Early tibial subchondral bone texture changes after arthroscopic partial meniscectomy in knees without radiographic OA: a prospective cohort study

Marcin Wolski,1 * Jonas B. Thorlund,2,3 Gwidon W. Stachowiak,1 Anders Holsgaard-Larsen,4,5 Mark W. Creaby,6 Gitte M. Jørgensen,7 Martin Englund,8,9 Pawel Podsiadlo1

1 Tribology Laboratory, School of Civil and Mechanical Engineering, Curtin University, Australia
2 Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark
3 Research Unit for General Practice, Department of Public Health, University of Southern Denmark, Odense, Denmark
4 Department of Orthopedics and Traumatology, Odense University Hospital, Odense, Denmark
5 Department of Clinical Research, University of Southern Denmark, Odense, Denmark
6 School of Behavioural and Health Science, Australian Catholic University, Brisbane, Queensland, Australia
7 Department of Radiology, Odense University Hospital, Odense, Denmark
8 Clinical Epidemiology Unit, Orthopedics, Department of Clinical Sciences Lund, Lund University, Lund, Sweden
9 Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, USA

Address correspondence:
Marcin Wolski
School of Civil and Mechanical Engineering
Curtin University, GPO Box U1987, Perth, WA 6845, Australia
Phone: +61 (8) 9266 1471
E-mail: marcin.wolski@curtin.edu.au

RUNNING TITLE: Early bone texture after meniscectomy

This is the author manuscript accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jor.24593.

This article is protected by copyright. All rights reserved.
AUTHOR CONTRIBUTIONS: MW, PP, GWS, JBT and ME conceived and designed the study. AHL and JBT participated in the data collection. MW, PP, GWS, JBT, ME, MWC, AHL and GMJ participated in the analysis and/or interpretation. MW and PP drafted the manuscript with feedback from the co-authors. All authors approved the submitted version.

ABSTRACT: Arthroscopic partial meniscectomy (APM) may lead to changes in underlying trabecular bone structure potentially promoting development of knee joint osteoarthritis. Our aim was to investigate if there are early changes occurring in tibial subchondral trabecular bone texture in the leg undergoing medial APM compared with the unoperated non-injured contra-lateral leg. The bone texture was measured as the medial-to-lateral ratio of fractal dimensions (FD) calculated for regions selected on weight-bearing anteroposterior tibiofemoral x-rays. Twenty-one subjects before and 12 months after APM were included from 374 patients scheduled for unilateral medial APM. The medial-to-lateral ratio was calculated for horizontal, vertical and roughest FDs respectively. Higher FD means higher bone roughness. Each FD was calculated over a range of scales using a variance orientation transform method. Mean values of medial-to-lateral horizontal FD calculated for APM knees at follow-up were higher than those at baseline. For un-operated knees the values were lower. The difference in the horizontal FD change from baseline to follow-up between APM and contra-lateral legs was 0.028 (95% CI 0.004 - 0.052). The bone roughness changes may reflect the increase in peak knee adduction moment.
(KAM) and KAM impulse during walking reported for the same cohort in a previous study. They may also reflect early signs of osteoarthritis development and thus, we speculate that individuals with increased bone texture roughness ratio after APM might be at higher risk of knee osteoarthritis development.

**Keywords:** meniscectomy; osteoarthritis; tibiofemoral; fractal analysis

### INTRODUCTION

Arthroscopic partial meniscectomy (APM) can lead to changes in articular cartilage (e.g., structural defects, loss of volume) and underlying bone (e.g., avascular necrosis, expansion) that promote development and progression of knee osteoarthritis (OA). Alteration of load distribution in the knee due to APM has been identified as a potential key contributor to knee OA risk. Unlike in other studies, we have examined *in-vivo* changes of knee loading in subjects without radiographic OA (Kellgren and Lawrence (K/L) grade < 2) from before medial compartment APM to 12 months after the surgery. We found that the load indices increased in the APM legs within 12 months from the surgery. The increase was observed in the medial knee compartment evaluated by peak knee adduction moment (KAM) and KAM impulse during and as alterations in total lower limb support moment in the stance phase of walking.

In the current study, using the same cohort of patients we investigated structural changes in tibial subchondral trabecular bone (TB).
Previous studies have shown that the tibial medial to lateral (M:L) ratio of subchondral bone volume fraction (BV/TV) in knee joints with OA increases with indicators of M:L joint loading (mechanical axis deviation, KAM, internal rotational moment).\textsuperscript{13,14} Associations of tibial plateau M:L bone mineral density (BMD) ratio with meniscal damage and also with joint space narrowing (JSN), bone sclerosis and bone marrow lesions in subjects at different stages of knee OA have been reported.\textsuperscript{15-17} A link between M:L ratio of subchondral bone surface area and M:L load distribution in subjects with knee OA has been found.\textsuperscript{18} Unlike the other studies, here we use subjects without radiographic OA (Kellgren and Lawrence (K/L) grade < 2) and we test the hypothesis that the ratio of M:L trabecular bone roughness texture increases in the leg undergoing APM compared to the non-injured contra-lateral leg. The M:L ratio was obtained using fractal dimensions (FDs) calculated by applying a variance orientation transform (VOT) method\textsuperscript{19} to medial and lateral tibial bone regions selected on weight-bearing radiographs of knees. The method may hypothetically serve as an objective and relatively inexpensive method for OA risk prediction.

SUBJECTS AND METHODS

Design and reporting

This prospective cohort study (level of evidence: II) reports ancillary data on previous published studies on changes in knee joint biomechanics and muscle strength following APM.\textsuperscript{11,12,20,21} The study was reported following the “Strengthening the Reporting of Observational Studies in Epidemiology”
(STROBE) Statement as a guideline. Ethical approval was provided by the Regional Scientific Ethics Committee of Southern Denmark (ID: S-20120006). All patients provided written informed consent.

Subjects
Recruitment of subjects has been published elsewhere. Briefly, 21 subjects were included from 374 patients (aged 35-55 years) scheduled for medial APM between April 2012 and September 2013 in two public hospitals (Odense University Hospital, Odense and Lillebaelt Hospital, Kolding) and one private clinic in Odense. Symptom onset was established via self-report, with patients excluded if they were with clear traumatic symptom onset (i.e., caused by a sports injury, crash or collision), previous knee surgery or tibiofemoral and/or patellofemoral OA defined as having K/L grades 2 or higher in either knee, back pain within last 30 days limiting physical activity, other injuries limiting physical activity within last 30 days, body mass index (BMI) above 36 kg/m² and very low physical activity level. Patients who did not have radiographs or did not participate in follow-up were also excluded.

At baseline (approximately two weeks prior to APM) age, gender, height, weight and the leg to undergo APM were recorded.

Gait Analysis
For all subjects, external peak KAM, KAM impulse and peak knee flexion moment (KFM) were measured before and 12 months after APM using a six-camera 3D motion analysis system (100Hz, Nexus version 1.8.5, Vicon, Oxford,
UK), in synchrony with two force plates (1000Hz, AMTI, 0R6-7 Series Inc., Watertown, MA, US). The subjects walked barefoot at self-selected speed. Details of the gait analysis have been previously described.¹¹

Knee Radiographs and OA grading
Each subject had fixed-flexion posteroanterior radiographs taken for both knees before APM (baseline) and one year after the surgery (follow-up) using PCR Eleva computed radiography system (Philips Medical System DMC GmbH, Hamburg, Germany). The Synaflexer frame was used to standardize knee positioning.²² The total number of x-ray images was 84. The resolution was not the same for all images, i.e.: 252 (for 66), 159 (for 2) and 126 (for 16 images) DPI. The corresponding pixel sizes were 0.10, 0.15 and 0.20 mm respectively.

Trabecular bone regions of interest
A 12.8 mm × 12.8 mm TB texture region of interest (ROI) was selected under medial and lateral tibial cortical plates using a validated and fully automated method.²³ An example of a knee radiograph with medial and lateral ROIs marked is shown in Fig. 1.

VOT method
The VOT method has been validated in several cohorts.²⁴-²⁷ This includes the prediction of knee replacement in patients with OA²⁶ and the longitudinal study of associations between TB and radiographic OA incidence and an increase in JSN in 3026 subjects from the Multicenter Osteoarthritis Study (MOST).²⁷
detailed description of the method is available elsewhere. Here we briefly describe the method and provide details of the calculation of directional FDs.

The VOT method calculates differences in grey-scale values of all pairs of pixels within a ring region (Fig. 2a). The inner and outer radii of the region are 4 and 16 pixels respectively. As the region moves pixel-by-pixel across the bone texture image the grey-scale differences between pixels and the corresponding directions and distances are stored. The direction is defined as an angle $\alpha$ between a line running through the pair of pixels and the image horizontal axis (Fig. 2a). For each direction, variances of the absolute values of the differences stored are plotted against the distances in log–log coordinates (Fig. 2b). The log–log data points are divided into overlapping subsets of 5 points, and a line is fitted to each subset (Fig. 2b). The line slope is the Hurst coefficient ($H$) at a single scale that is used to calculate FD, i.e., $FD = 3 - H$. The scale is defined as the distance associated with the middle point of the subset (Fig. 2b).

The Hurst coefficients are plotted in polar coordinates as a function of direction and an ellipse is fitted to the plot (Fig. 2c). From the ellipse fitted, three directional FDs are calculated, i.e.:

- $FD_{Sta}$ which is FD calculated along the roughest part of the TB texture, i.e., the direction with the highest FD value. This direction is the angle between a line parallel to the horizontal axis of the image and the minor
axis of the fitted ellipse. FDSta is defined as 3 – Sta, where Sta is half of the minor axis length of the ellipse.

- FDH and FDV are FDs calculated in the horizontal and vertical direction respectively.

In the current study, the scale [mm] ranged from 0.6 to 1.4 in steps of 0.1 (high), 0.9 to 2.4 in steps of 0.15 (medium), and 1.2 to 3.2 in steps of 0.2 (low resolution) respectively. The ranges have the common scale of 1.2 mm. In order to analyse same size features/parts of bone texture in all x-ray images, the FDs calculated at the scale were only used.

Statistics
Normality was checked for M:L FDSta, M:L FDH and M:L FDV using Shapiro-Wilk tests. Paired two-tailed t-tests (Wilcoxon signed-rank tests whenever appropriate) were used to compare differences in change from baseline to follow-up in M:L FDs between APM and contra-lateral knees. FDs that produced statistically significant differences had effect sizes calculated using the Cohen’s d statistic for matched samples. Differences in proportions of categorical variables were evaluated by Fisher's exact test. For the tests, P-values < 0.05 were considered statistically significant. The statistical analysis was performed using SPSS software (version 16.0, SPSS, Cary, NC).

RESULTS
Characteristics of subjects at baseline are listed in Table I. Values of FDSta, FDH and FDV and the corresponding M:L ratios are listed in Tables II and III. The
Shapiro-Wilk tests indicated that changes in M:L FDs were approximately normally distributed (p > 0.15). Therefore, for the comparison of differences, the paired t-tests were used.

Mean values of M:L FDH at baseline and follow-up were 0.983 (95% CI 0.965 - 1.001) and 0.993 (95% CI 0.978 - 1.008) for APM legs and 1.006 (95% CI 0.990 - 1.021) and 0.988 (95% CI 0.972 - 1.003) for contra-lateral legs (Table III). Changes of M:L FDH from baseline to follow-up were 0.010 (95% CI -0.010 - -0.030) and -0.018 (95% CI -0.033 - -0.003) for the legs respectively, indicative of increase (APM) and decrease (contra-lateral) of M:L FDH at follow-up. Difference between the changes is 0.028 (95% CI 0.004 – 0.052, P = 0.024), representing an increase of the change of M:L FDH in APM compared to the contra-lateral. Value of the effect size d calculated for M:L FDH was 0.54. For M:L FDSta and M:L FDV, there were no statistically significant differences (P = 0.61 and 0.14, respectively).

**DISCUSSION**

In this prospective cohort, we found that horizontal trabecular bone texture roughness increased in the medial compartment after medial compartment APM as compared to non-injured contra-lateral legs. Our findings were obtained for M:L ratios of fractal parameters calculated in the roughest (FDSta), vertical (FDV) and horizontal (FDH) directions.
M:L FDH increases from baseline to follow-up in APM legs. The effect size was > 0.5, which in accordance with Cohen represents medium size of the effect. The increase can be attributed to the fact that FDH increased in the medial compartment and remained relatively unchanged in the lateral compartment. These findings indicate that the medial bone texture is rougher than the lateral bone texture in the horizontal direction. The increase in M:L FDH could be related to an adaptive response of trabecular bone to altered loading after APM. On the same cohort of patients we have reported that from baseline to follow-up the KAM impulse increases after APM and decreases in contra-lateral legs, respectively. We ran a post hoc correlation analysis of M:L FDH with KAM impulse. The results obtained, however, were not statistically significant (data not shown) and Pearson coefficients ranged from -0.289 to 0.124. In another study a positive linear correlation between KAM impulse and tibiofemoral compressive contact force was reported. Taken together, these studies suggest that the subchondral TB in APM knees could be over- and under-loaded in the medial and lateral compartments, respectively, as compared to the un-injured knees. Studies based on animal models of OA (mouse, canine and bovine) and finite element analysis of TB (human) suggested that a bone volume fraction (BV/TV) and a trabecular thickness (Tb.Th) decrease and a trabecular number (Tb.N) and a trabecular separation (Tb.Sp) increase with compressive loads. The changes in morphometric parameters indicate that bone patches decrease in size, and exhibit more interconnections, i.e. the complexity of TB.
structure increases. In general, increased in structural complexity results in higher FD.\textsuperscript{34}

Increase of M:L FD could also be related to knee OA development. A longitudinal study of 3026 subjects from the Multicenter Osteoarthritis Study (MOST) showed that higher bone roughness (higher FD) is associated with increase in JSN score.\textsuperscript{27} Our current findings and evidence from the previous study suggest that the increase in M:L FD could reflect early stage of subchondral bone changes such as bone matrix formation and degradation by osteoblasts and osteoclasts.\textsuperscript{35}

There are important limitations to this study. First, the analysis is powered for a different analysis. Nevertheless, the sample size is relatively small and may therefore be underpowered to detect differences in bone texture parameters between the APM and contralateral legs. However, the subjects used in our study met strict inclusion criteria. So far, no other work has investigated TB texture changes in APM subjects without radiographic knee OA (K/L < 2) and at a short time point after the surgery. Second, statistical results were not corrected for multiple testing. This was intentional since the study is exploratory in nature and the adjustment for multiplicity could result in finding no differences while there were differences.\textsuperscript{36} Third, the statistical analysis was performed at the common scale of 1.2 mm. However, if other scales are included, i.e., scales that are not same for all radiographs, results obtained could be largely due to differences in size and location of TB features between baseline and follow-up.
Our findings need to be verified using a larger cohort and radiographs taken with same resolution.

In conclusion, our results indicate that the medial-to-lateral ratio of TB texture roughness of knee joints without radiographic OA increases in legs from before to after APM as compared to the un-injured legs. The increase could be related to thinning and micro-damage of medial compartment trabeculae caused by higher knee loading after APM in the medial compartment. Thus, we speculate that individuals with an increased medial-to-lateral ratio of bone texture roughness after APM are at higher risk of knee OA development. Bone texture analysis could serve as a potential biomarker and a risk prediction tool for OA.37-39 However, further longitudinal studies are required to determine if TB bone texture measured in APM knees without OA can predict OA development.

Acknowledgements

The authors wish to thank the Curtin University and the School of Civil and Mechanical Engineering for their support during preparation of the manuscript. We would also like to acknowledge the efforts of the participating patients, MSc Dennis Brandborg Nielsen for help with data collection and the Department of Orthopedics and Traumatology, Odense University Hospital (Odense and Svendborg), Lillebaelt Hospital (Kolding), Orthopedic Clinic – Funen and nurses Annie-Gam Pedersen and Lene Feldstedt for assistance with patient recruitment.
Funding

This research was supported under Australian Research Council's Discovery Early Career Research Award funding scheme (project number DE130100771) and by funds from Independent Research Fund Denmark | Medical Sciences, The Danish Rheumatism Association and IMK Almene Fond.

References


This article is protected by copyright. All rights reserved.


subchondral bone microarchitecture in end-stage knee osteoarthritis. Osteoarthritis Cartilage 26:547-556.


---

**Figure Legends**

**Figure 1.** An example of X-ray image with selected trabecular bone (TB) texture regions of interest (white squares). The regions cover an image area of 12.8 mm × 12.8 mm.
Figure 2. A schematic illustration of the variance orientation transform (VOT) method: (a) a ring region, (b) a log-log plot along with lines fitted to subsets and (c) a rose plot of Hurst coefficients.

Table I

<table>
<thead>
<tr>
<th>Subject characteristics at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects (men/women)</td>
</tr>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
</tr>
<tr>
<td>APM leg, right/left</td>
</tr>
<tr>
<td>Symptom onset, slowly evolved/specific incident</td>
</tr>
<tr>
<td>Gait Speed, m/s</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>K/L grade 0, baseline/follow-up, no.</th>
<th>APM leg</th>
<th>Contra-lateral leg</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>18/17</td>
<td>20/20</td>
<td>0.143/0.190</td>
<td></td>
</tr>
<tr>
<td>K/L grade 1, baseline/follow-up, no.</td>
<td>3/4</td>
<td>1/1</td>
<td>0.891</td>
</tr>
<tr>
<td>Static knee alignment</td>
<td>177 (1.6)</td>
<td>178 (2.0)</td>
<td>0.654</td>
</tr>
<tr>
<td>Peak KAM, Nm/BM*HT%</td>
<td>3.05 (0.56)</td>
<td>3.02 (0.68)</td>
<td>0.265</td>
</tr>
<tr>
<td>KAM impulse, Nm<em>s/BM</em>HT%</td>
<td>1.15 (0.27)</td>
<td>1.19 (0.3)</td>
<td>0.690</td>
</tr>
<tr>
<td>Peak KFM, Nm/BM*HT%</td>
<td>2.45 (1.23)</td>
<td>2.82 (0.82)</td>
<td>0.265</td>
</tr>
</tbody>
</table>
APM, arthroscopic partial meniscectomy; BMI, body mass index; K/L, Kellgren and Lawrence; KAM, knee adduction moment; KFM, peak knee flexion moment.

Values are mean (SD) unless otherwise stated.

* Fisher’s exact test.

**Table II**

Mean values (95% confidence intervals) of FDSta, FDH and FDV calculated at baseline and 12-month follow-up for the APM and contra-lateral legs in the medial and lateral compartments.

<table>
<thead>
<tr>
<th>Fractal dimension</th>
<th>APM leg</th>
<th>Contra-lateral leg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medial</td>
<td>Lateral</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FDSta</td>
<td>2.893 (2.869 – 2.916)</td>
<td>2.937 (2.926 – 2.948)</td>
</tr>
<tr>
<td>FDH</td>
<td>2.883 (2.938 – 2.927)</td>
<td>2.934 (2.907 – 2.961)</td>
</tr>
<tr>
<td>FDV</td>
<td>2.883 (2.838 – 2.927)</td>
<td>2.845 (2.820 – 2.870)</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FDSta</td>
<td>2.895 (2.877 – 2.913)</td>
<td>2.912 (2.919 – 2.944)</td>
</tr>
<tr>
<td>FDH</td>
<td>2.909 (2.870 – 2.950)</td>
<td>2.931 (2.902 – 2.960)</td>
</tr>
<tr>
<td>FDV</td>
<td>2.793 (2.764 – 2.823)</td>
<td>2.864 (2.842 – 2.886)</td>
</tr>
</tbody>
</table>

APM, arthroscopic partial meniscectomy; FDH, fractal dimension in the horizontal direction; FDSta, fractal dimension along the roughness part of trabecular bone texture; FDV, fractal dimension in the vertical direction.
Table III

Mean values (95% confidence intervals) of M:L FDSta, FDH and FDV calculated at baseline and 12-month follow-up along with changes from baseline for the APM and contra-lateral legs and differences between the legs are listed. Statistical significant difference is indicated in bold.

<table>
<thead>
<tr>
<th>Ratio of fractal dimensions</th>
<th>Baseline APM leg</th>
<th>Baseline Contra-lateral leg</th>
<th>Follow-up APM leg</th>
<th>Follow-up Contra-lateral leg</th>
<th>Change from baseline APM leg</th>
<th>Change from baseline Contra-lateral leg</th>
<th>Between-leg difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:L FDSta</td>
<td>0.985 (0.976 - 0.994)</td>
<td>0.988 (0.980 - 0.996)</td>
<td>0.988 (0.980 - 0.995)</td>
<td>0.987 (0.978 - 0.996)</td>
<td>0.003 (-0.008 - 0.013)</td>
<td>-0.001 (-0.008 - 0.007)</td>
<td>0.004 (-0.011 - 0.018)</td>
</tr>
<tr>
<td>M:L FDH</td>
<td>0.983 (0.965 - 1.001)</td>
<td>1.006 (0.990 - 1.021)</td>
<td>0.993 (0.978 - 1.008)</td>
<td>0.988 (0.972 - 1.003)</td>
<td>0.010 (-0.010 - 0.030)</td>
<td>-0.018 (-0.033 - -0.003)</td>
<td>0.028 (0.004 - 0.052)</td>
</tr>
<tr>
<td>M:L FDV</td>
<td>0.984 (0.972 - 0.996)</td>
<td>0.983 (0.968 - 0.998)</td>
<td>0.976 (0.965 - 0.986)</td>
<td>0.989 (0.973 - 1.005)</td>
<td>-0.008 (-0.026 - 0.009)</td>
<td>0.006 (-0.013 - 0.025)</td>
<td>-0.015 (-0.035 - 0.006)</td>
</tr>
</tbody>
</table>

APM, arthroscopic partial meniscectomy; FDH, fractal dimension in the horizontal direction; FDSta, fractal dimension along the roughness part of trabecular bone texture; FDV, fractal dimension in the vertical direction; M:L medial to lateral ratio.