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Associations between muscle perfusion and symptoms in knee osteoarthritis: a cross sectional study

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SUMMARY

Objective: To investigate the association between muscle perfusion in the peri-articular knee muscles assessed by dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) and symptoms in patients with knee osteoarthritis (KOA).

Design: In a cross-sectional setting, muscle perfusion was quantified by DCE-MRI in KOA. Regions of interest (ROI) were drawn around the peri-articular muscles, summed and averaged into one single "Total Muscle Volume" volume of interest (VOI). Symptoms were assessed via the Knee injury and Osteoarthritis Outcome Score (KOOS) (0: worst; 100: best).

Results: DCE-MRI and clinical data were analyzed in 94 patients. The typical participant was a woman with a mean age of 65 years, and a body mass index (BMI) of 32 kg/m^2. Reduced multiple regression models analyzing the association between KOOS and DCE-MRI perfusion variables of Total Muscle Volume showed a statistically significant association between $N_{voxel\%}$ and KOOS pain (0.41 (SE 0.14); $P = 0.0048$). $N_{voxel\%}$ was defined as the proportion of highly perfused voxels; i.e., the voxels that show an early and rapid increase on the signal intensity vs time curves, reach a plateau state (plateau pattern) and then showing a relatively rapid decline (washout pattern) relative to the total number of voxels within the muscle VOI.

Conclusions: More widespread perfusion in the peri-articular knee muscles was associated with less pain in patients with KOA. These results give rise to investigations of the effects of exercise on muscle perfusion and its possible mediating role in the causal pathway between exercise and pain improvements in the conservative management of KOA.

Introduction

Knee osteoarthritis (KOA) is considered a whole-joint disease, including affection of peri-articular structures such as muscles and bursa[1]. Pain is the cardinal symptom in KOA[2–4]. The pathology of pain has been a main target in understanding the disease with bone marrow lesions (BMLs), synovitis[4–6], and the infrapatellar fat pad (IPFP) suggested to play important roles in the generation of pain in KOA[7,8]. KOA pain is predominantly localized to the joint lines, but patients may also experience a more generalized and unspecific pattern of knee pain involving the whole knee region including peri-articular structures such as muscles[9–12].

It has become evident that inflammation plays an important role in the pathogenesis of osteoarthritis[4,13,14], and both synovitis and BMLs have shown to be associated with pain and structural progression in KOA[15,16]. The role of muscle tissue in the symptomatology of KOA is not clear, but findings of inflammatory markers in peri-articular knee muscles in patients with KOA suggest that inflammatory processes are not only confined to articular structures, and that inflammatory processes in peri-articular muscles may contribute to the development of pain[17,18].

In current practice, conventional radiographs (CR) remain the central component in diagnosing KOA and assess structural progression[19] although there is a poor association between radiographic findings and clinical features[19,20]. This may be due to the fact that CR cannot capture key elements of KOA pathology

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including inflammation and soft tissue pathology[19–21]. In contrast to CRs, MRI provides a unique visualization of all the anatomical structures involved in KOA including bone marrow and musculature[21,22]. The use of dynamic MRI sequences recorded prior to and during intravenous (IV) bolus infusion of a Gadolinium (Gd) contrast medium (Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI)[23] can be used to extract perfusion parameters in both hand and knee joints where the speed, degree, and distribution of the contrast uptake using time–intensity curves reflects the histological degree of inflammation in the tissue[24] and the change in enhancement over time can be used to assess treatment response in RA[25,26]. DCE-MRI is a valid method to describe musculoskeletal tumors, where high perfusion parameters correlate to higher degree of histologically proven high-grade malignant tumor tissue[27]. In KOA, DCE-MRI has only been used in a few studies[8,28], but associations between synovial perfusion and synovitis grading assessed both macro- and microscopically have been described[28], and recently higher perfusion of the IPFP was associated with pain severity and function[8].

When analyzing DCE-MRI images in KOA patients, we have observed that tissue enhancement (i.e., tissues with contrast agent uptake) is not confined to intra-articular structures but also includes different patterns of contrast enhancement in the peri-articular knee muscle tissue as well. It is unknown if the degree of enhancement in these muscles is pathological and contributes to the symptoms in KOA or if the contrast uptake seen is due to the basis perfusion of skeletal muscle tissue[29–31].

The purpose of this study was to investigate the association between muscle perfusion in the peri-articular knee muscles assessed by DCE-MRI and symptoms in patients with KOA. We hypothesized that higher contrast enhancement, and thus perfusion in the peri-articular muscles, would be associated with worse symptoms in patients with KOA. Understanding the role of perfusion in the peri-articular knee muscles in KOA symptomatology may contribute to our understanding of how exercise exerts its impact on symptomatic relief in KOA, which can be used to optimize recommended exercise therapies.

Method

Study population

Cross sectional data from a weight-loss maintenance study in obese patients with radiographically verified tibiofemoral KOA were included in this study (the LIGHT study; ClinicalTrials.gov: NCT00938808). Data used in the present study were gathered at the 1 year follow-up. The LIGHT study was approved by the local health research ethical committee and conducted in accordance with the Helsinki Declaration, as revised in 2000. Written and oral informed consent was obtained from each patient. All participants had previously participated in a 68 week weight-loss study; the CAROT study (ClinicalTrials.gov identifier: NCT00655941). The main inclusion criteria were age >50 years, a body mass index (BMI) $\geq$ 30 kg/m^2, and clinical KOA diagnosis verified by radiographs obtained at baseline of the LIGHT study[32]. At inclusion, the participants chose a target knee, defined as the most symptomatic knee, for all subsequent assessments.

DCE-MRI

MRI of the target knee, i.e., the most symptomatic knee, was performed on a 3T Siemens Verio® system. The patients were scanned in supine position using a dedicated 16-channel send/receive knee coil. The MRI protocol used has been described in detail earlier[8]. As recommended by the Danish Health and Medicines Authority, decreased renal function with an estimated glomerular filtration rate (eGFR <60 ml/min/1.73 m^2) contra-indicated administration of IV contrast medium, and thereby DCE-MRI. The DCE-MRI sequence was always performed a minimum of 25 min into the scan assuming a relaxed state of the patient with normalization of potential perfusion changes induced by movement.

Image analysis

The DCE-MRI sequence was performed in the axial plane in all patients, covering the suprapatellar recess to the insertion of the patellar ligament on the tibia. All DCE-MRI analyses were performed by an investigator blinded to the clinical data (EB) supervised by MB and RR. DCE-MRI slices were analyzed using the computer software Dynamika® version 2.4.4.1 (Image Analysis LTD, London, http://www.imageanalysis.org.uk)[33,34]. Motion correction between temporal slices was applied on all the available axial DCE-MRI slices[35] before regions of interest (ROIs) were drawn around each of the following muscles: vastus lateralis, vastus medialis, biceps femoris, sartorius, gracilis, triceps surae, popliteus, semitendinosus and semimembranosus. Major vascular branches were avoided when drawing the ROIs [Fig. 1(A)]. All the drawn ROIs were summed and averaged into one single “Total Muscle Volume” VOI. Osirix® v. 5.7.1 was used to confirm the anatomical boundaries of the muscles.

As previously described in detail[34]; signal intensity vs time curves can be generated for each voxel within a ROI by using appropriate software. Dynamika® uses a robust classification scheme[34] where each signal intensity vs time curves automatically are assigned to one of the following enhancement patterns: Tissues with high perfusion are likely to show an early and rapid increase on the signal intensity vs time curves, reach a plateau state (plateau pattern) and then potentially show a relatively rapid decline (washout pattern), whereas tissues with lower perfusion showing a slower increase and potentially do not reach a plateau state (persistent pattern), and tissue with no contrast uptake (no enhancement pattern)[25,34]. The voxels are automatically assigned and color coded in a Gadolinium (Gd)-enhancement map to one of the four enhancement patterns: washout (red), persistent (blue), plateau (green), or no enhancement (no color)[26,34][Fig. 1(B)].

Various DCE-MRI perfusion variables can be extracted from the signal intensity vs time curves, the most relevant in the setting of musculoskeletal imaging being: i) maximal enhancement (ME), calculated as the maximum signal intensity relative to the baseline signal intensity; ii) the Initial Rate of Enhancement (IRE) i.e., the speed of enhancement or upslope on the signal intensity vs time curve calculated as the relative increase in signal intensity per second (%/s) from time of enhancement onset (in seconds after the contrast injection) until ME is reached, and iii) N_{voxel}, the sum of voxels with plateau or washout enhancement patterns, i.e., the highest perfused voxels[24,34,36].

Values and maps of IRE and ME were generated, color-coded and superimposed on the grey scale dynamic images. The highest values for IRE and ME were shown in bright yellow and lower values in a spectrum of red colors [Fig. 1(C)–(D)]. Intra- and inter-observer reliability analysis for the Total Muscle Volume (cm^3) was performed on a random, repeated subsample (n = 10) with a minimum of 4 weeks between drawings using single measures intraclass correlation coefficients (ICC) as a measure of relative reliability and measurement errors (MErr) calculated as the square root of the residual mean square values obtained from analyses of variance, as a measure of absolute reliability. The intra-observer reliability of the total muscle volume (cm^3) was ICC = 0.99 and MErr = 6.5 cm^3; inter-observer reliability: ICC = 0.96 and