Title

Compound Effects Of Bmi And Sustained Depressive Symptoms On Knee Osteoarthritis Over 4 Years: Data From The Osteoarthritis Initiative

Authors

Joseph, GB
McCulloch, CE
Nevitt, MC
et al.

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regions, and measure cross-sectional area and average thickness (i.e., the total cross-sectional area divided by the length of the cartilage-bone border) for each region. The intercondylar region was defined as 25% the width of the cartilage centered around the deepest point of the trochlear groove. All images were also manually segmented by a single investigator with experience in the segmentation technique who was blinded to the automated segmentation. Automated and manual segmentations were compared using Sorenson-Dice similarity coefficients (DICE). Intraclass correlation coefficients (ICC) were employed to evaluate reliability between the manual and automatic segmentations for average thickness measurements. Bland Altman plots were utilized to assess agreement between the two methods.

Results: One hundred sixty-eight ultrasound images from 29 individuals the femoral cartilage were utilized for validation. Of the 168 images, 26 were omitted from analysis due to poor image quality and similarities (DICE < 0.85). The remaining 142 images produced a mean (SD) DICE of 0.91 (0.17). For each region, average thickness measurements are reported for both segmentation techniques in Table 1. Average thickness measurements showed good reliability between techniques for lateral (ICC = 0.88), intercondylar (ICC = 0.77), and medial (ICC = 0.84) regions. Bland Altman plots demonstrated a consistent bias where the automated program overestimated average thickness for all regions. The bias was 0.51 mm in the lateral region (Figure 2), 0.25 mm in the intercondylar region (Figure 3), and 0.51 mm in the medial region (Figure 3).

Conclusions: Our newly developed automated technique validly measures average femoral articular cartilage thickness when compared to the manual segmentations of a skilled reader. However, the program consistently overestimates cartilage thickness when compared to the manual technique. This fully-automated technique may provide clinicians with a way to quickly measure femoral cartilage morphology with less user dependency enabling clinicians to screen for and monitor early-stage knee OA changes in clinic without expensive or additional tests.

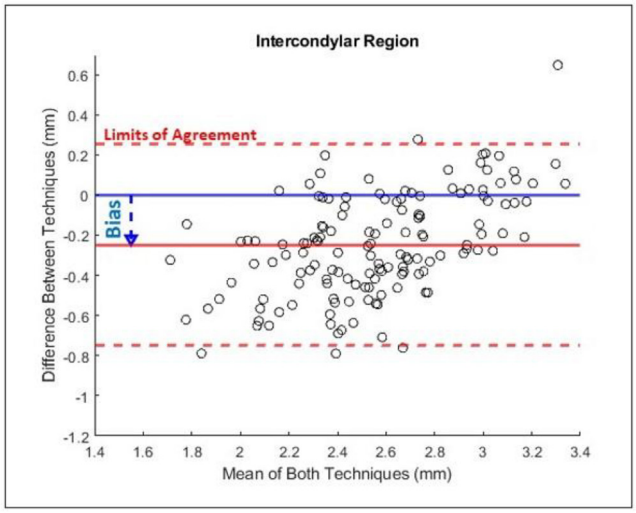

Figure 3. Bland Altman plots for average thickness in intercondylar region. Blue line represents 0. Solid red line represents the mean difference between the techniques (automated – manual). Dotted red line represents limits of agreement (mean difference ± 1.96*standard deviation). Dotted blue line represents the overestimation bias of the automated program.

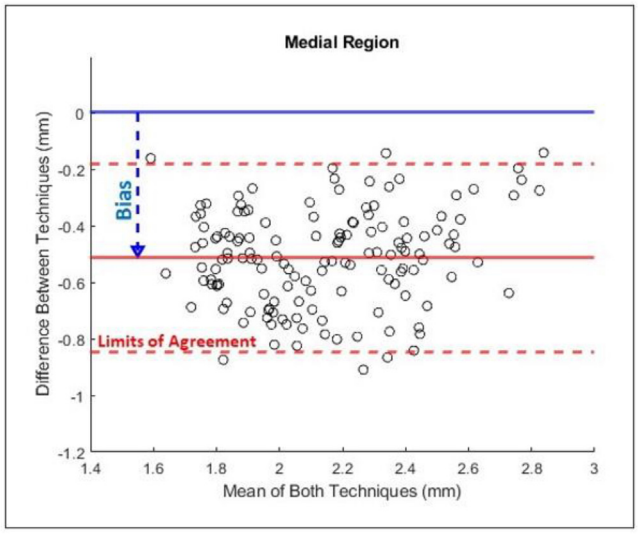

Figure 4. Bland Altman plots for average thickness in medial region. Blue line represents 0. Solid red line represents the mean difference between the techniques (automated – manual). Dotted red line represents limits of agreement (mean difference ± 1.96*standard deviation). Dotted blue line represents the overestimation bias of the automated program.

261
COMPOUND EFFECTS OF BMI AND SUSTAINED DEPRESSIVE SYMPTOMS ON KNEE OSTEOARTHRITIS OVER 4 YEARS: DATA FROM THE OSTEOARTHRITIS INITIATIVE

G.B. Joseph [1], C.E. McCulloch [1], M.C. Nevitt [1], J. Lynch [1], N.E. Lane [2], V. Pedoia [1], S. Majumdar [1], T.M. Link [1]. [1] *Univ. of California San Francisco, San Francisco, CA;* [2] *Univ. of California Davis, San Francisco, CA*

Purpose: Obesity and depressive symptoms are two potentially modifiable risk factors for osteoarthritis (OA). Obesity is associated with increases in knee pain and disability, joint space narrowing (JSN), prevalence of knee cartilage lesions, and cartilage biochemical degeneration. Depressive symptoms in adults are also associated with increases in joint pain and disability. While previous studies have reported associations of both excess weight and depressive symptoms on symptomatic OA, the knowledge gap on the compound effects of these risk factors on longitudinal changes in cartilage biochemical composition (i.e., MRI knee cartilage T_2) remains to be investigated. The purpose of this study was to assess the compound effects of BMI and sustained depressive symptoms on changes in knee structure, cartilage composition, and knee pain over 4 years using statistical interaction analyses.

Methods: A total of 1844 individuals with data on depressive symptoms at baseline and 4-year follow-up from the Osteoarthritis Initiative database were analyzed. Individuals were categorized according to their BMI and presence of depressive symptoms (based on the Center for Epidemiological Studies Depression Scale (threshold≥16)) at baseline and 4-year follow-up. A total of 68 individuals had sustained depressive symptoms and obese BMI (30-49 kg/m^2), 33 had sustained depressive symptoms and normal BMI (16.9-24.9 kg/m^2), 971 had no sustained depressive symptoms and obese BMI (30-49 kg/m^2) and 772 had no sustained depressive symptoms and normal BMI (16.9-24.9 kg/m^2). 3T MRI was used to quantify knee cartilage T_2 in 5 regions (medial/lateral femur, medial/lateral tibia, and patella) from which the mean T_2 in the knee was calculated, while radiographs were used to assess JSN (maximum score of the medial and lateral joint sides in each knee) at baseline, 2 and 4 years. Knee pain was assessed using the WOMAC (Western Ontario McMaster Universities Osteoarthritis) Index annually over 4 years in both knees.

Two types of mixed effects models were performed: the first set of mixed models were *interaction analyses* to assess whether having both sustained depressive symptoms and obese BMI had a greater effect on knee outcomes (JSN, cartilage T_2, knee pain) over and above the additive effects of each predictor. The mixed models included a test for statistical interaction between BMI (normal/obese) and sustained depressive symptoms over 4-years (yes/no). A second set of mixed models (that did not include an estimate for and test for an interaction) were *group-based analyses* that investigated the overall differences in outcomes (JSN, cartilage T_2, knee pain) over all timepoints between participants subdivided into four groups based on baseline BMI (normal/obese) and sustained depression over 4 years (yes/no). All statistical models were adjusted for age, sex, race, and Physical Activity Scale for the Elderly (PASE) score.

Results: The BMI-depressive symptoms interaction was significant for knee pain ($p<0.001$) changes over 4 years, but not for changes in cartilage T_2 ($p=0.27$), Figure 1. For JSN, the p-value for the depression-BMI interaction on JSN in all participants was $p=0.08$, while it was significantly associated ($p=0.01$) in women. In a group-based analysis, participants with obesity and depression had significantly greater 4-year changes in knee pain ($coeff._{(obesity+depression\ vs.\ no\_obesity+no\_depression)}=4.09$, 95% CI=3.60-4.58, $p<0.001$), JSN (coeff.=0.60, 95%CI=0.44-0.77, $p<0.001$), and cartilage T_2 (coeff.=1.09, 95%CI=0.68-1.49, $p<0.001$) than participants without depression and normal BMI.

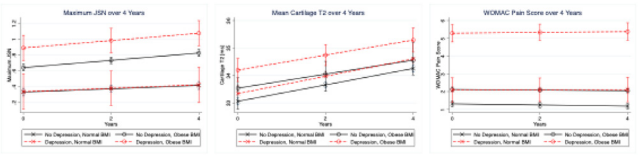

Figure 1: The graphs (derived from the interaction models) illustrate the longitudinal changes in maximum JSN (maximum score of the medial and lateral joint sides), mean knee cartilage T_2, and WOMAC pain score over 4 years. The depression-BMI interactions were statistically significant with WOMAC pain ($p<0.001$). The p-value for the depression-BMI interaction on JSN was $p=0.08$; the interaction was not significant for mean cartilage T_2 ($p=0.27$). The figure illustrates that the compound effects of obesity and depression on OA are greater than their individual effects: in all three outcomes, the difference between the normal BMI groups (denoted by X) is less than the obese groups (denoted by O). Thus, the effect of depression is stronger in the obese groups than the normal weight groups.

Conclusions: Overall, the results of this study suggest that comorbid obesity and depressive symptoms are associated with progression of symptomatic OA, evidenced by increased knee pain and increased JSN. The compound effects of obesity and depression on OA are greater than their individual effects. Thus, concurrent treatment of obesity and depressive symptoms (potentially through increases in physical activity) may be beneficial when developing individualized non-invasive strategies aimed to slow progression of OA.

262
TANTALUM AND IODINE BASED DUAL-CONTRAST PHOTON-COUNTING COMPUTED TOMOGRAPHY METHOD FOR ASSESSMENT OF ARTICULAR CARTILAGE COMPOSITION

P. Paakkari [1,2], S.I. Inkinen [3,4], J. Jäntti [1,2], J. Tuppurainen [1,2], M.C. Fugazzola [5], A. Joenathan [6], S. Ylisiurua [4,7], M.T. Nieminen [4], M.W. Grinstaff [6], H. Kröger [2], J. Töyräs [1,2,8], J.T. Honkanen [2], J.T. Mäkelä [1,2]. [1] *Univ. of Eastern Finland, Kuopio, Finland;* [2] *Kuopio Univ. Hosp., Kuopio, Finland;* [3] *Helsinki Univ. Hosp., Helsinki, Finland;* [4] *Univ. of Oulu, Oulu, Finland;* [5] *Utrecht Univ., Utrecht, Netherlands;* [6] *Boston Univ., Boston, MA;* [7] *Oulu Univ. Hosp., Oulu, Finland;* [8] *The Univ. of Queensland, Brisbane, Australia*

Purpose: Photon-counting detector computed tomography (PCD-CT) is a novel spectral CT imaging technique, where individual photons are classified into fixed energy bins. Thus, the technique enables the separation of multiple contrast agents retrospectively from a single scan. For the first time, a mixture of cationic tantalum oxide nanoparticles (TaO-NPs) and non-ionic iodixanol is utilized in PCD-CT to assess equine articular cartilage composition. We hypothesize that the two contrast agents reflect different cartilage compositional properties, while simultaneously complementing each other. Albeit, in this preliminary investigation, the compositional inspection is narrowed down to consider only proteoglycan (PG) content.

Methods: *Samples:* Intercondylar notch ($n = 15$) and medial femoral condyle ($n = 15$) articular cartilage samples (cylindrical plugs, $d = 8.5$ mm, $n = 30$) were extracted from equine stifle joints (Fig. 1a). The plugs were split into quarters: three quarters of each plug were used for reference methods and one quarter of each plug was immersed for 96 h ($T = 37$ °C) in a dual contrast agent mixture of cationic TaO-NPs (Ta_2O_5, 20 mg·Ta_2O_5/mL) and non-ionic iodixanol (Visipaque™, 40 mg·I/mL). *PCD-CT:* The setup consisted of PCD (XC-Flite FX15, XCounter AB), motorized rotator (NR360S, Thorlabs Inc.), and mini-focus X-ray source (IXS1203MF, VJX) with 3 mm Al and 0.5 mm Cu filters. The tube voltage was 120 kVp and the used low and total energy bins were 10-80 keV and 10-120 keV, respectively. The samples were imaged before the immersion (0 h) and at multiple diffusion timepoints (3.5, 6, 12, 24, 48, and 96 h). The concentration estimation was based on separately scanned calibration solutions with ten different contrast agent concentrations. Voxel size was 68 × 68 × 68 μm^3 in the reconstructed volume. *PG content:* Spatial PG content was determined from Safranin-O-stained histological sections using digital densitometry. *Analysis of CT images:* A custom-made MATLAB (R2020b, MathWorks) code was used in the estimation of the contrast agent concentrations inside the samples from the low and total energy bin reconstructions (Fig. 1b).

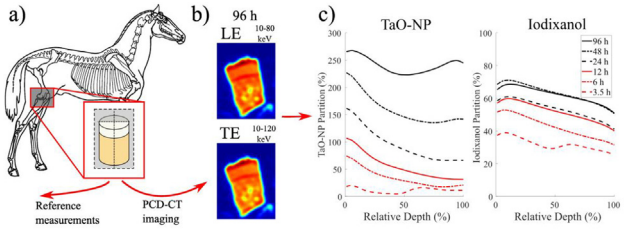

Figure 1: a) Cylindrical plugs (n = 30) were extracted from equine stifle joint. **b)** Low and total energy bin (LE and TE, respectively) reconstructions were used to determine the contrast agent partitions, and **c)** depthwise partition profiles were calculated at each timepoint. Relative depth of 0% indicates articular surface and 100% cartilage-bone interface.

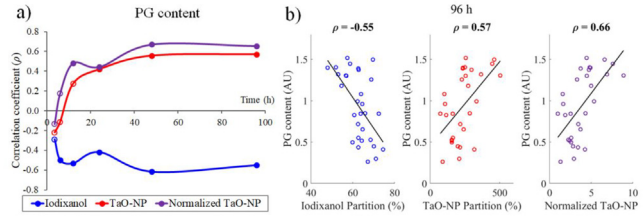

Figure 2: a) The Spearman's correlation coefficients between proteoglycan (PG) content and contrast agent partitions at each timepoint. The significant ($p < 0.05$) correlations are marked with filled markers. **b)** Scatterplots of the correlation between PG content and each contrast agent partition at the 96-hour timepoint. PG content is determined in arbitrary units (AU).

Subsequently, depthwise contrast agent partition (i.e., ratio against the original bath concentration) profiles (Fig. 1c) and bulk (full-thickness) values were calculated for each timepoint. *Statistics:* Spearman's correlation coefficients (ρ) between bulk contrast agent partitions and PG content were calculated using MATLAB.

Results: Concentration estimation was validated with nine different concentration mixtures of contrast agents: the mean errors were 18.7% and 8.3% for TaO-NP and iodixanol, respectively. Average contrast agent partitions at 96-hour timepoint were 236.1% and 62.7% for TaO-NP and iodixanol, respectively. TaO-NP partition correlated positively ($\rho = 0.42$, $p = 0.024$) with PG content after 24 hours (Fig. 2a). Iodixanol partition had a strong negative correlation ($\rho = -0.50$, $p = 0.007$) with PG content after 6 hours (Fig. 2a). Dividing TaO-NP partition with iodixanol's partition, i.e., normalization, strengthened and preponed the correlation between normalized TaO-NP partition and PG content, and a significant correlation was found at the 12-hour timepoint ($\rho = 0.48$, $p = 0.009$, Fig. 2a).

Conclusions: Based on this preliminary investigation, the normalization of TaO-NP with iodixanol improves the sensitivity of the proposed dual-contrast PCD-CT method. The linear correlation between TaO-NP partition and PG content was expected, as the negative net charge of PGs attracts cationic TaO-NPs. The iodixanol molecules' diffusion equilibrium was reached earlier compared to TaO-NPs due to their size difference (Fig. 1c): iodixanol reached its diffusion equilibrium around 48 hours, while TaO-NP diffusion equilibrium was not reached in 96 hours (Fig. 1c). We hypothesize that the TaO-NPs can block cartilage pores and leave less space for iodixanol, hence, strengthening negative correlation between iodixanol and PG content. However, additional experiments are needed to verify this. Also, further analysis of the cartilage's constituents, i.e., collagen content and orientation, water content, and biomechanical testing, will provide more information about the capabilities of the contrast agents to detect changes in cartilage structure and function. The proposed dual-contrast PCD-CT method exhibit potential to assess compositional properties of articular cartilage, and thus, could provide a novel method to detect early osteoarthritic changes in articular cartilage.

263
PATELLOREMORAL CARTILAGE MRI UTE-T2* CHANGES OVER THE FIRST 2 YEARS FOLLOWING ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION SHOW ASSOCIATIONS WITH PATIENT REPORTED OUTCOMES 9 YEARS LATER

A.A. Williams [1,2], N.P. Drain [3], Y. Qian [4], C.R. Chu [1,2]. [1] *Stanford Univ., Stanford, CA;* [2] *Palo Alto Veterans Hosp., Palo Alto, CA;* [3] *Univ. of Pittsburgh, Pittsburgh, PA;* [4] *NYU Grossman Sch. of Med., New York, NY*

Purpose: Patellofemoral joint osteoarthritis (PFOA) afflicts approximately 50% of patients 10-15 years after anterior cruciate ligament reconstruction (ACLR). Patellofemoral (PF) cartilage loss has been observed within the first 2 years after ACLR. Increased knee flexion