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Quantitative morphometric patterns in cartilage and bone from the humeral heads of end-stage osteoarthritis patients

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SUMMARY

Objective: The purpose of this work is to investigate in a quantitative manner, the gross and regional structural patterns in cartilage and bone from the humeral head of end-stage OA patients, with the goal of identifying patterns of disease. Since the prevalence of primary OA of the shoulder is increasing as the population ages and the non-traumatic degenerative changes leading to this disease are poorly understood, a site-specific morphometric analysis speaks to the structure-function remodelling relationship of the pathological anatomy.

Methods: Humeral heads were harvested from twenty-one patients undergoing shoulder arthroplasty for end-stage primary OA. The samples were scanned with micro-computed tomography and magnetic resonance imaging (MRI), and registered to provide reconstructed 3D datasets of the cartilage, cortical and trabecular bone tissues. Gross visual examination of the datasets allowed samples to be classified as OA-like, osteoporosis (OP)-like or OA/OP-like.

Results: Volumes of interest (VOI) separating the OA-like samples into five distinct regions showed positive correlations between bone and cartilage morphometric parameters; specifically in areas where more cartilage has been lost, the underlying subchondral cortical bone was more porous and thicker, while the subchondral trabecular bone was more dense, including more connections and trabeculae. These differences were site-specific, where the central humeral head saw the greatest destruction of cartilage and bone sclerosis, followed by the anterior aspects.

Conclusion: The ability to correlate bone and cartilage changes is valuable, as these structural cues may allow a more targeted diagnostic approach and a better classification of the disease, leading to improved therapies.

Introduction

Osteoarthritis (OA) of the glenohumeral joint is unusual in the absence of trauma, and non-traumatic degenerative changes are of interest, since the primary abnormalities observed, including osteophyte formation and eburnation, are specific to anatomical regions with mechanical involvement. Thus it would be beneficial to investigate and compare these regions of interest in the humeral head because it speaks to the structure-function remodelling relationship of the pathological anatomy. Other bone and joint diseases may be observed concurrently with OA, including osteoporosis (OP)[1,2], rheumatoid arthritis (RA), and rotator cuff tear arthropathy, although there is extensive debate in literature as to whether OP and OA are mutually exclusive[1–6]. While there is little information regarding regional specific bone structure in the glenohumeral joint, there is evidence of higher bone mineral density (BMD) in the inferior and posterior regions, with the central region displaying the highest overall BMD[7].

Considerable attention has been given to the role of articular cartilage in the pathogenesis of OA, and a lesser amount to the involvement of subchondral bone. Subchondral bone, however, plays a fundamental role in events surrounding OA, because it forms the main supporting structure for the cartilage, transmits

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loads from cartilage into the trabecular bone and through to the diaphyseal shaft for skeletal load-bearing[8], and radiographically, is a key structure for clinical examination[9]. Typically in OA, bone sclerosis, cartilage degradation, lesions in the trabecular structure, and osteophyte growth on the external cortex are often visible[10]. In hip and knee joints it has been shown that OA results in an increase in cortical porosity, significantly more so than in OP[8,11]. There is further evidence that vascular pathology affects skeletal pathology, and it has long been suggested that obstruction of venous blood flow through the subchondral bone may actually trigger the initiation of OA *via* production of excess bone[12]. In calcified cartilage, degenerative changes occurring early in the progression of OA, involve a remodelling response along with vascular insertion into articular cartilage due to a rapid increase in the amount of subchondral bone and microfracturing[9,13,14]. However, it has been shown that in OA joints microfractures are reduced, inferring that remodelling of bone into thicker, less compliant trabeculae may be the primary cause of cartilage damage, as opposed to microfractures in the cartilage itself[15–18]. In short, despite calls to precisely define the condition in order to understand it's pathogenesis[19], there is no definite evidence describing morphometric relationships between cartilage and bone in the proximal humeral head with OA[10] which would lend understanding to the mechano-spatial interplay between joint and tissue changes.

Qualitative and quantitative evaluation of structural abnormalities for diagnostic and therapeutic improvement, require sophisticated imaging and image processing techniques. Magnetic resonance imaging (MRI) is commonly utilized in clinical practice for joint imaging[20,21]. Graichen *et al.*[22] have demonstrated the feasibility of cartilage thickness and volume measurement in human shoulders with quantitative MRI, and bright signals defined as bone marrow edema (BME) are often seen[23]. In order to understand how these lesions correspond to the intricate trabecular structure in which they are embedded, one can use micro-computed tomography (microCT). MicroCT is a preclinical technique for high-resolution imaging, and has been used extensively in OP and fracture research in order to analyse osteoporotic bone[24,25], image microcracks[26] and microarchitectural defects[27,28], and assess the fracture healing process[29]. However, due to the small sample sizes required, it is rarely used to monitor disease progression in humans[30], and is mostly limited to preclinical work. Clinical CT, on the other hand, while it does allow patient scanning, does not provide the same structural detail due to the lower resolution. Therefore, in this work, MRI and microCT are implemented for *ex vivo* visualisation of the humeral head. If it can be shown that there exists a comparable structural relationship between changes observed in cartilage and bone, then it holds that *in vivo* MR imaging of the intact cartilaginous structure would be sufficient to predict subchondral bone changes in OA.

The aim of this study is to observe gross and site-specific structural patterns in cartilage and bone from the humeral heads of end-stage OA patients with the goal of identifying patterns of disease, and relating microCT morphometry to the clinically-accepted MRI. In this study, we investigate humeral head samples with a primary diagnosis of OA, and in some cases a secondary diagnosis of OP or RA. We hypothesise that there are predictable and quantifiable morphometric relationships, that could in future lead to a decoding of mechanical, structural and biological responses of OA disease.

Methods and materials

Harvesting of samples

Humeral head samples were harvested from 13 female and 8 male patients undergoing joint replacement surgery for end-stage OA, diagnosed using the Samilson and Prieto scale[31]. Consent from patients and approval from the local ethics committee was received (Kantonale Ethikkommission Zürich, Spezialisierte Unterkommission Orthopädie/Bewegungsapparat, Ref. Nr. EK-29/2007). Average patient age at resection for males and females was 63 ± 15 years; and 71 ± 11 years, respectively, with body mass index (BMI) of 28 ± 7 kg/m^2; and 26 ± 4 kg/m^2, respectively. Patient history was also provided including previous low-energy fracture, secondary conditions (e.g., OP or RA) and any ongoing OP or glucocorticoid treatment, i.e., treatments with potential structural effects (Table I). Patients with a history of rotator cuff tears were excluded from the study.

microCT and MR imaging

Following surgery, samples were scanned with microCT (μCT80, Scanco Medical AG, Brüttisellen, CH) in phosphate-buffered saline (PBS) to prevent dehydration of the cartilage. Samples were scanned at an isotropic voxel resolution of either 30 μm or 60 μm, integration time of 600 ms, frame averaging of 2, energy of 70 keV, and intensity of 114 μA. This provided image data of the mineralized, subchondral bone in each humeral head.

All samples were then scanned with MRI (Achieva, 3.0 Tesla, Philips Health Care, The Netherlands) at 150 μm in-plane (300 μm out-of-plane) resolution using a T1-enhanced Gradient Echo Sequence (T1 enhancement with RF spoiling, TR = 18 ms/TE = 5.7 ms, flip angle 10°) with water selective excitation[32]. During scanning, samples were immersed in a perfluorocarbon liquid (Fomblin Mechanical Pump Fluid, Y/LVAC 16/6, BOC Edwards Limited, West Sussex, England), which has no MR signal is matched to the tissue to limit dehydration, enhance cartilage contrast, and avoid susceptibility artifacts[33]. MRI provided image data of the cartilage as well as bright signals in the bone marrow, possibly indicating the presence of BME.

Registration and volume of interest definition

Data reconstruction and all 3D quantitative analyses were performed using the software of Scanco Medical AG; where MRI data was first converted from DICOM to the proprietary file format. A 3D constrained Gauss filter was used to partly suppress noise in the raw microCT volumes (σ = 1.2 voxels, s = 1), followed by a threshold of 15.8% of the maximum greyscale value to segment the bone. All images were rotated to a common orientation, and MRI images were registered to microCT images. Cartilage was similarly segmented from MR images (0.2% of maximum greyscale). Prior to this, the bone volume was subtracted from each MR image using the masked CT volume, in order to ensure no bright spots in bone were mistaken for cartilage. Trabecular and cortical bone were found as separate compartments in the microCT images, using previous automatic compartmentalisation techniques[34,35]. Finally, each humeral head was divided into five volumes of interest (VOI) similar to Fox *et al.*[36] for investigation of anatomical variation; i.e., postero-superior (PS), postero-inferior (PI), antero-superior (AS), antero-inferior (AI) and central (CN), thereby creating a cortical (CORT), trabecular (TRAB), and cartilage (CART) compartment for each VOI (Fig. 1).

Visual examination and sample categorisation

Visual examination of the image data revealed structural defects indicative of OA as well as OP, leading to a decision to classify the samples into three groups; namely those displaying primarily OA changes (n = 11), primarily OP changes (n = 3), and both OP and OA changes; OA/OP (n = 5). Classification criteria were defined as