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Relationship between knee pain and the presence, location, size and phenotype of femorotibial denuded areas of subchondral bone as visualized by MRI

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Original article

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ABSTRACT:

Objective: Conflicting associations between imaging biomarkers and pain in knee osteoarthritis (OA) have been reported. A relation between pain and denuded areas of subchondral bone (dABs) has been suggested and this study explores this relationship further by relating the presence, phenotype, location and size of dABs to different measures of knee pain.

Methods: 633 right knees from the OAI (250 men, age 61.7±9.6yrs, BMI 29.4±4.7 kg/m²) were included. Manual segmentation of the femorotibial cartilage plates was performed on 3T coronal FLASHwe images. dABs were defined as areas where the subchondral bone was uncovered by cartilage. The following measures of pain were used: weightbearing-, non-weightbearing-, moderate-to-severe-, infrequent- and frequent knee pain.

Results: Using pain measures from subjects without dABs as a reference, those with at least one dAB had a 1.64-fold higher prevalence ratio (PR, 95% CI 1.24 - 2.18) to have frequent and 1.45-fold higher for moderate-to-severe knee pain (95% CI 1.13 - 1.85). Subjects with dABs in central subregions had a 1.53-fold increased prevalence of having weightbearing pain (95% CI 1.20 - 1.97), especially when the central subregion was moderately (>10%) denuded (PR 1.81, 95% CI 1.35 - 2.42). Individuals with cartilage-loss-type dABs had a slightly higher prevalence (PR 1.13, 95% CI 1.00 - 1.27) of having frequent knee pain compared to individuals with intra-chondral-osteophyte-type dABs.

Conclusion: This study supports a positive relation between femorotibial dABs and knee pain, especially when the dABs are located centrally (i.e. in weightbearing regions) or when the respective central subregion is moderately denuded.

INTRODUCTION

Osteoarthritis (OA) accounts for a large proportion of the global disease burden in the industrialized world [1] and is most commonly seen in the knee joint. Among individuals with knee OA, pain is the main reason for seeking medical care [2] however, pain perception is a multifactorial and complex issue [3-7]. Pain in knee OA likely originates from richly innervated structures such as the joint capsule [8], the synovium [9] or the subchondral bone [10] and consequently, pathologies affecting these structures have been suggested to be directly or indirectly related to pain in knee OA [11-15]. Several studies have correlated structural biomarkers to the incidence and the severity of knee pain in knee OA [12,16-21] but only few have presented significant associations, between joint pathologies such as bone marrow lesions, meniscal tears or synovitis and knee pain [16,19-21].

Magnetic resonance imaging (MRI) provides several quantitative structural measures of cartilage morphology [22]. Denuded areas of subchondral bone (dAB) are defined as areas where the subchondral bone is not covered by articular cartilage and was presented as one of three variables providing independent information on progressive cartilage loss [23]. Previous histo-pathological and in immune-histochemical studies in both animals and humans revealed evidence for the presence of sensory nerve fibres in layers of cartilage next to the subchondral bone [10,24-26]. It was hypothesized, that nerve fibres could be growing from the subchondral bone (along with blood vessels) into the non-calcified cartilage during osteochondral remodelling due to OA progression [24]. The authors suggest that this neovascularization may represent a new potential source of pain, occurring when subchondral bone is exposed to mechanical stimuli due to a lack of overlaying cartilage. In support, the presence of dABs in OA affected knees was shown to be associated with the prevalence and incidence of knee pain, also after adjustment for bone marrow lesions [14]. Our group recently showed a significant positive relationship between the grade of radiographic OA (ROA) and the presence of dABs [27], and this agrees well with the report of a positive relationship between

individual radiographic features of OA progression (such as advanced Kellgren and Lawrence grades) and knee pain [17].

In a previous report from the sample used in this study, we identified at least two different phenotypes of dABs: cartilage-loss-type and intra-chondral-osteophyte-type (Fig. 1) [27]. We have also shown that dABs occur both in the central (i.e. weightbearing) and the peripheral (non-weightbearing) region of the knee [27], which may be of importance for knee pain experiences during weightbearing and/or non-weightbearing activities. Thus, the presence, location, size, and phenotype of a dABs in the femorotibial joint could lead to different aspects of knee pain experiences in OA.

The objective of this cross-sectional study was therefore to investigate the relationship between the presence, location, size and phenotype of dABs and aspects of knee pain (weightbearing-, non-weightbearing-, moderate-to-severe-, infrequent- and frequent knee pain). We specifically hypothesized that individuals with at least one femorotibial dAB are more likely to experience frequent pain and have a greater risk of reporting moderate-to-severe knee pain than individuals without femorotibial dABs, that individuals with at least one centrally located dAB report more weightbearing knee pain than individuals with peripheral dABs (whereas the location is less important in context of non-weightbearing pain) and that individuals with at least one cartilage-loss-type dAB are more likely to report frequent pain and have a greater risk of having moderate-to-severe pain than subjects with intra-chondral-osteophyte dABs alone.

METHODS:

Study sample

The Osteoarthritis Initiative (OAI) is a large cohort study aiming to identify biomarkers of OA. The sample analyzed in this study was based on a convenience sample of OAI participants from industry partners, the OAI coordinating centre and an image analysis company (Chondrometrics GmbH). We used baseline knee MRIs from 633 OAI subjects, including participants from the healthy reference cohort, from the progression cohort, and from the incidence cohort. The radiographic grading relied on the baseline calculated KLG, derived from osteophyte and JSN grades as determined by the OARSI-atlas scores assigned by centrally trained and certified readers at the clinical OAI recruitment sites [28]. The study sample and a detailed description of how calculated KLGs were derived has been previously described in detail [27].

In summary: 158 right knees with Kellgren and Lawrence grades [KLG] ranging from 0 to 4 from the OAI progression subcohort; 418 right knees with definite radiographic knee OA corresponding to KLG 2 and 3; 13 right knees with radiographic knee OA corresponding to KLG 4; 44 right knees from the healthy reference cohort without symptomatic or radiographic knee OA (corresponding to KLG 0) [27].

Demographic and radiographic data was obtained from the OAI public database (version 0.2.2 for clinical data and version 0.E.1 for the imaging data, www.oai.ucsf.edu). Grading of radiographic OA relied on calculated Kellgren and Lawrence grades, provided by the OAI and aggregated from the clinical site readings of osteophytes and joint space narrowing according to the OARSI atlas for the purpose of recruitment [28]. Table 1 shows demographic data of the total sample stratified by location and size of the dABs (no dABs, peripheral dABs, central dABs). Knees with central dABs were further divided into mildly denuded (denuded area more than 0% but ≤ 10% of the respective central cartilage subregions) and moderately

denuded (denuded area >10% of the respective central cartilage subregions) as described below.

MRI assessment and analysis

This study relied on the double oblique coronal 3D fast low angle shot (FLASH) images with water excitation (we), acquired in the right knees of all OAI participants in this study [27], as the FLASH we sequence was appropriately validated for articular cartilage analysis using morphometry, with test-retest precision error for analyzing dABs of 6.8% (expressed as root mean square of standard deviations) [29-31]. Quality control as well as the manual segmentation process performed at the image analysis center (Chondrometrics GmbH, Ainring, Germany) was described in detail previously [27,32-34]. Data was handled blinded to the aims of this study and to clinical and radiographic data.

Denuded areas of subchondral bone

Denuded areas of subchondral bone (dABs) represent regions of subchondral bone not covered by articular cartilage. As reported previously in this sample, dABs could be of two types: cartilage loss or intra-chondral osteophytes (Fig. 1) [27]. Classification of type and number of dABs was performed by two expert readers (S.C. and R.F.) in each cartilage plate affected by dAB. Any discrepancies in classifying dABs were resolved immediately in consensus between the two readers [27]. Since both types could occur in one plate (or in one knee) we used the following categories in our analysis:

- Exclusive cartilage-loss-type dABs = Plates or knees with dABs originating from only cartilage-loss-type dABs
- Exclusive intra-chondral-osteophyte-type dABs = Plates or knees with dABs originating from only intra-chondral-osteophyte-type dABs

- Combined cartilage-loss & intra-chondral-osteophyte-type dABs = Plates or knees with dABs originating from a combination of the two types (i.e. cartilage-loss-type and intrachondral-osteophyte-type dABs).

None of the individual dABs showed a combination of the two types and consequently each individual dAB were of one single type. The size and location of dABs of this sample was determined for each cartilage plate (medial and lateral tibia and central medial and lateral femur) using custom software (Chondrometrics GmbH, Ainring, Germany) [27,32,33]. In brief, dAB size was determined in relation to the area of subchondral bone in each cartilage plate and was expressed in percent. The location was automatically determined in five tibial (central, external, internal, anterior, and posterior), and three femoral (central, external, internal) subregions for the medial and lateral compartment respectively using an algorithm previously described [27,32,35]. The algorithm did however not differentiate between one single or several dABs. We defined central dABs as dABs affecting one of the four central femorotibial subregions (central medial and lateral tibia [cMT, cLT] and central medial and lateral central femur [ccMF, ccLF]) with dAB>0%. Respectively, a dAB was classified as peripheral, when NOT affecting one of the 4 central subregions (dAB=0% in cMT, cLT, ccMF, ccLF). DABs affecting both subregions (f.i. marginally located) were classified as central dAB, when dAB>0% in cMT, cLT, ccMF, ccLF, disregarding the extent of affection of the neighbouring peripheral subregion [27,35] (Fig. 3).

To investigate the influence of size of dABs in the central subregions of knees with definite dABs, we applied a 10% threshold to classify between mildly vs. moderately denuded central subregions. In knees with definite central dABs, the central subregion was considered as moderately denuded when >10% of the respective cartilage subregion was denuded and mildly denuded when ≤10% of the respective cartilage subregion was denuded [27].

Assessment of pain measures

Measures of knee pain were obtained from the OAI database (version 0.2.2) and since all MR images were from right knees, only pain measures from the right knee were used.

Weightbearing and non-weightbearing pain were assessed using the pain subscore items of the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) [36]. In agreement with previous publications [15,37], we used the three pain subscore items: "pain during climbing stairs"; "pain during walking"; "pain during standing" to assess weightbearing pain and the two pain subscore items: "pain during sitting"; "pain during lying in bed" to assess non-weightbearing pain. A score of at least 2 (i.e. moderate pain) for each item was regarded as a positive outcome and a score of less than 2 in any of the items was regarded as a negative outcome. Positive outcomes for all respective items was regarded as having weightbearing or non-weightbearing knee pain whereas at least one negative outcome in any of the items was regarded as not having weightbearing or non-weightbearing knee pain [15].

Pain severity was evaluated using the numerical rating scale (NRS) where subjects were asked to grade their knee pain severity during the last 30 days ranging from 0 (no pain) to 10 (pain as bad as you can imagine). In agreement with previous reports, we defined the presence of moderate-to-severe knee pain as 'yes' if the answer was ≥ 4 or 'no' if the answer was < 4 [14,38].

Pain frequency was evaluated using the OAI "baseline symptom status assessment of the right knee" (P01RKSX, www.oai.ucsf.edu): 0 (no pain in past 12 months); 1 (pain in past 12 months but not most days of a month); 2 (pain most days of a month in the past 12 months). We defined 1 as infrequent knee pain and 2 as frequent knee pain.

Statistical analysis

All statistical analyses were performed using PASW 18 (SPSS Inc, Chicago, IL). To evaluate the relation between different aspects of knee pain and dABs we used Poisson-regression-models with robust variance estimator (Huber/White/sandwich estimator) to calculate the prevalence with adjustment for age, sex and body mass index (BMI). Results are presented as

prevalence ratio (PR) in combination with the 95% confidence intervals (CI). Kruskal-Wallis test was used for comparisons of independent test samples for variables deviating from a normal distribution. Pearson's Chi-Squared tests were used to analyze crosstabulation tables. A significant relation was reported for p-values less than 5%. Further, a post-hoc approach for multiple testing using Bonferroni correction was conducted when estimating the prevalence ratio for dAB phenotype ($p < 0.0125$) and dAB location ($p < 0.0025$).

RESULTS

The knees included in this analysis represent a broad spectrum of the severity of radiographic OA with most knees having mild to moderate radiographic OA. Individuals without dABs in their analyzed knee comprised the control group (n = 388), including forty-four individuals from the OAI healthy reference cohort with bilateral KLG0 and no risk factors of knee OA. In this group, 112 (28.9%) reported weightbearing knee pain, 49 (12.6%) non-weightbearing knee pain, 96 (24.7%) moderate-to-severe knee pain, 113 (29.1%) infrequent knee pain and 157 (40.5%) frequent knee pain, whereas the subset from the healthy reference cohort reported no pain in all of the measured pain estimates. Two-hundred-and-forty-five participants had at least one dAB in their analyzed knee, with 125 (19.8%) of those having central dABs and with 62 (9.8%) having moderately denuded central dABs. Of those 93 (38%) reported weightbearing knee pain, 43 (18%) non-weightbearing knee pain, 87 (36%) reported moderate-to-severe knee pain, 129 (53%) frequent knee pain and 72 (29%) reported infrequent knee pain, and (Table 1).

Pain relationships in those with at least one dAB versus those without any dABs

Compared to those without dABs in the femorotibial joint (Fig. 2), participants with at least one femorotibial dAB had a higher prevalence to report weightbearing knee pain (PR 1.29, 95% CI 1.03 - 1.61), moderate-to-severe knee pain (PR 1.45, 95% CI 1.13 - 1.85), infrequent knee pain (PR 1.50, 95% CI 1.11 - 2.03) and frequent knee pain (PR 1.64, 95% CI 1.24 - 2.13). The prevalence of non-weightbearing knee pain was not significantly higher in those with at least one femorotibial dAB, compared to those without dABs (PR 1.37, 95% CI 0.93 - 2.01). Compared to those without dABs, those with at least one dAB in the central subregions were more prevalent to have weightbearing knee pain (PR 1.53, 95% CI 1.20 - 1.97), moderate-to-severe knee pain (PR 1.67, 95% CI 1.27 - 2.19), infrequent knee pain (PR 2.11, 95% CI 1.20 - 3.71) and frequent knee pain (PR 2.93, 95% CI 1.74 - 4.94), and (Fig. 2). No

statistically significant relationship for any pain measure was found between participants with only peripheral dABs when compared to participants without any dABs (p>0.11; Figure 2).

Pain relationships with regard to location, size and phenotype of dAB in those with dABs

Using individuals with peripheral dABs as reference, individuals with at least one central dAB had a higher prevalence of having weightbearing knee pain (PR 1.40, 95% CI 1.02 - 1.93), moderate-to-severe knee pain (PR 1.41, 95% CI 1.01 - 1.97) and frequent knee pain (PR 1.19, 95% CI 1.06 - 1.34) (Tbl. 2). Further, those with at least one moderately denuded central subregion had a higher prevalence to report weightbearing pain (PR 1.62, 95% CI 1.15 - 2.30) and frequent knee pain (PR 1.48, 95% CI 1.19 - 1.85) (Tbl. 2) compared to individuals with peripheral dABs.

No statistical significant relationships were seen between individuals with mildly denuded central subregions compared to individuals with moderately denuded central subregions. However, a trend was visible for individuals with moderately denuded central areas towards a higher prevalence of reporting weightbearing and frequent knee pain (Tbl. 3)

With regard to dAB phenotypes, participants with combined cartilage-loss-type and intra-chrondral-osteophyte-type dABs in the femorotibial joint had a slightly higher prevalence of reporting frequent knee pain compared to individuals with exclusive intra-chondral-osteophyte-type dABs (PR 1.13, 95% CI 1.00 - 1.27, not significant after correction for multiple testing) (Tbl. 4).

On the cartilage plate level, individuals with a dAB in the central medial femur (PR 1.22, 95% CI 1.08 - 1.38) and in the lateral tibia (PR 1.15, 95% CI 1.02 - 1.30, not significant after correction for multiple testing) had an increased prevalence to report frequent knee pain.

Remarkably, individuals with a dAB in the central lateral femur were less prevalent to report non-weightbearing knee pain (PR 0.51 95% CI 0.26 - 0.97, not significant after correction for multiple testing) compared to those with a dAB in any other plate (Tbl. 5).

DISCUSSION:

To our knowledge, this is the first study to assess the cross-sectional relationship between the presence, location, the size and the phenotype of femorotibial denuded areas of subchondral bone (dABs) and different aspects of knee pain. Using a larger sample, this study confirms a positive relation between femorotibial dABs and ipsi-lateral knee pain, previously shown by Moiso et al [14]. In extension of that report however, our results also suggest that those with at least one dAB report more weightbearing pain, but not more non-weightbearing knee pain, than subjects without dABs and that individuals with central dABs (i.e. dABs affecting at least one weightbearing subregion) report more weightbearing, moderate-to-severe, and frequent knee pain than those with peripheral dABs, especially when more than 10% of the central subregion was denuded.

This study has certain limitations. First, cross-sectional pain assessment is a challenge, mainly due to the large individual variation influenced by multiple endogenous and exogenous factors in the subjective pain experience [3-7]. However, we used a standard definition for the assessment of frequency of knee pain, a previously published strategy to assess knee pain during (femorotibial) weightbearing and non-weightbearing conditions, and an established classification for the absence/presence of moderate-to-severe knee pain [15,37,38]. It is noteworthy, that pain during sitting, classified here as non-weightbearing knee pain, could originate from femoropatellar joint disease but evaluation of the femoropatellar compartment was technically not possible from a coronal FLASHwe imaging protocol, which was the basis of the current analysis. Secondly, dAB is an MR imaging finding derived from manual segmentation of cartilage and subchondral bone and may not directly relate to clinically relevant findings reported by experienced radiologists or to focal chondral defects seen at arthroscopy. Thirdly, the MR sequence used here (FLASHwe) does not adequately visualize other relevant joint pathologies, such as bone marrow lesions, meniscal tears or synovitis, previously shown to have a relation to knee pain in OA [12,16-21]. However,

appropriate sequences were acquired by the OAI but since we concentrated on the FLASHwe sequence we lack information on other joint pathologies and have not assessed their potential relation to pain in this sample. Future work is needed to light up to what extent these and dABs are correlated and/or provide independent information.

We are aware of one publication reporting associations between dABs and knee pain where knees with dABs larger than the median size in the patellar and the medial, but not the lateral, femorotibial compartment had more frequent and moderate-to-severe knee pain than those without dABs, also after adjusting for age, sex, BMI and the presence of bone marrow lesions (BML)[14]. The previous study and our study were similar in the cross-sectional design and in the methodology used to detect and quantify dABs however, our sample size was three times larger, we used a more detailed description of dABs and we extended the pain analysis. In agreement with Moisio et al [14], we found a significant relation between frequent and moderate-to-severe ipsi-lateral knee pain and a presence of dABs however, we found this relation regardless of dAB size. In extension of previous findings, we could also identify a relation between weightbearing, but not non-weightbearing knee pain in those with dABs. Interestingly, the relation between all measures of knee pain, except non-weightbearing knee pain, was stronger when the dAB was located in a central (i.e. weightbearing) subregion and when more than 10% of the central subregion was denuded. These findings are interesting since it is well known that articular cartilage is aneural and thereby insensate to mechanical stimuli [39]. It is also unclear whether intra-chondral osteophytes are formed by protrusion of the richly innervated subchondral bone or if they are formed by other processes. Although neurovascular invasion of osteophytes were suggested in OA [10], firm relations between the presence of osteophytes and ipsi-lateral knee pain is lacking [17,19,40-42]. On the other hand, subchondral bone has been shown to undergo osteochondral turnover with sensory nerve fibres breaching from the subchondral bone into adjacent layers of non-calcified articular cartilage during OA progression[10,24-26] and the mechanism driving pain remains unclear. It is

also not known whether dABs in fact contribute to the pain experience or if they are a manifestation of disease severity, relating to knee pain only indirectly. Still, the positive relationship between dABs and ipsi-lateral knee pain found here, and before [14], suggest that that dABs may play one role for different aspects of knee pain in OA however, properly designed longitudinal studies need to confirm such relations.

Cartilage-loss-type dABs, as visualized on MR images, were shown to be highly associated with knee pain in both young and elderly individuals [43,44]. Moreover, our study shows that subjects with moderately denuded central subregions have a higher prevalence of reporting weightbearing, but not non-weightbearing, knee pain than do individuals with only peripheral dABs. Such prevalence was however not found when comparing individuals with moderately and mildly denuded central subregions. This finding is interesting since central subregions of the femorotibial joint are more exposed to peak loads under weightbearing conditions [22,45], in part due to the lack of the protective meniscal tissue. One possible explanation could be that pain is produced from the exposed subchondral bone, independent of the size of the dAB, which may explain the reduced mobility and the limited range of motion seen in knee OA patients. The results of this study generate the hypothesis that both phenotypes and the location (but not the size) of dABs play a role in OA related knee pain.

Having dABs in the central medial femur, but not in any other cartilage plate, slightly increased the prevalence of frequent knee pain compared to having a dAB at another location. The central medial femur was not the plate most frequently affected by dABs [27], but interestingly, this specific location was reported to show the greatest longitudinal change in cartilage thickness and volume amongst the femorotibial cartilage plates [33,46,47]. In addition, the central medial femur was reported to display cartilage thickening at early stages of OA disease, particularly in the external subregion [48]. Although no linkage between pain and cartilage morphology changes has been established, our results agree with other reports in suggesting that the central medial femur might be an important location in knee OA.

CONCLUSION:

This study confirms, in a large sample, an association between the presence of denuded areas of subchondral bone (dABs) and different aspects of ipsi-lateral knee pain. Our extended analysis also suggest that subjects with at least one dAB in the femorotibial joint report significantly more frequent, moderate-to-severe and weightbearing, but not non-weight bearing, ipsi-lateral knee pain than those without dABs. This relationship may be stronger for dABs located in central subregions and for dABs covering more than 10% of a central subregion. Furthermore, cartilage-loss-type dABs seem to increase the possibility of reporting frequent ipsi-lateral knee pain as compared to those having intra-chondral-osteophyte-type dABs.

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Sebastian Cotofana and Wolfgang Wirth have part time appointments with Chondrometrics GmbH. Felix Eckstein is CEO and co-owner of Chondrometrics GmbH, a company providing MR image analysis services to researchers in academia and industry. He provides consulting services to Pfizer, MerckSerono, Wyeth and Nordo Nordisk. Brad Wyman and Jennifer Gardiner are employed by Pfizer Inc., Olivier Benichou by Eli Lilly & Co, Donatus Dreher by MerckSerono SA.. Richard Frobell and Michael Nevitt have no competing interest.

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CONTRIBUTIONS:

Study design and study protocol: SC, MN, KK, FE, RBF

Data collection: SC, MN, WW, KK, FE, RBF

Statistical analysis plan: SC, MN, WW, WH, KK, FE, RBF

Data analysis: SC, MN, KK, FE, RBF

Manuscript writing: SC, RBF

Manuscript review: SC, BTW, OB, DD, MN, JG, WW, WH, KK, FE, RBF

Approval of final manuscript version: SC, BTW, OB, DD, MN, JG, WW, WH, KK, FE, RBF

All authors agreed to publish and have approved this final version.

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Table 1: Demographic data, stages of radiographic osteoarthritis (OA) and the presence, location, size and phenotype of denuded areas of subchondral bone (dAB) in the study sample (n = 633). The last 2 columns show mildly (defined as ≤10% in size of the respective cartilage plate) and moderately denuded (defined as >10% in size of the respective cartilage plate) central dABs.

* **Demographics (total sample size: n = 633)**	**no dABs (n = 388)**	**peripheral dABs (n = 120)**	**central dABs (n = 125)**	**central dABs mildly denuded (n = 63)**	**central dABs moderately denuded (n = 62)**
Age, mean (SD)	60.7 (9.7)	64.2 (8.9)	62.7 (9.4)	61.5 (9.5)	64.0 (9.2)
BMI mean (SD)	29.0 (4.9)	30.4 (4.7)	29.6 (4.0)	29.2 (4.3)	30.0 (3.8)
Sex (male), n (%)	130 (33.5)	58 (48.3)	62 (49.6)	33 (52.4)	29 (46.8)
* **Radiographic OA stage**[1], n (%)	**n = 388**	**n = 120**	**n = 125**	**n = 63**	**n = 62**
cKLG 0	46 (11.9)	1 (0.8)	0	0	0
cKLG 1	24 (6.2)	6 (5.0)	4 (3.2)	4 (6.3)	0
cKLG 2	184 (47.4)	51 (42.5)	24 (19.2)	17 (27.0)	7 (11.3)
cKLG 3	131 (33.8)	61 (50.8)	69 (55.2)	37 (58.7)	32 (51.6)
cKLG 4	3 (0.8)	1 (0.8)	28 (22.4)	5 (7.9)	23 (37.1)
* **Pain measures,** n (%)	**n = 388**	**n = 120**	**n = 125**	**n = 63**	**n = 62**
Weightbearing knee pain[2]	112 (28.9)	39 (32.5)	54 (43.2)	22 (34.9)	32 (51.6)
Non-weightbearing knee pain[3]	49 (12.6)	19 (15.8)	24 (19.2)	10 (15.9)	14 (22.6)
Infrequent knee pain[4]	113 (29.1)	39 (32.5)	33 (26.4)	18 (28.6)	15 (24.2)
Frequent knee pain[5]	157 (40.5)	52 (43.3)	77 (61.6)	35 (55.6)	42 (67.7)
Moderate-to-severe knee pain[6]	96 (24.7)	36 (30.0)	51 (40.8)	25 (39.7)	26 (41.9)
* **Phenotype of dABs,** n (%)	**n = 388**	**n = 120**	**n = 125**	**n = 63**	**n = 62**
Exclusive cartilage-loss-type dABs	0	22 (18.3)	36 (28.8)	20 (31.7)	16 (25.8)
Exclusive intrachondral-osteophyte-type dABs	0	88 (73.3)	36 (28.8)	27 (42.9)	9 (14.5)
Cartilage-loss & intrachondral-osteophyte-type dABs combined	0	10 (8.3)	53 (42.4)	16 (25.4)	37 (59.7)

SD=standard deviation;BMI=body mass index;WOMAC=Western Ontario McMaster Universities Osteoarthritis Index;NRS=numerical rating scale

* Significant difference between groups using Kruskall-Wallis (age, BMI) or Pearson-Chi-Squared Test (sex, radiographic OA stage, pain measures and dAB phentotype); $p < 0.05$

[1] Assessed by calculated Kellgren and Lawrence grades

[2] At least moderate pain in one of the WOMAC items stand, stair, walk

[3] At least moderate pain in one of the WOMAC items sit, lie

[4] Knee pain in the past 12 months, but not in most days of the month

[5] Knee pain in most days of a month in the past 12 months

[6] At least 4 in the NRS ranging from 0-10

Table 2: Relationship between location (peripheral vs. central) and size (mildly vs. moderately denuded) of denuded areas of subchondral bone (dAB) within those with dABs (n = 245). Values are presented as prevalence ratio with adjustment for age, sex, BMI. The last 2 columns show mildly (defined as ≤10% in size of the respective cartilage plate) and moderately denuded (defined as >10% in size of the respective cartilage plate) central dABs.

Pain measures	**Reference: Peripheral dABs[1] (n = 120)**	**Central dABs[2] (n = 125)** PR (95% CI)	**Mildly denuded central subregion[3] (n = 63)** PR (95% CI)	**Moderately denuded central subregion[4] (n = 62)** PR (95% CI)
Weightbearing knee pain p-value (crude)	1	1.40 (1.02 - 1.93) 0.039	1.20 (0.80 - 1.81) 0.382	1.62 (1.15 - 2.30) 0.006
Non-weightbearing knee pain p-value (crude)	1	1.29 (0.74 - 2.24) 0.386	1.80 (0.54 - 2.18) 0.827	1.49 (0.80 - 2.77) 0.206
Moderate-to-severe knee pain p-value (crude)	1	1.41 (1.01 - 1.97) 0.046	1.43 (0.97 - 2.11) 0.071	1.41 (0.94 - 2.11) 0.094
Infrequent knee pain p-value (crude)	1	1.08 (0.94 - 1.23) 0.279	1.01 (0.88 - 1.17) 0.845	1.20 (0.94 - 1.54) 0.151
Frequent knee pain p-value (crude)	1	1.19 (1.06 - 1.34) 0.004	1.11 (0.97 - 1.27) 0.133	1.48 (1.19 - 1.85) <0.001

PR = Prevalence Ratio; 95% CI = 95% confidence interval; dAB = denuded area of subchondral bone

[1] Knees with at least one dAB not including a central subregion in any of the four cartilage plates

[2] Knees with at least one dAB affecting one central subregion of the femorotibial joint

[3] Knees with at least one dAB affecting at least one central subregion where ≤ 10% of the central subregion is denuded (mildly denuded)

[4] Knees with at least one dAB affecting at least one central subregion where >10% of one central subregion is denuded (moderately denuded)

Table 3: Relationship between size (mildly vs. moderately denuded) of centrally located denuded areas of subchondral bone (dAB) within those with central dABs exclusively (n = 125). Values are presented as prevalence ratio with adjustment for age, sex, BMI.

	Reference: Mildly denuded central subregions[1] (n = 63)	**Moderately denuded central subregions[2] (n = 62)** PR (95% CI)
Weightbearing knee pain p-value (crude)	1	1.45 (0.97 - 2.18) 0.071
Non-weightbearing knee pain p-value (crude)	1	1.46 (0.70 - 3.02) 0.313
Moderate-to-severe knee pain p-value (crude)	1	1.07 (0.71 - 1.61) 0.766
Infrequent knee pain p-value (crude)	1	1.07 (0.95 - 1.21) 0.275
Frequent knee pain p-value (crude)	1	1.11 (0.99 - 1.24) 0.073

PR = Prevalence Ratio; 95% CI = 95% confidence interval; dAB = denuded area of subchondral bone

[1] Knees with at least one dAB affecting at least one central subregion where ≤ 10% of the central subregion is denuded (mildly denuded)

[2] Knees with at least one dAB affecting at least one central subregion where >10% of one central subregion is denuded (moderately denuded)

Table 4: Relationship between different phenotypes (cartilage-loss-type vs. intrachondral-osteophyte-type) of denuded areas of subchondral bone (dAB) within those with dABs (n = 245). Values are presented as prevalence ratio with adjustment for age, sex, BMI.

	Reference: Exclusive intrachondral-ostephyte-type dAB[1] (n=124)	**Exclusive cartilage-loss-type dABs[2] (n = 58)** PR (95% CI)	**Unspecific cartilage-loss-type dABs[3] (n=121)** PR (95% CI)
Weightbearing knee pain p-value (crude)	1	1.22 (0.80 - 1.86) 0.359	1.35 (0.98 - 1.87) 0.066
Non-weightbearing knee pain p-value (crude)	1	1.80 (0.91 - 3.55) 0.090	1.58 (0.88 - 2.84) 0.129
Moderate-to-severe knee pain p-value (crude)	1	1.20 (0.80 - 1.81) 0.382	1.08 (0.77 - 1.52) 0.641
Infrequent knee pain p-value (crude)	1	0.98 (0.85 - 1.13) 0.745	1.07 (0.94 - 1.22) 0.341
Frequent knee pain p-value (crude)	1	1.00 (0.88 - 1.14) 0.950	1.13 (1.00 - 1.27) 0.050

PR = Prevalence Ratio; 95% CI = 95% confidence interval; dAB = denuded area of subchondral bone

[1] Knees with at least one intra-chondral-osteophyte-type dAB (not combined with cartilage-loss-type dABs) in the femorotibial joint

[2] Knees with at least one cartilage-loss-type dAB (not combined with intrachondral-osteophyte-type dABs) in the femorotibial joint

[3] Knees with at least one cartilage-loss-type dAB (including the possibility of a combination of cartilage-loss-type and intra-chondral-osteophyte-type dABs)

Table 5: Relationship between location (medial and lateral tibia and central femur) of denuded areas of subchondral bone (dAB) within those with dABs (n = 245). Values are presented as prevalence ratio with adjustment for age, sex, BMI. Reference group were those with at least one dAB in the femorotibial joint but without any dAB in the respective cartilage plate.

	Reference: No dAB in cMF (n = 151)	**At least one dAB in cMF (n=94)** PR (95% CI)	**Reference: No dAB in cLF (n = 156)**	**At least one dAB in cLF (n=89)** PR (95% CI)
Weightbearing knee pain p-value (crude)	1	1.28 (0.94 - 1.76) 0.119	1	0.99 (0.71 - 1.36) 0.931
Non-weightbearing knee pain p-value (crude)	1	1.20 (0.70 - 2.05) 0.517	1	0.51 (0.26 - 0.97) 0.040
Moderate-to-severe knee pain p-value (crude)	1	1.16 (0.83 - 1.61) 0.396	1	0.99 (0.70 - 1.39) 0.931
Infrequent knee pain p-value (crude)	1	1.13 (0.99 - 1.29) 0.076	1	0.92 (0.81 - 1.06) 0.246
Frequent knee pain p-value (crude)	1	1.22 (1.08 - 1.38) 0.001	1	0.95 (0.84 - 1.07) 0.355
	Reference: No dAB in MT (n = 155)	**At least one dAB in MT (n=90)** PR (95% CI)	**Reference: No dAB in LT (n = 129)**	**At least one dAB in LT (n=116)** PR (95% CI)
Weightbearing knee pain p-value (crude)	1	1.23 (0.90 - 1.69) 0.203	1	1.09 (0.80 - 1.49) 0.588
Non-weightbearing knee pain p-value (crude)	1	1.65 (0.96 - 2.83) 0.071	1	0.87 (0.51 - 1.50) 0.662
Moderate-to-severe knee pain p-value (crude)	1	1.31 (0.94 - 1.82) 0.113	1	0.95 (0.68 - 1.32) 0.746
Infrequent knee pain p-value (crude)	1	1.00 (0.88 - 1.15) 0.950	1	1.13 (0.99 - 1.29) 0.076
Frequent knee pain p-value (crude)	1	1.06 (0.93 - 1.20) 0.371	1	1.15 (1.02 - 1.30) 0.024

PR = Prevalence Ratio; 95% CI = 95% confidence interval; dAB = denuded area of subchondral bone; cMF/cLF = central medial/lateral femur; MT/LT = medial/lateral tibia.

Figure 1: Different phenotypes of the denuded areas of subchondral bone (dABs) as visualized quantitatively by MRI cartilage morphometry:
Image A & B: Cartilage-loss-type dAB in the central medial femur (cMF) and medial tibia (MT) with (A) and without (B) segmentation.
Image C & D: Intrachondral-osteophyte-type dAB in the lateral tibia (LT) with (C) and without (D) segmentation.

Figure 2: Adjusted (age, sex, BMI) prevalence ratio and the 95% confidence interval for: ● = "weightbearing" knee pain; ○ = "non-weightbearing" knee pain; ▲= "frequent" knee pain; △ = "infrequent" knee pain and ★= "moderate-to-severe" knee pain in subjects with at least one femorotibial denuded area of subchondral bone (dAB, n=245), peripheral dABs (n=120), central dABs (n=125), mildly denuded central subregions (≤10% of the subchondral bone area, n=63) and moderately denuded central subregions (>10% of the subchondral bone area, n=62). Bars display the upper and lower 95% confidence intervals. Reference category (set as 1) is those without femorotibial dABs (n = 388).

Figure 3: The femorotibial regions and subregion.
Image A: Showing the 4 femorotibial regions: medial and lateral tibia (MT, LT) and medial and lateral central femur (cMF, cLF) and the 16 femorotibial subregions (10 tibial and 6 femoral): external, central, internal, anterior and posterior medial and lateral tibia (eMT, cMT, iMT, aMT, pMT and eLT, cLT, iLT, aLT, pLT) and external, central, internal central medial and lateral femur (ecMF, ccMF, icMF and ecLF, ccLF, icLF). The central subregions are highlighted in bold.
Image B: Showing an intrachrondral-osteophyte-type dAB in the central cMF
Image C: Showing a cartilage-loss-type dAB in the central cMF (and MT)
Image D: Overview of the segmentation displayed in image B, showing the intrachrondral-osteophyte-type dAB in the central cMF comprising less than 10% of the central subregion. Additionally a small peripheral dAB can be seen in the posterior lateral tibia.
Image E: Overview of the segmentation displayed in image C, showing a cartilage-loss-type dAB affecting the central cMF and the external cMF but comprising more than 10% of the central subregion.