Title

Bile Acid Profile Is Associated To Synovitis In Knee Osteoarthritis

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little is known on the relationship between sCOMP concentration (resting or load-induced changes) and articular cartilage quality or the effect of injury or age on this relationship. We aimed to investigate the relationship between load-induced sCOMP concentration kinetics and knee cartilage MRI T2 relaxation time in persons 2 to 10 years after anterior cruciate ligament (ACL) injury compared to healthy control participants in two age groups.

Methods: This study is a preliminary analysis of 81 participants of a larger study with a target population of 96. Participants were recruited in four subgroups: ACL injured with an increased risk for cartilage degeneration and healthy controls, each aged 20 to 30 years; ACL injured and healthy controls, each aged 40 to 60 years. General exclusion criteria were: musculoskeletal or metabolic disease; BMI>30kg/m^2; joint replacement. Additional exclusion criteria for patients with previous ACL injury were: lower extremity injuries other than ACL injury; surgically treated medial or lateral collateral ligament rupture; total or partial meniscectomy; posterior cruciate ligament rupture. MRIs of both knees were acquired using a custom quantitative double echo at steady state (DESS) sequence. MRI data were segmented by readers blinded to groups (Chondrometrics GmbH, Freilassing, Germany) and mean T2 time was used as surrogate for cartilage quality computed for the deep and superficial zone in medial and lateral femorotibial cartilage regions. Participants had to refrain from sport or vigorous physical activities for 24 hours before the stress test and were not allowed to consume food and only allowed to drink water for 1 hour before the test. Blood samples were taken from an antecubital vein after 60 minutes of seated rest immediately before (t_0) and immediately after (t_1) a 30-minute treadmill walking stress. Blood samples were allowed to clot for 30 minutes, centrifuged for 15 minutes, separated, stored in aliquots, and frozen at -80°C until analysis. Samples were assessed in duplicates using commercially available enzyme-linked immunosorbent assay (Human COMP protein ELISA kit, BioVendor). Pearson correlation between sCOMP (t_0, t_1), ΔsCOMP (t_1-t_0) and relative ΔsCOMP ((t_1-t_0)/t_1) with mean T2 time of the different subregions were computed ($p<0.05$) for ACL injured and uninjured limb and for the right and left knee of healthy control participants.

Results: Participant characteristics are listed in Table 1.

In healthy participants, none of the sCOMP parameters correlated with T2 time (Fig.1). In ACL injured participants, absolute and relative load-induced ΔsCOMP correlated with the mean T2 time of the superficial zone of the lateral tibia plateau (R=-0.54, p=0.001; R=-0.60, p<0.001; Fig.2). For the 20 to 30 year olds this association was even stronger (R=0.71, p<0.001; Fig.2). To a smaller degree ΔsCOMP correlated with medial and/or lateral T2 relaxation times of the ACL injured and the contralateral limb (Fig.1). sCOMP (t_0, t_1) only correlated positively to T2 times of the deep zone of the central medial femur of the ACL injured side (R=0.36, p=0.042; R=0.38, p=0.027).

Conclusions: Our preliminary results showed that those patients with smaller load-induced ΔsCOMP had poorer cartilage quality in the lateral and medial tibia of the ACL injured limb. To the best of our knowledge, this is the first evidence of an association between the systemic biomarker ΔsCOMP and knee cartilage quality. This finding is remarkable because systemic sCOMP may not only originate from the affected joint. However, the presence of this correlation in ACL injured participants and the lack thereof in healthy subjects suggests an altered mechanoresponse of knee articular cartilage after trauma such as an ACL injury. Hence, to further study articular cartilage metabolism *in vivo* it will be critical to implement experiments with cyclic loading as a stimulus to amplify differences in articular cartilage metabolism.The strong association between ΔsCOMP and T2 time in the lateral tibia cartilage of the injured knee was striking. ACL injuries often occur during knee valgus injury where the lateral knee cartilage experiences stress beyond its physiological limits. Independent of the type of treatment (surgically or conservatively), ambulatory knee mechanics - mainly of the lateral compartment - are altered. These factors may play a role in the early changes in cartilage quality observed here. Overall, load-induced ΔsCOMP may reflect an altered metabolic response to mechanical load in knee cartilage in patients after ACL injury that appears to manifest as poorer cartilage quality. Funding: SNF:#320030_184912

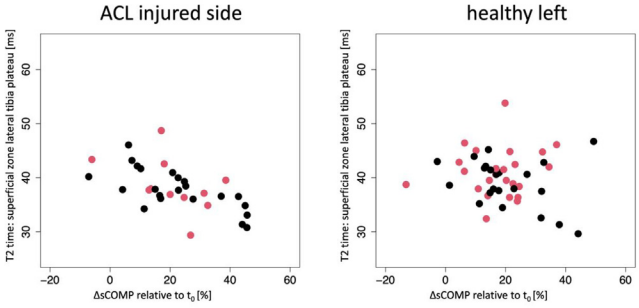

Fig. 2: Scatterplot of the relative load-induced ΔsCOMP and mean T2 time of the superficial zone of lateral tibia plateau for 20 to 30 (black) and 40 to 60 (red) year old participants of the ACL injured limb (left) or the left side of healthy control participants (right).

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BILE ACID PROFILE IS ASSOCIATED TO SYNOVITIS IN KNEE OSTEOARTHRITIS

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Purpose: Increasing evidence indicates that low grade systemic and local inflammation contributes to osteoarthritis (OA) progression. Bioactive lipid mediators are signaling molecules involved in inflammatory processes. Among them, bile acids (BAs), once known only for their role in nutrients absorption, are signaling molecules that regulate various cellular processes. Gut bacteria metabolize primary BAs such as chenodeoxycholic and cholic acid, which are synthesized in the liver from cholesterol, to secondary BAs such as deoxycholic and lithocholic acid. BAs modulate intestinal permeability and have been detected in the systemic circulation and related to insulin resistance and homeostasis of the mucosal immune function in the gut. However, the role of BAs in OA has not been explored.

Methods: Twenty-eight patients with a diagnosis of radiographic knee OA (KOA) with Kellgren and Lawrence (KL) $\geq$ 2 were recruited in our study A thorough clinical examination was conducted. Patients completed the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire. Ultrasound examination (US) for effusion, synovial hypertrophy, popliteal cysts, and power Doppler (PD) signal within the synovium was performed. PD assessment was focused on areas of synovial hypertrophy and recorded as absent or present. Synovitis was defined as the presence of synovial hypertrophy and or/effusion and scored from 0 to 3, according to the OMERACT guidelines. Patients were stratified by degree of synovitis in low-grade (scores 0 and 1) and high-grade (scores 2 and 3). Plasma LPB (Lipopolysaccharide LPS-binding protein) was measured by ELISA (ng/ml). Plasma BA profiling was determined by mass spectrometry. Data processing and statistical analysis were performed in R and Metaboanalyst.

Results: Plasma from twenty-eight older adults (average age 65.4 (SD 8.01), 64% males, body mass index (BMI); 30.9 (SD 5.1)) were analyzed. Ultrasound examination classified 16 patients as having low-grade whereas 12 had high-grade synovitis. Fig. 1 shows a partial least-squares discriminant analysis (PLS-DA) with all identified BAs that achieved partial discrimination among the groups, with several BAs that were dysregulated in the group with high-grade synovitis. Plasma LBP concentration was significantly increased in samples with high-grade synovitis (4456 ±1184 vs 3180±1309, p=0.01 in high vs low-grade synovitis respectively). Moreover, circulating BAs were associated with OA outcome scores. The association with cholic acid and the WOMAC score (r=0.44, p=0.01) was the strongest. Interestingly, BAs were also associated with synovitis (glycoursodeoxycholic acid, r=0.39, p=0.04), BMI (taurocholic acid, r=0.38, p=0.05) and with LBP, a biomarker of KOA progression (cholic acid, r=0.41, p=0.03). These associations differed between obese (BMI>30) and non-obese subjects (Fig. 2).

Conclusions: We have identified several BAs that are associated with high-grade synovitis, BMI, and LPS binding protein, suggesting that gut-microbiome derived BAs may be not only key mediators of OA development and progression, but also predict KOA progression by identifying subjects with synovial inflammation and altered microbiome and intestinal permeability.