THICKER CARTILAGE IN PRESERVED FEMORAL CARTILAGE AREAS IN KNEE OSTEOARTHRITIS:

A TRI-DIMENSIONAL CROSS-SECTIONAL STUDY USING CT-ARTHROGRAPHY

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ABSTRACT

Knee osteoarthritis (OA) is no longer seen as a simple "wear and tear" disease in which cartilage thickness decreases on its whole surface through the severity of the disease. Recent research, based on the study of cartilage thickness at some specific areas of the femur, has proved that cartilage could be thicker in OA knees in its non-weight-baring parts. This study uses a new method of 3D cartilage thickness mapping based on CT-arthrography images aiming to confirm what was shown two-dimensionally in the past. The aim was: 1/ to show whether cartilage at the posterior aspect of the medial condyle (PMC) was significantly thicker in OA compared to non-OA knees, 2/ whether cartilage at the posterior part of lateral condyle (PLC) was also thicker in OA knees, and 3/ whether cartilage thickness at this location is correlated to Kellgren and Lawrence grade. After exclusion of secondary causes of OA seen on CTA images, 138 patients were included with different KL grades. OA was defined as KL≥2. Maximal and mean cartilage thickness were significantly thicker in OA (max: 2.45mm [2.34-2.56], mean: 1.59mm [1.51-1.67]) compared to non-OA (max: 2.14mm [2.00-2.26], mean: 1.46mm [1.36-1.55]) knees in the PMC (max: $P<0.001$, mean: $P=0.049$) but not in PLC (max: $P=0.20$, mean: $P=0.56$). The multiple linear regressions showed that on the medial condyle, maximum cartilage thickness and mean cartilage thickness were associated to age ($r=-0.27$, $P=0.0018$, and $r=-0.29$, $P=0.0005$ respectively) and KL grade ($r=0.39$, $P<0.0001$, and $r=0.24$, $P=0.0049$ respectively). The cartilage being thicker in preserved regions could be correlated to a regenerative process, which needs to be confirmed by biochemical and histological studies, and could lead to new therapeutic options.

INTRODUCTION

Knee osteoarthritis (OA) is a major healthcare issue worldwide, for which research has failed to reach an efficient treatment to prevent or slow joint destruction. Up to now, once the cartilage has suffered significant damages, the only available treatment is joint replacement.(1) It has been demonstrated that the prevalence of knee OA in a population of European men and women were about 27% between 65 and 70 years and 44% in a population older than 80 years old.(2) In the last 20 years, prevalence of symptomatic knee osteoarthritis increased by about 65%.(3) Associated with hip osteoarthritis, knee osteoarthritis was ranked as the 11th highest contributor to global disability, in a study comparing 291 items.(4) The main risk factors for adults have been identified as overweight (OR 1.98), obesity (OR 2.66), previous knee injury (OR 2.86), female gender and old age.(5) The increase in the prevalence of obesity and the population ageing could explain the rise of knee osteoarthritis prevalence.

For a long time, OA has been seen as a wear and tear disease in which the cartilage was in the centre of the explanation of the pathogenesis. Nowadays, OA is seen as a pathology of the whole joint, including more structures, particularly subchondral bone, in the pathogenesis.(6–8)

The importance of cartilage loss is classically used as a tool to quantify the severity of knee OA seen as the consequence of the wear of the joint. Only a few research have focused on the morphological assessment of cartilage that is preserved until late stages of knee OA, usually in non-weight-bearing regions. These few studies have shown that, in different regions, cartilage could be either thinner or thicker and that those two states could even coexist in the same knee.(9–12) Classically, thinning is seen in weight-bearing regions as central part of the medial condyle (even if thickening could be seen in those kinds of subregions specially in early Kellgren and Lawrence (KL) stages(10)), and thickening is seen in more peripheral and non-weight-bearing subregions as external, posterior or extreme anterior part of medial condyle.(9,10) Most of those researches have been performed studying cartilage thickness at some isolated points chose on two-dimensional slices of CT-arthrography (CTA) or MR-arthrography (MRA).

We aimed to test three different hypotheses: first, that mean cartilage thickness of the posterior aspect of the **medial** condyle (P**M**C) is thicker in medial femorotibial OA compared to non-OA knees; second, that there is no significant difference in mean cartilage thickness at the posterior aspect of the **lateral** condyle (P**L**C) between those two groups; and third, that in the medial condyle, cartilage thickness is correlated to KL grade. We aimed at testing these hypotheses using a three-dimensional reconstructed map of femoral cartilage, based on CTA images, showing at every spatial point on the femur the thickness of the cartilage using segmentation and processing as explained in the methodology.

METHODOLOGY

PATIENT POPULATION

This study was approved by the institutional ethical committee and patient consent was waived due to the retrospective design.

This retrospective study uses data coming from consecutive patients having performed a CTA in prevision of a knee replacement in one institution over 2 years. We included patients over 50 years old who had performed a conventional radiography the same day of the CTA. The radiographs were read by a musculoskeletal radiologist to determine the KL grade of medial femorotibial, lateral femorotibial and femoropatelar OA. The final KL grade was defined as the worst of those three. OA was defined as a KL≥2. The reader was blind to the CTA findings while analysing the radiographs to determine KL grade.

The exclusion criteria were CTA signs of secondary OA as signs of knee traumatism, signs of microcrystalline and rheumatic arthritis and signs of past knee surgery. After exclusion of those patients, 138 knees remained.

CT ARTHROGRAPHY

10mL of ionic contrast material (meglumine ioxaglate and sodium ioxaglate, Hexabrix 320 (320mg of iodine per milliliter); Guerbet, Aulnay-sous-bois, France) were injected into the knee joint with fluoroscopic guidance by using a lateral approach. After the injection, active mobilization of the knee was performed to allow diffusion of the contrast material in the joint cavity. CT arthrograms were performed on a 40-detector row CT scanner (Somatom Definition AS; Siemens Healthcare, Forchheim, Germany). Patients were positioned supine, with extension of the knee. Previously described acquisition parameters were optimized for the knee joint: tube voltage, 120kVp; reference tube current time product, 350mAs with the application of a dose modulation protocol (Care Dose 4D; Siemens Healthcare); detector configuration: 16x0.6mm; pitch: 0.85; gantry rotation time: 1 s. The following image reconstruction parameters were used: field-of-view (FOV) 15x15cm; matrix 5122; section thickness/increment 0.6/0.3 mm; bone convolution kernel (U70u).

SEGMENTATION, 3D MESH AND POST-PROCESSING.

To create a 3D-mesh model of femoral bones and cartilages, segmentation were performed using a previously validated semi-manual method allowing sub-pixel resolution based on D-spline. This method reconstructs a 3D-mesh of both femoral bone and cartilage and calculates the thickness of the cartilage covering the subchondral bone. The segmentations were done by five researchers under the supervision of a musculoskeletal radiologist with eight years of

experience. This process is done in two steps. First, the femoral bone is segmented to its very cortical limit as shown on figure 1 (yellow line). The osteophytes were excluded of the segmentation. Second, cartilage is segmented using the same method following the line between cartilage and intra-articular contrast (red line on figure 1). Those segmentations are performed on every 5 slices of reconstructed sagittal slices in which femoral bone and cartilage are present to have an accurate mesh. Once both bone and cartilage are segmented, the distance between the two lines of segmentation represents the cartilage thickness, which is calculated at any point of the femoral subchondral bone. The cartilage thickness map is anatomically-standardized across knees using a method based on a matching of shapes to allow spatial comparison among samples. After that, two regions of interest were defined: the posterior aspect of medial condyle and the posterior aspect of lateral condyle. Those regions of interest were defined independently for each condyle, and corresponded to the area most cranial to the most posterior point of subchondral bone. On those to regions of interest, the mean cartilage thickness and the maximal cartilage thickness at any point of the subregions were determined.

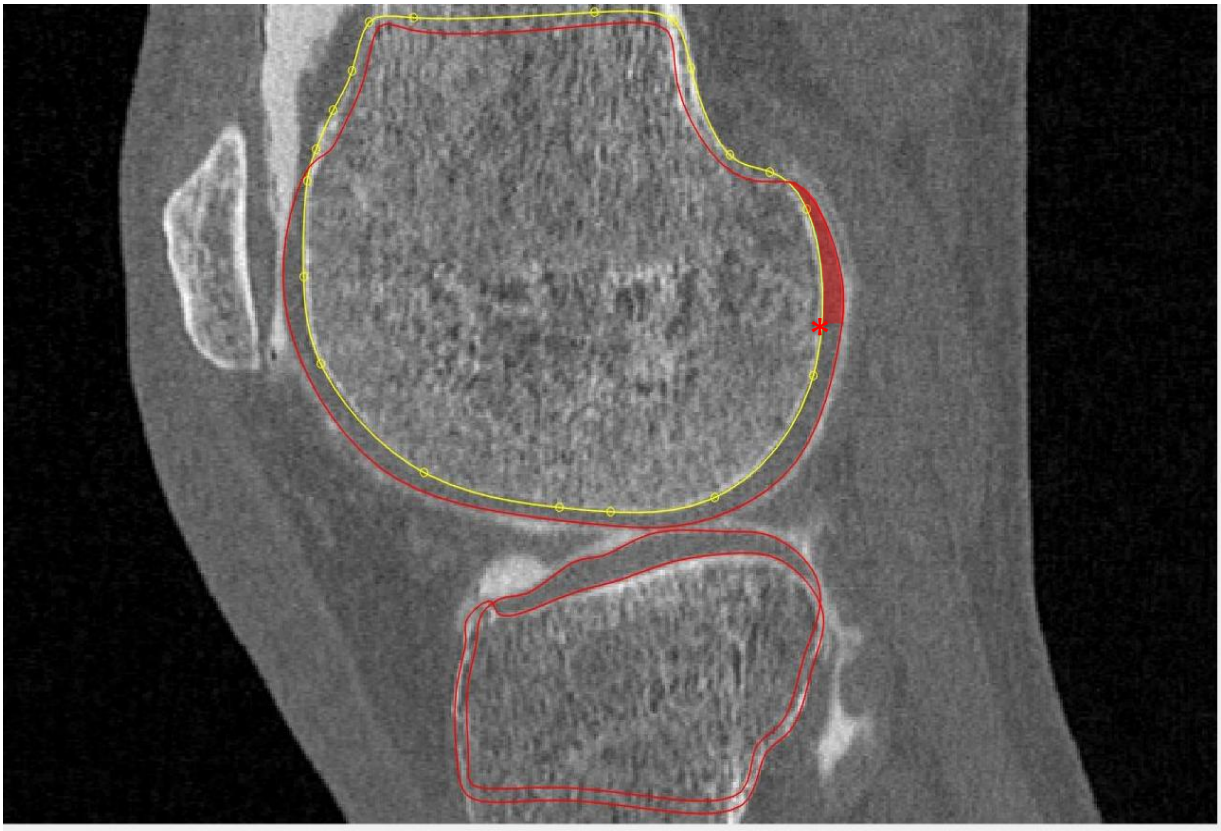

FIGURE 1: sagittal reformat of knee CT arthrogram showing the cartilage segmentation: yellow line: femoral bone segmentation, red line: femoral cartilage segmentation, (*): most posterior point of subchondral bone, red area: region of interest.

STATISTICAL ANALYSIS

To assess cartilage thickness in PMC and PLC, we focused on two variables: maximum cartilage thickness (CTh max) at any point of those two regions of interest, and mean cartilage thickness (CTh mean).

Those variables were compared statistically between two groups: OA and non-OA knees (OA being defined as a KL grade ≥2) on both lateral and medial condyle. Our first hypothesis to verify is that there is a statistically significant superiority of CTh max and CTh mean between OA knees and non-OA knees in the **medial** condyle. To compare those two groups, a student test was performed. The second hypothesis was that, comparing the same to groups with same variables, there is no significant superiority of any group on the **lateral** condyle.

To understand if the demographic parameters age and sex, morphometric parameters of bone size (bicondylar diameter and tibial diameter) and KL grade influenced those two variables. Multiple linear regression tests were performed to determine which of those parameters has a significant influence.

We used one-way analysis of variance, to assess differences in CTh max and CTh mean among groups of KL grades.

A significance level of $p = 0.05$ was considered for all tests. All statistical tests were performed with MedCalc (version 11.6, MedCalc Software).

RESULTS

We included a total of 138 patients (58.7% women, total mean age is 62.98±9.18). 40 were non-OA (KL≤1) with a mean age of 61.25±6.38 and 98 OA (KL≥2) with a mean age of 63.71±10.06 (Table 1).

KL	**0**	**1**	**2**	**3**	**4**
Number	26	14	28	40	30
Age [y]	61.78±7.70	60.36±3.27	61.11±8.85	64.80 ±11.01	64.63±9.52
Number of F	17	9	18	21	16
% of F	65.4%	64,3%	64.3%	52.5%	53.3%
Number of M	9	5	10	19	14
% of F	34.6%	35.7%	35.7%	47.5%	46.7%
BCD [cm]	8.01±0.69	7.99±0.58	8.05±0.73	8.10±0.61	8.10±0.55
TD [cm]	7.28±0.66	7.19±0.53	7.28±0.63	7.34±0.63	7.47±0.63

TABLE 1 : demographic distribution, in each KL group: number of patient, mean age with SD, number and % of female (F) and male (M), mean bicondylar diameter (BCD) in centimetres with SD, mean tibial diameter (TD) in centimetres with SD.

On the **medial** condyle, maximum and mean cartilage thickness showed a significantly thicker cartilage in the OA group compared to the non-OA group (P<0.001 and P= 0.049 respectively).

On the **lateral** condyle, no significant difference was found between OA and non-OA for either the maximum cartilage thickness (P=0.20), or for the mean thickness (P=0.56).

	OA		Non-OA				
	Mean	95% CI	Mean	95% CI	Difference	Standard error	P-value
Medial CTh max	2.45	2.34-2.56	2.14	2.00-2.26	0.33	0.085	**<0.001**
Medial CTh mean	1.59	1.51-1.67	1.46	1.36-1.55	0.13	0.069	**0.049**
Lateral CTh max	2.12	2.01-2.22	1.99	1.84-2.15	0.12	0.095	0.20
Lateral CTh mean	1.28	1.22-1.36	1.25	1.15-1.35	0.04	0.062	0.56

TABLE 2 : t-test values comparing OA and non-OA knees on the four different items we used. CTh max and Cth mean in millimetres.

The multiple linear regressions showed that on the **medial** condyle, maximum cartilage thickness and mean cartilage thickness were associated to age (r=-0.27, P=0.0018, and r=-0.29, P=0.0005 respectively) and KL grade (r=0.39, P<0.0001, and r=0.24, P=0.0049 respectively). On the **lateral** condyle, maximum cartilage thickness was associated to age (r=-0.22, P=0.0109), KL (r=0.18, P=0.0390) and sex (r=0.32, P=0.0002), while mean thickness was associated to age (r=-0.18, P=0.0377) and sex (r=0.35, P<0.0001).

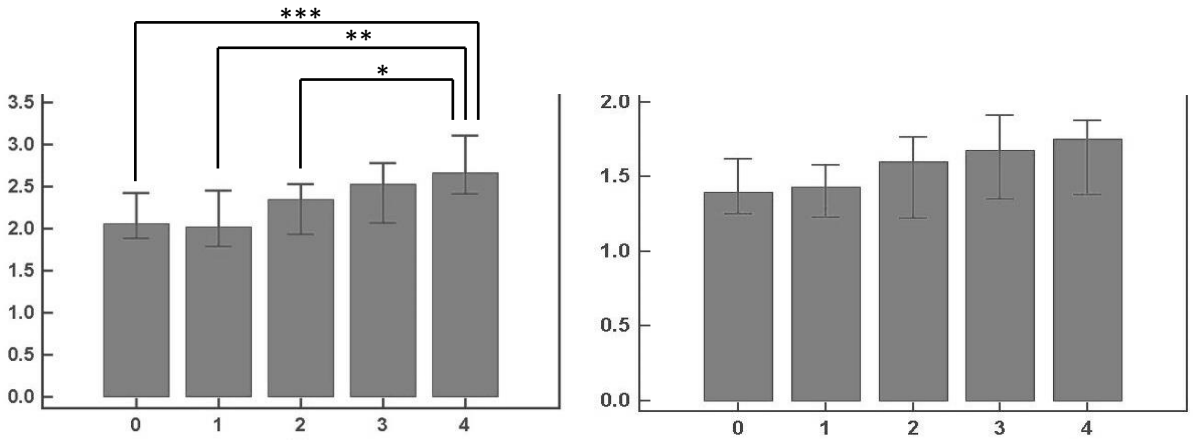

FIGURE 2 : mean and 95% CI of PMC CTh max in millimetres for every KL grade. (*) ANOVA test KL4 vs KL2 (P<0.05), (**) ANOVA test KL4 vs KL1 (P<0.05), (***) ANOVA test KL4 vs KL0 (P<0.05).

FIGURE 3 : mean and 95% CI of PMC CTh mean in millimetres for every KL grade. ANOVA test showed no significant P-value between different KL grades.

	Medial condyle		Lateral condyle	
	CTh mean [mm]	**CTh max [mm]**	**CTh mean [mm]**	**CTh max [mm]**
KL 0	1.48 ± 0.33	2.14 ± 0.42	1.28 ± 0.29	2.05 ± 0.50
KL 1	1.43 ± 0.29	2.08 ± 0.38	1.20 ± 0.35	1.90 ± 0.49
Total non-OA	**1.46 ± 0.31**	**2.14 ± 0.41**	**1.25 ± 0.31**	**1.99 ± 0.49**
KL 2	1.51 ± 0.32	2.25 ± 0.46	1.23 ± 0.34	1.99 ± 0.47
KL 3	1.61 ± 0.40	2.42 ± 0.59	1.29 ± 0.36	2.07 ± 0.59
KL 4	1.63 ± 0.44	2.66 ± 0.53	1.33 ± 0.31	2.29 ± 0.40
Total OA	**1.59 ± 0.39**	**2.45 ± 0.55**	**1.29 ± 0.34**	**2.12 ± 0.51**

TABLE 3: Mean and maximum values of cartilage thickness on PMC and PLC for every KL grades

Figures 2 and 3 both show the trend of CTh mean and CTh max with OA grade increase with the KL grade. One-way analysis of variance comparing every KL group showed significantly higher cartilage maximum thickness in KL grade 4 compared to KL grades 0, 1 and 2 ($P<0.001$). No significant difference between KL grades was seen for mean posterior cartilage thickness, although a trend is visible on figure 3.

DISCUSSION

This study showed that cartilage is statistically significantly thicker in OA knees compared to non-OA in the PMC, but not the PLC using two different variables as the mean CTh and the maximal CTh. Trough multivariate regression analysis, we also showed that cartilage thickness is positively correlated to KL grade.

Those results confirm what has been shown in 2D cartilage thickness previous studies.(13) Cartilage is significantly thicker at the PMC cartilage in OA patients compared to non OA patients. Furthermore, cartilage thickness increases with the severity of OA through the KL grades. This study is the first to show this finding using 3D data of cartilage thickness over the entire region of the posterior condyles, which allowed us to determine the maximum and the mean CTh in the PMC and PLC. Previous studies on the subject were performed measuring thickness at a specific point of interest, using a 2D analysis, on sagittal femur slices.(9–12)

The fact that CTh max shows more significant results than CTh mean could point to the fact that the thickening of cartilage in OA-preserved areas is irregular; some parts of the preserved subregion (PMC) may be more affected than others, leading to important differences in max CTh.

It has been demonstrated in animal models that the earliest stage of OA is a swelling of femoral and tibial cartilage seen on MR images and histologically which causes the thickening of cartilage in the early stage of OA.(14–16) This early thickening has also been associated with hypertrophy as an elevation of proteoglycan concentration and a synthetic response by the chondrocytes.(17) Our results show that cartilage thickness is also increased in the latest stages of the disease. Two hypotheses could be formulated on the fact that the thickening of preserved cartilage areas is

significant only in the last grade of OA (KL4): First, the cartilage thickening in humans could represent a slow regenerative process, which would explain why it is seen in late stages of the disease. Secondly, this thickening could be the result of the early degeneration with swelling and hypertrophy, as seen in animal models, only seen in border of the weight-baring part in KL4, where the disease is at it earliest stages due to lower mechanical constraints.(18)

Our study had limitations, mainly its retrospective, cross-sectional design, as well as the limited number of patients. Another limitation is the fact that we used the KL classification, which is a classification based only on radiological criteria. With a classification based on clinical scores, the results could be different. A confirmation of those results on a more important population would affirm the fact that cartilage in preserved areas is actually thickened in OA knees. Furthermore, to get more information on what happens in preserved areas of femoral cartilage in knee-OA patients, it is important to understand the biochemical phenomenon causing this thickening. As discussed above, it might be due to both swelling and hypertrophy of cartilage but what is its origin: is it some kind of cartilage healing? Or is it the expression of inflammatory processes? Future studies should include biochemical and histological assessment for a better understanding of those events, which could lead in turn to a better understanding of OA pathophysiology, a requirement to the development of news treatment pathways.

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