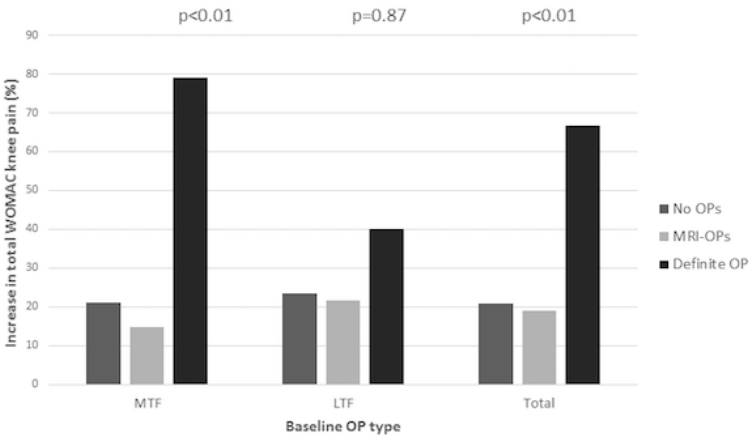

Figure 2

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