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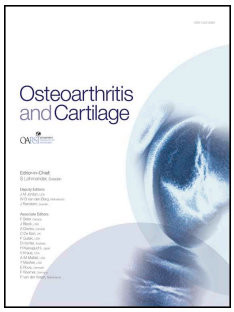

Where does meniscal damage progress most rapidly? An analysis using three-dimensional shape models on data from the Osteoarthritis Initiative

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ABSTRACT

Objectives. Meniscal pathology is integral to knee osteoarthritis (OA) and its progression; it provides a progression biomarker and a potential treatment target. MRI demonstrates large heterogeneity in meniscal damage; this structural complexity means measurement is difficult. The aim of this study was to apply novel 3D image analysis to determine which meniscal pathologies demonstrated most change during OA progression.

Methods. Knee images were selected from the progression cohort of the Osteoarthritis Initiative choosing participants with risk factors for medial OA progression. Medial and lateral menisci were manually segmented then analysed using a statistical shape model of the tibia as a reference surface. Responsiveness was assessed at 1 year using standardised response means (SRMs) for 4 constructs: meniscal volume, extrusion volume, thickness and tibial coverage; anatomical sub-regions of these constructs were also explored.

Results. Paired images from 86 participants (median age 61.5, 49% female, 56% obese) were included. Reliability of the novel meniscal measurements was very good (ICCs all > 0.98). Meniscal volume and extrusion demonstrated no significant change. Moderate responsiveness was observed for medial meniscus thickness (SRM -0.35) and medial tibial coverage (SRM - 0.36). No substantial change was seen for the lateral meniscus measures. Sub-region analysis did not improve responsiveness; while greater change was seen in the posterior medial compartment, it was associated with increased variance of the change.

Conclusions. The location of meniscal damage was consistently in the posterior medial region, and two measurements (thickness and tibial coverage) were most responsive. Meniscal measures should add to discriminatory power in OA progression assessment.

Key words: meniscus, longitudinal change, responsiveness, magnetic resonance imaging, 3D measures, osteoarthritis

INTRODUCTION

The development of disease modifying osteoarthritis (OA) drugs has been a frustrating process, in part due to lack of valid and responsive biomarkers to change [1], creating a vicious cycle where large numbers of people are required for trials resulting in higher costs to pharmaceutical companies who have thus become reluctant to pursue this area [2, 3] .To date OA biomarker development has focused mainly on cartilage measures, with cartilage relatively well validated as an OA imaging biomarker [4, 5] while measures reflecting subchondral bone changes have also demonstrated their potential as imaging biomarkers [6-8].

Healthy menisci protect the articular cartilage from concentrations of stress and are therefore important in load distribution [9-11]; a consequence of impairment in these structures is damage to articular cartilage and may consequently lead to the development of OA [12].While the importance of the meniscus in OA initiation and progression is well appreciated [13-19], there is however a paucity of data on the detailed changes in meniscal pathology that occur during OA progression. Such information is important not only to determine if the meniscus itself could be a biomarker of progression or whether it would add responsiveness when combined with other tissue biomarkers, but is increasingly of relevance with the development of meniscal repair and replacement therapies.

One of the main problems in accurately measuring meniscal pathologies has been the complex array of morphological changes that develop. A number of meniscal constructs such as volume, extrusion, thickness (or height) and tibial coverage (area of the tibia covered by meniscus) has been studied previously in OA [20-22] and nomenclature for these has been suggested [20]. The quantification of meniscal volume has been explored by segmentation of MRI images [21] and using 3D meniscal volume the effects of meniscal volume evaluated for OA and non-OA knees [23, 24].In another study, OA knees were shown to have less tibial coverage with increased meniscal body extrusion, while volume

measures did not differ from non-OA knees [23]. Evidence suggests meniscal extrusion is associated with knee pain in participants with knee OA [25] and with reduced tibial cartilage volume and increased bone marrow lesions [26], while meniscal thickness was shown to be greater in OA patients compared to controls [20, 27]. Current MRI semi-quantitative scoring [28-30] has been insightful in assessing the nature and location of meniscal pathology but may be insensitive to change as there is less scope for individuals to change by a full grade score over observation periods of 1-2 years, the feasible time for clinical studies [31].

Statistical shape modelling (SSM) provides a novel method of 3D quantification of MRI, correcting for both size and shape of the subject knee. This enables accurate identification of the spatial change at the population or cohort level [6-8, 32]. This technology also accounts for measurement issues due to pose, the position and rotation of knee bones that varies from image to image and confounds change over time. The aim of this study was therefore to apply this novel 3D image analysis in a cohort typical to that included in clinical trials, to determine the spatial distribution of change, and the meniscal pathologies most associated with change during 1-year of OA progression. To ensure that the meniscal shape was recorded accurately for measurement, we used careful manual segmentation of the MR images.

METHODS

Participants

This study used the first release (0.B.1 and 1.B.1, n=160) of the progression cohort of NIH OA initiative (OAI) database, which is available for public access at http://www.oai.ucsf.edu/. These subjects had both frequent knee symptoms (defined as “pain, aching or stiffness”) in the past 12-months and radiographic tibiofemoral-OA (defined as definite tibiofemoral osteophytes or Kellgren-Lawrence (KL) grade ≥2) in one knee. This subsample of “fast progressors” was chosen as most likely to undergo cartilage loss, as described previously

[33]. For the current study, one knee per subject was selected and where both knees fulfilled the inclusion criteria, the knee with the greater medial joint space narrowing (JSN) was selected. Inclusion criteria for this study were: evidence of medial JSN, medial JSN > lateral JSN, medial osteophytes, greater than 1º of varus mal-alignment, and availability of baseline and 12-month images. Exclusion criteria were any participants undergoing arthroscopy, meniscal surgery or ligament repair between baseline and the 12 month period of follow-up. This resulted in 86 pairs of knee images included in this analysis.

MR image acquisition and quantitative analysis

Images were acquired using Siemens-3T-Trio-Systems using the double-echo-in-steady-state-sequence (DESS). The DESS sequence produced a 160-slice image with a high spatial-resolution and signal-to-noise ratio. This optimised morphological analysis of menisci and facilitated segmentation. The medial meniscus and lateral meniscus in the chosen knee were manually segmented by an expert segmenter at Imorphics (Manchester, UK). The segmenter had passed a segmentation training protocol, which requires a coefficient of variation lower than 3% on paired test images. The segmenter was blinded to time point but not to subject.

Careful manual segmentation was done using Endpoint software (Imorphics, UK). A marching quads algorithm and quadratic smoothing converted segmented contours to 3D surfaces. Bone surfaces in the tibia were identified by automated segmentation using Active Appearance Models (AAMs) as described previously [8]. Fig 1a shows the mean shape of the menisci for this group of 86 individuals. Using AAMs returns the tibia surface as a dense set of anatomically corresponded points, which can then be used to take measurements of the menisci in a consistent manner, which corrects for patient shape and size (Figure 1b). Three dimensional images of the shape and position of the menisci relative to the tibia for each knee and time point were generated for visual review.

Four meniscus measures for volume, thickness, extrusion, and tibial coverage were calculated each for the medial and the lateral sides. Volumes were calculated using Gauss' theorem for measuring volume in which the volume is calculated by summing the vector product of the centroid, area and normal of each surface triangle [34]. Volume measures were obtained as total volume excluding the meniscal attachments (mm^3) from Figure 1b as described. Meniscal roots can be difficult to segment due to their visibility, and this measure excluded them by cutting the menisci at the boundary of the hyaline cartilage on the medial and lateral tibial plateaus.

Using the corresponded points on the tibial bone (Figure 1c), meniscal thickness was obtained by subdividing the meniscus into three approximately equal segments (anterior, central, and posterior) (Figure 1d) and reported as a mean value for each region; total thickness was the mean of all points in the combined 3 regions. Figure 1g shows how thickness measures were taken using the underlying correspondence points. We also measured sub-regional measures of thickness (anterior, central and posterior), to assess whether these might be more responsive than total thickness. Tibial coverage refers to the area of cartilage-covered bone that the meniscus directly overlies; this was calculated as the area of tibia which returned a thickness measure of >0 (mm).

Extrusion of the medial meniscus was measured using a novel method by first identifying the outermost points of the tibial plateau, and fitting a spline through those points. This line is extended into a plane in the sagittal direction, which is used to cut the meniscus (Figure 1e). Volume of meniscus extruded beyond this cutting plane was calculated as extruded volume (Figure 1f). The current measurement for assessing extrusion involves drawing a vertical line at the tibial joint margin on a single coronal MRI slice and extrusion past this point is measured in millimetres [35]

Reliability

An independent sample of 20 participants with no OA or mild OA was selected for a repeatability analysis of the 3D meniscus measures, using manual segmentation, with the repeat performed by the same individual blinded to subject. Intraclass correlation coefficients (ICC) were used to evaluate the intrarater reliability for each meniscal measure, while the smallest detectable difference (SDD) as well as SDD as a percentage of the baseline value were employed to assess absolute reliability. The SDD was calculated as $1.96 \times \sqrt{2} \times SEM$ [36].

Statistical analysis

Statistical analysis was conducted using STATA software, version 13 (College Station, TX, 2013) and MedCalc for Windows, version 15.6 (MedCalc Software, Ostend, Belgium). For each meniscal measure, the mean and standard deviation (SD) of the difference at 1 year follow-up were determined. Two measures of group level internal responsiveness, effect size (ES) and standardised response mean (SRM), were calculated to compare magnitude of change in a standardised manner, for each measure [37] . The confidence intervals for the SRMs were estimated using the bias-corrected and accelerated bootstrap methods, because in small samples the estimate of the standard deviation may be biased [38]. A paired student's *t*-test compared baseline and 12-month means to evaluate whether any changes were significantly greater than zero. Graphical checks were performed to ensure statistical assumptions were met prior to performing *t*-tests and these were satisfactory. The 86 participants were assumed to be homogenous in terms of their expected change over 1-year. Based on our selected sample of 86 we retrospectively calculated that we had 80% power to detect an effect size of 0.31.

Four measures as described above were assessed on the medial and lateral sides, and thickness was further evaluated using sub-regions. To adjust for multiple comparisons (on

the 14 tests performed) , a Bonferroni correction adjusted for mean correlation of the meniscal measures was applied and the level of significance set at (α=0.008) [39].

Lastly, exploratory analyses were performed on stratified sub-groups based on three demographic qualities important in OA: age, gender and body mass index (BMI). The strata were created based on median age (age<62 and age≥62), gender (males and females), and obesity status using WHO cut-offs (BMI≥30 and BMI<30). We also compared responsiveness between the groups that self-reported having previous arthroscopy or meniscectomy at baseline and the rest of the group.

RESULTS

The 86 participants had a median (IQR) age of 61.5 (52-71) with 49% being women. The mean BMI ± SD was 31.1 ± 4.60 kg/m² and median (IQR) pain score of 5.44 (2.4-6.3) as measured using the Western Ontario MacMaster Universities Osteoarthritis Index (WOMAC) scales (Table 1). The characteristics of the 74 participants that were not included in our study were very similar to our sample (age 61.0 vs 61.5 and gender 53% vs 49% respectively) see Table 1. As expected, visual review confirmed the heterogeneity of meniscal pathologies and Figure 2 demonstrates these using examples from this study.

Repeatability

The ICC values were very high for both medial and lateral measures, lowest for lateral extrusion (ICC 0.97, 95% CI 0.92, 0.99) and highest for medial tibial coverage (ICC 0.99, 95% CI 0.97, 0.99). Low SDD values were realised in the repeatability study. The SDDs (SDD as % of baseline) on the medial side for volume, extrusion, thickness and coverage were 32.2 mm^3 (1.9%); 15.7 µL (9.2%); 0.03 mm (2.6%) and 9.2 mm^2 (2.3%) respectively, all very small values. Similar low SDD values were found for the lateral measures: 55.5 mm^3

(3.6%) for total volume; 9.7 µL (16.2 %) extrusion; 0.03mm (2.3%) thickness and 6.1mm^2 (1.6%) for lateral meniscal coverage.

Change in measures over 1-year

Although mean medial volume decreased by 1.1% while medial extrusion showed an increase of 4.1 %, neither change was statistically significant and only that of extrusion exceeded SDD (Table 2). Mean medial total thickness decreased by 6.1% from baseline to follow-up ($p<0.001$) while mean tibial coverage decreased by 4.4% ($p<0.001$) with both changes being greater than SDD. On the lateral side no changes were greater than SDD except for volume and none were statistically significant. However, sub-regional analysis showed a significant increase of 2.6% for mean central thickness ($p<0.001$), although the amount of mean change was very small (0.05 mm) (Table 3).

A visualisation of the spatial position of change in meniscal thickness is shown in Figure 3. The posterior region of the medial meniscus showed the greatest change in thickness.

Responsiveness

The SRM and ES are reported in Table 2 for the four constructs investigated. Specifically in the primary analyses: the volume and extrusion measures showed no significant change (Table 2) while meniscal thickness (SRM - 0.35, 95% CI -0.55,-0.14) and tibial coverage (SRM of -0.36, 95% CI -0.58,-0.13) showed moderate responsiveness. Of the lateral measures none showed any significant change with only the regional measure of central thickness showing a small response (SRM +0.33, 95% CI 0.13, 0.51) (Table 3).

Analysis of the thickness measures as sub-regions on the medial side did not improve sensitivity compared to total thickness measures, posterior thickness was similar to total thickness, central thickness was less responsive, and anterior thickness did not change.

Exploratory analyses of drivers of change

The mean differences in meniscal measures after stratification for age, gender, BMI or previous arthroscopy/meniscectomy at 1-year were not substantial nor statistically significant (Table 4) while responsiveness indices (SRMs) were comparable within each stratum (SRM results not shown). To investigate ceiling effects, we divided the dataset into quartiles based on volume extruded in the medial meniscus at baseline, and assessed the amount of change in extrusion over time. Overall, positive change over time was seen in all quartiles, with greater change in quartiles with more baseline extrusion (data not shown), suggesting that ceiling effects were not important.

DISCUSSION

This study is the first using SSMs to measure 3D longitudinal change in a range of meniscal pathologies in an OA cohort typical of that used in an OA clinical trial. A major benefit of SSM technology stems from the 3D registration capability that corrects for both size and shape of knees; this may be the reason for the good repeatability shown in this study. We found that the most responsive meniscal measure was tibial coverage which changed by 4.4% (SRM -0.41) during follow up. Although most change was demonstrated in the medial posterior thickness measure (7.4% reduction in 1-year) (SRM -0.38), responsiveness in that region was similar to that of tibial coverage because the change in thickness was subject to more variation. The responsiveness of these meniscal measures compare favourably with 12 month radiographic joint space width measures (SRM -0.22) and MRI cartilage thickness measures (SRM -0.32) in one study [40]. Results from a systematic review showed that studies with similar follow-up to ours (1-2 years), reported pooled SRM of 0.25 for JSW[41].

The meniscal pathology demonstrating the most responsiveness to change in the 4 primary measures was medial tibial coverage (SRM -0.36). Our finding is similar to another small study employing 3D meniscal measures that also found tibial coverage to be the most responsive meniscal measure at 2-year follow-up with a reported SRM of 0.82 [42]. A

strength of the current study is that we applied a bootstrapping method to provide confidence in our SD estimates, as estimating SD from small populations is sensitive to outliers. The responsive decrease in coverage could be as a result of diminishing tibial coverage in OA-affected subjects due to meniscal destruction and radial displacement [15]. No significant changes were seen for lateral coverage which could possibly be due to our inclusion criteria of medial OA progression. Previous work has used “meniscal window” as a measure of a similar construct, which intrinsically relates the size of (shrinking) meniscus to that of the (expanding) tibia but does not correct for this tibial expansion [8] which could result in systematic over-estimation of change. Our meniscal coverage measure is not affected by tibial size.

Overall, medial thickness measures decreased significantly at one-year follow-up and appeared moderately responsive compared to other measures. We found a 6% reduction at 1-year follow up that was both statistically significant and in excess of measurement error. This result is consistent with findings from a 2-year pilot study that found a significant reduction of about 4% in meniscal height over the tibia (similar to our measure for total thickness) [42], however that study only measured thickness in one region. We have in addition evaluated changes in three sub-regions of the meniscus, some of which appear to provide promising measures of change based on their responsiveness. Similarly for thickness, in a study with 257 participants Hunter *et al* found a reduction in thickness on the medial side which was associated with cartilage loss [15]. Cross–sectionally thickness measures in OA knees have been found to be greater than in non-OA knees [24] and future studies could evaluate if the longitudinal changes in this measure are associated with OA progression. While sub–regional analysis showed that most change occurred in the posterior region of the meniscus, measuring the whole meniscus thickness was more responsive (SRM -0.35) than using three separate regions. Separating the regions into smaller sub-sections offers some advantages but may be noisier (SRM -0.38), accompanied by a 7.4% change for posterior thickness. Surprisingly the lateral thickness measures

increased during follow up although not statistically significant except for the central thickness sub-region; however this was less responsive than the medial measures.

We found a decrease in medial volume but an increase on the lateral side (both changes not statistically significant)... Measurement of volume has previously yielded conflicting results with one study reporting greater lateral volume in OA knees compared to non-osteoarthritic knees [23], with no differences in medial volume, while one study from the OAI showed no differences in either compartment over time [24]. A pilot study evaluating 2-year longitudinal data [42] found a similar longitudinal decrease on the medial side to that observed in our study. Manual segmentation of volume proved difficult as damaged menisci and meniscal roots have complex shape that they can take, moreover correctly determining where the roots begin is a challenge. Variations in volume results could possibly be a result of measurement error as a result of varying techniques employed by different studies in measuring meniscal volume. Some of these studies did not report how the change scores varied with measurement noise therefore what might be perceived as a lack of sensitivity could be small changes masked by large measurement error. Segmentation of volume measures is laborious and although these different findings for volume highlight the need for further investigation, the lack of responsiveness observed in our study and the difficulty in segmentation could undermine its use as a potential tool for clinical trials.

This study employed a novel way of measuring extrusion on a 3D plane which facilitated the calculation of extruded volume. Notably we found poor responsiveness for meniscal extrusion which was surprising since extrusion has previously been linked to several OA features in longitudinal and cross-sectional studies [16, 23, 43]. Meniscal extrusion measured using semi-quantitative methods has been associated with cartilage volume loss longitudinally [44, 45] and is thought to contribute to subchondral bone changes [26] but our finding suggests it may be a less responsive measure in a cohort selected for clinical trial characteristics. We used quantitative measures of meniscal extrusion that assess the entire 3D meniscus and are not just confined to single slices, as in previous studies [16], and it

may be that we are measuring a somewhat different meniscal construct to that assessed by current semi-quantitative measures. Our 3D methodology may also explain why we found no substantial relationship between decreased tibial coverage and increased meniscal extrusion as has been reported previously. Bruns *et al* in their study using controls from the OAI reported increased meniscal extrusion that did not affect meniscal coverage which they postulated could be due to increased bulging of the peripheral meniscal margin and less radial displacement[46]. As previously established, meniscal extrusion is a combined construct of radial displacement and change in meniscal width [23, 47]. Few studies have directly evaluated the internal responsiveness of meniscal pathologies and specifically for extrusion, using 3D technology to the best of our knowledge only one other study reported such a longitudinal analysis. In their study using 3D, similarly Blocker *et al* also found poor responsiveness for meniscal extrusion (SRM 0.22) in the central five slices and longitudinal change was not statistically significant. However, their measure for extrusion distance across the entire meniscus (including anterior and posterior horns) was significantly different over a 2–year period but responsiveness still poor to moderate (SRM 0.32)[42].

Extrusion is important in the development of other meniscal pathologies as it impairs load transmission [48] leading to the knee compensating by increasing tibia bone area to ensure load redistribution [49]. In this 12 month cohort, little change in meniscus extrusion was noted. Our inclusion criteria meant that we expected more extrusion on the medial side than the lateral side; in fact 65% of participants in this study had no extruded volume on the lateral side. Our methodology for identifying the outer limit of the tibia differs from other methods, in that it uses all of the 3D information from the tibia to generate a plane, outside of which is considered extrusion. The plane is constructed using points in the shape model which may fall in areas which become osteophytic, and these may be handled differently in other measurement systems.

Exploratory analyses aimed at evaluating if any drivers of change existed based on specific factors did not yield any important results, with suggestions that responsiveness varied by

weight status (obese vs non-obese using WHO cut-offs) for total thickness and that of tibial coverage varied by meniscectomy status, although both findings should be interpreted with caution in view of the sample size. Patient size has an effect on the size of the medial plateau, a point highlighted by Stone *et al* [50].

In terms of limitations, it should be noted this work was focussed on a cohort typical of that in clinical trials and does not necessarily reflect the meniscus natural history in a general population. We selected for medial progression only. Like most of the reported MRI meniscal studies, we used non-weight-bearing images; changes in the meniscus might be more responsive under load. We did segmentations of the DESS images, which offer the best compromise for identification of multiple OA tissues (here meniscus and bone) but may not be the optimal sequence for detecting particular meniscal pathologies. OA is a long-term disease, and 12 months is insufficient to study the long-term pathogenesis of menisci in the OA knee, and it would be useful to follow OA knees for a much longer period, especially using shape modelling to quantify any spatial change which occurs, while removing confounding by the pose of the knee. The repeatability of the method is likely to provide an optimistic assessment of measurement precision, as only healthy menisci were used for the test-retest manual segmentation method due to resource constraints. Based on this preliminary work, it seems likely that in the future meniscal segmentation may be fully automated using statistical models, however in this study we wanted to ensure that meniscal shape was identified as accurately as possible to avoid averaging effects.

In conclusion, using modern image analysis we found that the spatial location of meniscal damage in patients at risk of medial progression was predominantly in the posterior sub region of the medial meniscus. In this 12 month OA knee cohort, medial tibial coverage and thickness were the most responsive measures of change, with change comparable to other MRI outcomes and better than radiographic JSN. However, as clearly demonstrated in Figure 1, the type of morphological pathology may vary across cohorts. Meniscal measures

should now be investigated for their ability to add discriminatory power in OA progression assessment.

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AUTHOR CONTRIBUTIONS

BD, MB, SK, EH, SM, and PC contributed to the planning and design of this analysis. BD & MB drafted the article and SK, EH, SM, and PC, revised the article. All authors approved the final version for publication.

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COMPETING INTERESTS

Mike Bowes is an employee and shareholder of Imorphics Ltd (a wholly owned subsidiary of Stryker Corp).

Philip Conaghan, Sarah Kingsbury, Bright Dube, Elizabeth Hensor and Siddhant Muzumdar have nothing to disclose.

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504

Figure 1: Identification of anatomical regions and measurement

Figure A shows the mean shape of the menisci for this group of 86 individuals. Figure B shows the anatomical correspondence points (blue spheres) from the tibia bone shape model which are used to subdivide the tibial plateaus, from which measurements are taken. Figure C shows the anterior (purple), central (light blue) and posterior (dark blue) regions on the lateral and medial tibial plateaus, selected using the correspondence points, and D shows the mean meniscus split into 3 regions for each meniscus. Figure E shows the correspondence points identified along the outer boundary of the medial tibia. These points are joined into a line, and extruded into a plane in the superior direction, which cuts the meniscus into an inner and outer section. F shows the extruded section. Figure G shows how thickness measures are taken using the underlying correspondence points on the tibia bone.

Figure 2: Variety of meniscus shapes; examples from the data set and healthy mean shape

Menisci are shown in red, with slight transparency to visualise extrusion beyond tibial bone. Figure A shows the mean medial and lateral meniscus shape from a group of healthy (KL0) knees from the OAI for comparison with cases. B shows a damaged medial meniscus, which is much thinner than the healthy meniscus, the central section is almost all extruded beyond the tibia. C shows both the medial and lateral menisci deformed by a tibial osteophyte (red arrow, posterior medial osteophyte pushing the meniscus anteriorly; black arrow anterior lateral osteophyte pushing the meniscus posteriorly). D shows both menisci are damaged.

Figure 3: Mean thickness of baseline and 12 month menisci, and difference map

Left hand figures show mean thickness (height above the tibia) at baseline and 12 months, with the colour scale shown below the figures. Measurements were taken as shown in Figure 1G. The figure at the right shows the areas which showed significant change at each

model correspondence point, as described in the text. Blue represents thinning of the meniscus, and red is thickening.

Table 1: *Characteristics of 86 participants in meniscus study*

	Included in the study	Not included in study
Age, years, median (IQR)	61.5 (52-71)	61.0 (53-69)
Gender, female	42 (49)	39 (53)
Ethnicity, white	67 (78)	65 (88)
BMI, kg/m² ,mean (SD)	31.1 (4.64)	29.4 (4.57)
Height ,m, mean (range)	1.7 (1.5-1.9)	1.7 (1.5-1.9)
High school education or less	21 (24)	7 (10)
Study knee, Right	43 (50)	35 (47)
Arthroscopy /meniscectomy on study knee	25 (29)	17 (23)
Health care insurance	84 (98)	71 (97)
WOMAC pain score ,median(IQR)	4.1 (2.4-6.3)	3.5 (2.0-6.0)

Values are N (%) unless stated. m (metres). BMI (body mass index) IQR (interquartile range)

Table 2: ***Changes in medial meniscus measures***

Meniscal measure	Baseline	12 months	Change (95% CI)	% change (95% CI)	SRM (95% CI)	ES	p-value (t-test)
Volume (mm3)							
Total volume	2527.69	2498.97	-28.72 (-108.89,51.46)	-1.1 (-0.04,2.03)	-0.08 (-0.27,0.13)	-0.02	0.48
Extrusion (µL)							
Extruded volume	507.26	528.12	+20.86 (-2.56,44.27)	+4.1 (-0.50,8.72)	+0.19 (-0.03,0.40)	+0.08	0.08
Area (mm2)							
Tibial coverage	414.74	396.32	-18.42 (-29.33,-7.52)	-4.4 (-7.07,1.81)	-0.36 (-0.58,-0.13)	-0.12	<0.001*
Thickness (mm)							
Total thickness	1.14	1.07	-0.07 (-0.11,-0.03)	-6.1 (-9.64,-2.64)	-0.35 (-0.55,-0.14)	-0.16	<0.001*
Anterior thickness	0.40	0.41	+0.01 (-0.02,0.03)	+2.5 (-5.00,7.50)	+0.04 (-0.18,0.26)	+0.02	0.71
Central thickness	0.81	0.76	-0.05 (-0.10,-0.01)	-6.1 (-12.35,-1.23)	-0.27 (-0.47,0.04)	-0.11	0.02
Posterior thickness	2.16	2.00	-0.16 (-0.24,0.07)	-7.4 (-11.11,3.24)	-0.38 (-0.53,-0.21)	-0.20	<0.001*

ES: Effect Size. SRM: Standardised response mean. *: significant p-value when using paired student's t-test.

Table 3: ***Changes in lateral meniscus measures***

Meniscal measure	Baseline	12 months	Change (95% CI)	% change (95% CI)	SRM (95% CI)	ES	p-value (t-test)
Volume (mm3)							
Total volume	2131.21	2177.11	+45.90 (11.75,80.05)	+2.2 (0.55,3.76)	+0.29 (0.01,0.50)	+0.05	0.009
Extrusion (µL)							
Extruded volume	25.77	25.02	-0.75 (-8.44,6.93)	-2.9 (-32.75,0.32)	-0.02 (-0.23,0.19)	-0.01	0.85
Area (mm2)							
Tibial coverage	507.24	513.11	+5.87 (0.69,11.06)	+1.1 (0.14,2.18)	+0.24 (0.03,0.44)	-0.06	0.03
Thickness (mm)							
Total thickness	1.88	1.92	+0.04 (0.01,0.06)	+2.1 (0.53,3.19)	+0.32 (0.12,0.50)	+0.09	0.04
Anterior thickness	1.90	1.92	+0.02 (-0.008,0.05)	+1.1 (-0.42,2.63)	+0.16 (-0.07,0.37)	+0.05	0.15
Central thickness	1.95	2.00	+0.05 (0.02,0.08)	+2.6 (1.03,4.10)	+0.33 (+0.13,0.51)	+0.09	0.002*
Posterior thickness	1.84	1.88	+0.04 (-0.004,0.09)	+2.2 (-0.22,4.89)	+0.19 (0.01,0.38)	+0.06	0.07

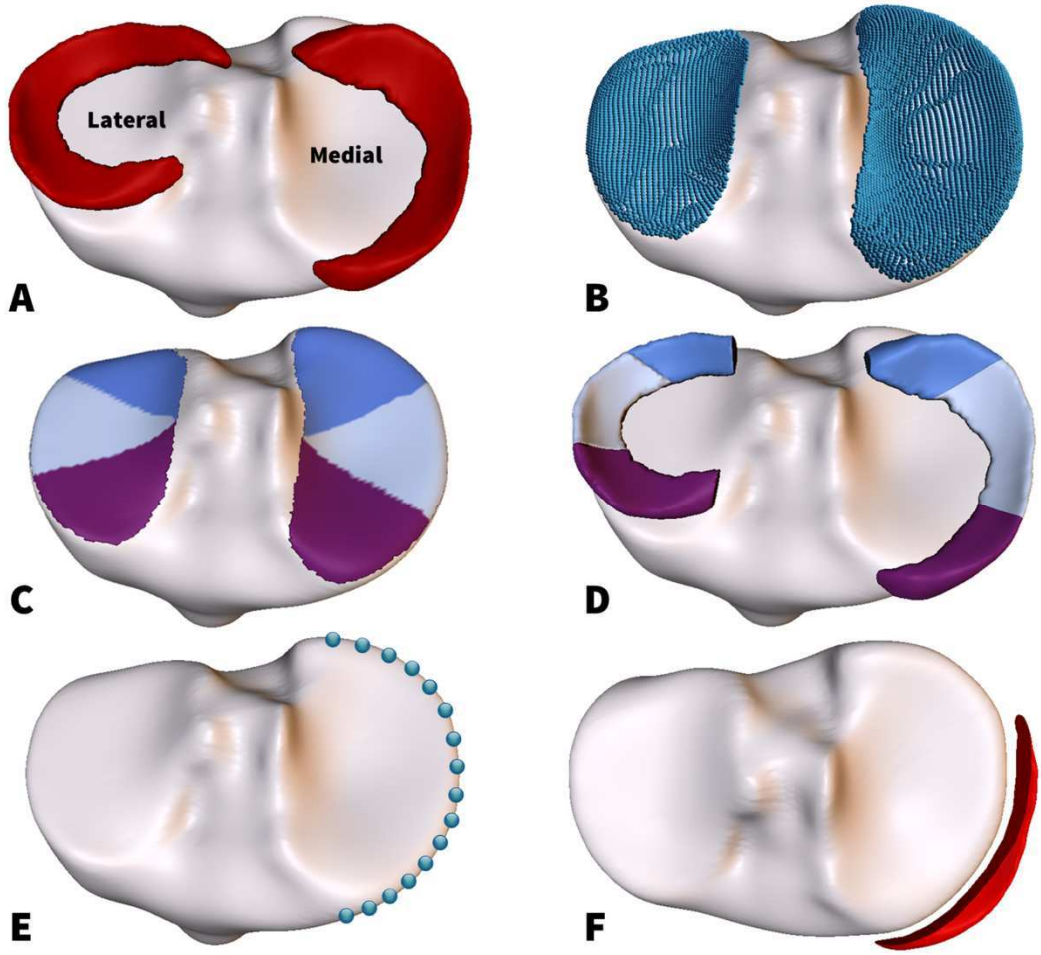
ES: Effect Size. SRM: Standardised response mean. *: significant p-value when using paired student's t-test.

Table 4: ***Longitudinal change in meniscus measures after stratification***

	Total volume (mm^3)	Volume Extruded (µL)	Tibial coverage (mm^2)	Meniscal Thickness (mm)
Meniscectomy status				
Single meniscectomy	-111.38 (-273.30,50.54)	-12.67 (-57.78,32.44)	-30.95 (-25.46,-1.69)	-0.09 (-0.18,-0.01)
None	+3.28 (-90.26,96.83)	+33.83 (6.36,61.31)	-13.57 (-56.05,-5.86)	-0.06 (-0.11,-0.01)
Difference between groups (95% CI)	114.66 (-63.45,292.77)	46.51 (-5.03,98.05)	17.38 (-6.79,41.56)	0.03 (-0.11,-0.03)
p-value	0.20	0.08	0.16	0.60
Age				
< median age	-31.66 (-132.05,68.71)	10.90 (-18.40,40.20)	-13.35 (-27.50,0.80)	-0.03 (-0.08,0.01)
> median age	-25.77 (-155.10,103.57)	30.81 (-6.72,68.34)	23.50 (-40.56,-6.44)	-0.11 (-0.18,-0.04)
Difference between groups (95% CI)	-5.90 (-167.22,155.43)	-19.91 (-66.83,27.01)	10.15 (-11.69,32.00)	0.08 (-0.006,0.16)
p-value	0.94	0.40	0.36	0.07
Weight status				
Obese	-28.37 (-117.21,60.48)	21.48 (-11.90,54.87)	-19.30 (-35.77,-2.88)	-0.07 (-0.12,-0.02)
Non-obese	-28.97 (-153.93,95.99)	19.99 (-13.24,53.21)	-17.22 (-30.66,-3.77)	-0.07 (-0.14,-0.03)
Difference between groups (95% CI)	0.60 (-162.90,164.11)	-1.50 (-49.25,46.26)	2.08 (-20.17,24.32)	0.00 (-0.08,0.09)
p-value	0.99	0.95	0.85	0.98
Gender				
Male	-72.83 (-222.99,77.32)	15.57 (-24.71,55.86)	-24.00 (-42.20,-5.81)	-0.08 (-0.15,-0.01)
Female	+17.50 (-36.31,71.31)	26.39 (1.75,51.03)	-12.58 (-24.81,-0.34)	-0.06 (-0.11,-0.01)
Difference between groups (95% CI)	-90.33 (-250.52,69.84)	-10.82 (-57,89,36.26)	-18.42 (-29.33,-7.51)	-0.02 (-0.11,0.07)
p-value	0.27	0.65	0.30	0.64

Values are paired mean differences (95%CI)

FIGURE 1


Lateral
Medial
A
B
C
D
E
F

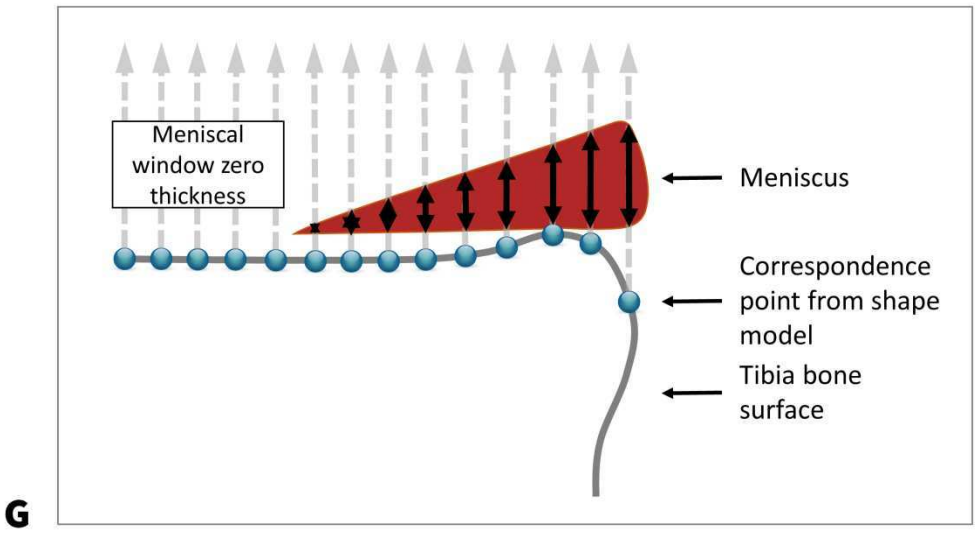

Meniscal window zero thickness
Meniscus
Correspondence point from shape model
Tibia bone surface
G

FIGURE 2

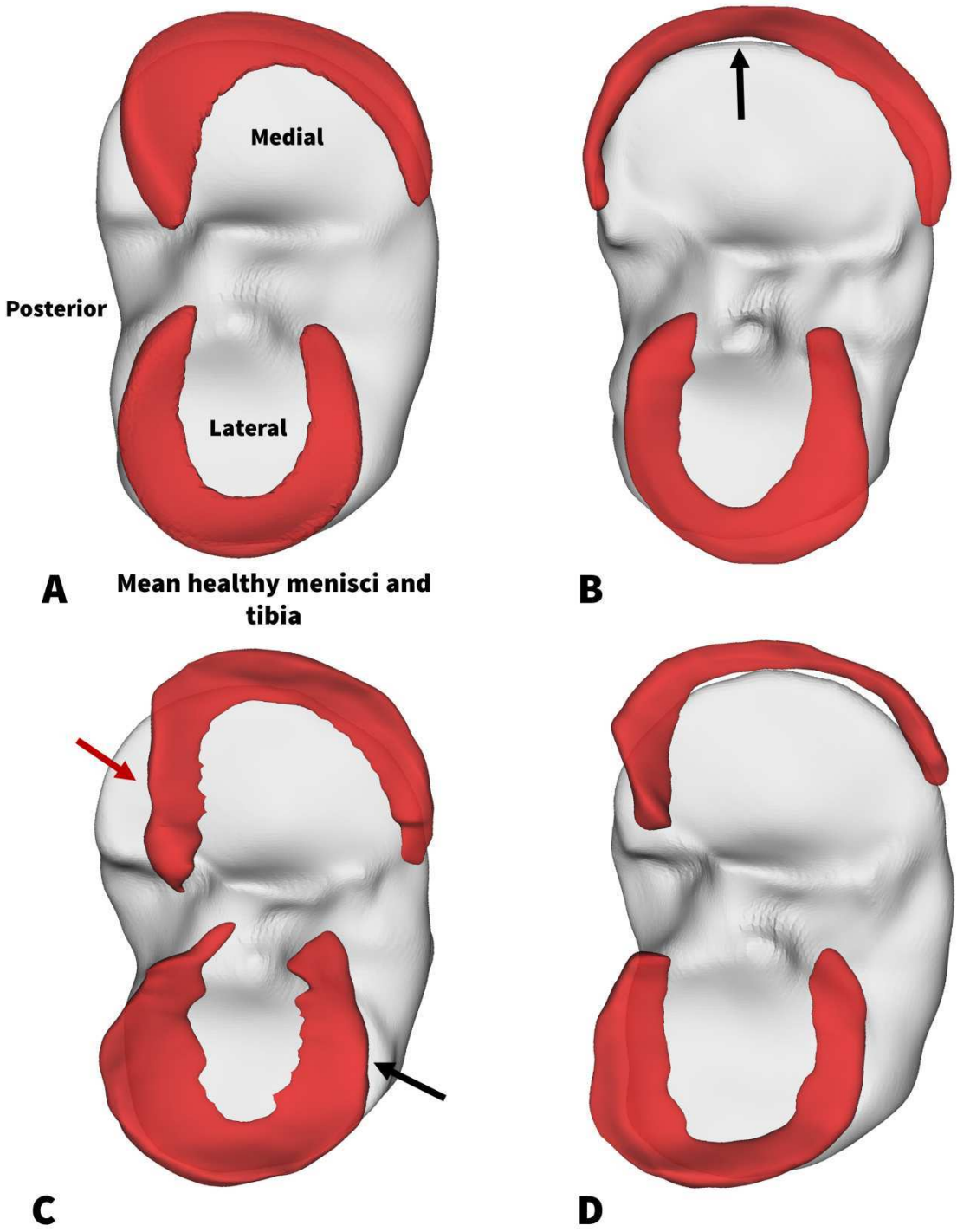

Medial
Posterior
Lateral
A
Mean healthy menisci and tibia
B
C
D

FIGURE 3