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The Application of Imaging in Osteoarthritis

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1. Introduction

Osteoarthritis (OA) is the most common articular disorder worldwide and affects multiple tissues of a joint in response to biomechanical factors. Novel developments in radiographic techniques allow imaging at a macroscopic and microscopic level, quantifying this dynamic process allowing the application of metrics to both disease progression and response to different treatment modalities. This chapter aims to outline how both invasive and non-invasive radiographic modalities can be implemented to allow quantification of the structure of osteoarthritic joints.

Plain-film radiography remains the most common imaging modality for initial assessment and grading of osteoarthritis. Newer techniques such as magnetic resonance imaging (MRI), ultrasound (US) and computed tomography (CT) allow a multimodal approach to the assessment of architectural change within the articular and peri-articular tissues.

We performed a literature search to identify pertinent review articles investigating advances in imaging techniques in humans using the MesH terms and Boolean operators 'osteoarthritis' AND 'ultrasound' OR 'magnetic resonance imaging' OR 'computed tomography'. We identified 24165 relevant articles and limited our search to review articles on humans in English. The structure of the chapter is divided into subheadings covering the different imaging modalities: conventional radiography (CR), MRI, US, CT and bone scintigraphy. Within each subheading, further sections address the use of imaging to quantify disease progression with grading techniques and also cover the use of radiopharmaceuticals such as SPECT (single positron emission computed tomography) and dGEMRIC (delayed gadolinium enhanced MRI of cartilage). A further section outlining the use of imaging as a measure of the molecular composition and structure of osteoarthritic joints is included prior to the final section outlining future advances.

2. Conventional radiography

Conventional radiography (CR) is the primary investigative tool for the diagnosis and follow-up assessment of osteoarthritis (OA). Radiographs are typically obtained in two standardised orthogonal planes. Their acquisition is relatively inexpensive, technically simple, non-invasive and readily available. Differing attenuation of X-ray signal within soft tissues compared to bone allows excellent visualisation of the pathological changes of the osseous structures of a joint. Recognised pathological features include marginal osteophytosis, subchondral sclerosis with joint space narrowing, subchondral cysts and deformation of the bone ends (Figure 1).

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a. Bilateral hip involvement in OA with superior joint space loss and subchondral sclerosis



b. Severe joint space narrowing, osteophyte formation and cysts in the elbow joint



c. Knee MRI demonstrating severe cartilage damage and joint space narrowing



d. Osteoarthritis of the glenohumeral joint

Fig. 1. X rays and MRI demonstrating range of joints involved in OA

In 1957 Kellgren and Lawrence incorporated the common features of OA into a grading system (Kellgren and Lawrence 1957) that was subsequently adopted by the world health organisation in 1961. They produced an atlas of standard radiographs demonstrating increasing grades of OA. Grades 0 and 1 were normal and doubtful respectively. Grades 2, 3 and 4 showed definite OA divided into mild, moderate and severe (Figure 2). Similar grading system atlases have been produced as variations on the same theme. Of these the most notable is the Osteoarthritis Research Society International (OARSI) score published by Altman et al. (Altman and Gold 2007). These grading systems are used to monitor the progression of OA. The primary variable used for the assessment of progression of OA is the joint space width (JSW) which is a surrogate for cartilage thickness and demonstrates cartilage loss with decreased JSW. There are a number of pitfalls in the acquisition and subsequent measurement of JSW with CR that increase error and subsequently increase the number of participants needed in a study to achieve adequate power. Changes in the position of the joint relative to the x-ray source and film will alter the JSW through magnification, parallax or superimposition of normal bone.



a. Kellgren-Lawrence grade 2, showing minimal joint space narrowing and osteophyte formation



b. Kellgren-Lawrence grade 4, showing severe bilateral tricompartmental knee OA with multiple ossific loose bodies

Fig. 2. Kellgren Lawrence grading

Typically the knee is used in assessment of JSW in disease modifying OA drugs (DMOAD) trials. Standardised protocols have evolved to improve the reliability of the JSW measurement. The JSW is most accurate when measured perpendicular to the x-ray beam and joint, and parallel to the film (Buckland-Wright 2006). Non-weight bearing films are inaccurate and their use is historical. Partial flexion of the knee or tilting of the x-ray beam is required to achieve the perpendicular alignment of beam to joint. The degree of flexion or tilt can be ascertained with fluoroscopic assistance or using standardised positioning. The semi-flexed anteroposterior view described by Buckland-Wright (Buckland-Wright, Marfarlane et al. 1995) and the Lyon Schuss view use fluoroscopy to ensure that the joint line is parallel to the x-ray beam before taking the radiograph. The fixed flexion and metatarso-phalangeal views (Buckland-Wright, Ward et al. 2004) are simpler in that they don't require fluoroscopy to obtain radio-anatomic alignment (Figure 3).

Although CR is the primary investigation in osteoarthritis, it has significant limitations. The earliest histological changes in the development of OA occur within the cartilage and precede radiographically detectable changes. Such changes are unable to distinguish primary from secondary OA. In the former, there is no other underlying cause identified; in the latter, OA changes may be secondary to other underlying joint pathology such as haemochromatosis or other inflammatory arthropathies. There is little difference in the x-ray absorption between varying soft tissues such as cartilage, ligaments, tendons and synovium. As a result the "whole organ" of the synovial joint cannot be assessed directly. Progression of the early stages of OA, which are a target for (DMOADs), is therefore not adequately characterised.

Bagge *et al.* conducted a study of 79 to 85 year-olds and found that more than half of patients with advanced radiographic signs of disease have no significant self-reported complaints (Bagge, Bjelle et al. 1991). Another disadvantage of these CR grading systems is their lack of sensitivity to change. Amin *et al.* conducted a longitudinal study (Amin, LaValley et al. 2005) of participants with knee OA, showing radiographic progression of joint space narrowing (JSN) was predictive of cartilage loss on MRI. However, 42% had cartilage loss visible on MRI with no radiographic progression of JSN. Radiographic progression appeared specific (91%) but not sensitive (23%) for cartilage loss. Conventional radiographs are a 2 dimensional (2D) representation of a 3 dimensional (3D) structure. The pathological changes of OA can also be obscured by superimposed normal bone. Chan *et al.* demonstrated a 60% detection rate of osteophytes in conventional knee radiographs versus 100% on MR imaging (Chan, Stevens et al. 1991).

Microfocal radiography utilises a micron sized x-ray source which emits divergent x-rays. The joint to be imaged is close to the source, but the film is approximately 2 meters away. The resultant image is of high resolution and magnified four to twenty times (Buckland-Wright, MacFarlane et al. 1995). These magnified images can yield a more accurate quantitative assessment of JSW measurements and also allow computerised Fractal Signature Analysis to quantify the changes in the trabeculae of subchondral bone seen in OA (Messent, Ward et al. 2007). The authors hypothesise that these changes in the subchondral and subarticular bone will correspond to the severity of knee OA defined by the reduction in JSW (Messent, Ward et al. 2007).

Conventional radiography still remains the primary imaging modality in the diagnosis and follow up of OA. However, the inability of CR to visualise the "whole organ" of the joint and differentiate early pathological changes is a major weakness that other modalities, particularly MRI, do not share.



a. Fixed flexion knee radiographs stressing the importance of correct views for assessing changes on plain X ray



b. Bilateral hand OA demonstrating predominantly proximal and distal interphalangeal joint involvement

Fig. 3. Optimal views for assessing degree of change

3. The contribution of MRI and CT to our understanding of OA pathophysiology

Radiographic imaging advances over recent years have led to a better understanding of the hierarchical structure of cartilage allowing delineation of early OA change at a molecular level. Articular cartilage is primarily hyaline cartilage which exhibits 3D anisotropic characteristics (physical and biological properties are direction dependent). The matrix composition and organization vary according to the depth from the articular surface including a superficial zone, a transitional zone, a radial zone and a zone of calcified cartilage (Potter, Black et al. 2009).

Cartilage can be conceptualized as a biphasic model consisting of a solid phase (glycoproteins, collagen, proteoglycans and chondrocytes) and a fluid phase (water and ions) that comprises 75% of cartilage by weight (Peterfy and Genant 1996). Proteoglycans (PG) consist of a protein core and glycosaminoglycans (GAG) side chains (Xia, Zheng et al. 2008). An osmotic pressure is generated by the heavily sulphated GAG molecules that carry a high concentration of negative charge. Counter ions such as Na^+ draw water into cartilage osmotically with the osmotic pressure contributing to the stiffness of cartilage thereby defining its load bearing properties both in healthy and disease states (Xia, Zheng et al. 2008). The collagen fibrils are thus maintained under pressure by the 'swelling pressure' that maintains the articular cartilage in an 'inflated' form (Peterfy and Genant 1996). Equilibrium exists between the swelling pressure that is resisted by the collagen framework which in turn determines the degree of compression of the PG molecules and the ensuing number of negative charges exposed (Peterfy and Genant 1996).

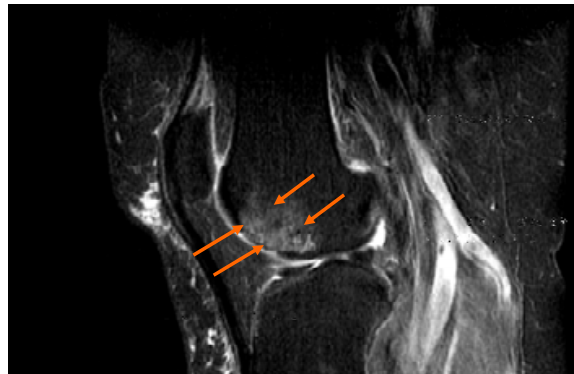
Disease states that disrupt the collagen framework allow PGs to expand resulting in exposure of more negatively charged moieties and a resultant increase in water content typically found to varying degrees in osteoarthritis, rheumatoid arthritis and traumatic cartilage damage (Peterfy and Genant 1996). Reduction of GAG concentration is also the biomarker of early disease and can be exploited by newer imaging modalities which provide a nondestructive high resolution image of hierarchical structure.

Newer imaging techniques primarily involving MRI (magnetic resonance imaging) have evolved to allow quantitative assessment of zonal changes in cartilage architecture in OA. Semi-quantitative scoring methods include WOMBS (whole organ MR imaging score), BLOKS (Boston-Leeds osteoarthritis knee score and KOSS (knee osteoarthritis scoring system) (Peterfy, Guermazi et al. 2004; Kornaat, Ceulmans et al. 2005; Hunter, Lo et al. 2008). Conventional MRI techniques that can be exploited include spin-echo (SE) and spoiled gradient-recalled echo (SPGR) sequences, fast SE sequences and 3D sequences (Crema, Roemer et al. 2011). Fast SE sequences can be performed in 2D and 3D.

Two dimensional fast SE has been tested in clinical trials and provides excellent contrast between fluid and cartilage as well as allowing assessment of bone marrow oedema, synovial thickening, menisci and ligaments (Crema, Roemer et al. 2011) (Figure 4). However 2D fast SE has the disadvantage of producing 2D images in all planes with gaps between images, meaning that detail can be lost when assessing thin 3D structures such as cartilage. 3D fast SE obtains information from the entire volume of the scanned joint which therefore allows manipulation of images in all planes and construction of volumetric images for quantitative assessment of cartilage morphology. It also permits assessment of bone marrow lesions (BMLs), menisci and ligaments but as yet has not been tested in clinical trials (Crema, Roemer et al. 2011).



a. MRI hip demonstrating synovial thickening (orange arrows)



b. MRI knee demonstrating bone marrow lesions (orange arrows)

Fig. 4. Magnetic Resonance Imaging in Osteoarthritis

Spoiled gradient-recalled echo sequences (SPGR) also obtain 3D information, allowing multi-planar reformatting and have the advantage of higher sensitivity when compared to 2D fast SE (Crema, Roemer et al. 2011). However they are susceptible to artifacts due to a long acquisition time making them less reliable for assessment of bone marrow oedema when compared to fast SE.

Other imaging techniques include sampling perfection with application-optimized contrast using different flip-angle evolutions (SPACE), dual-echo steady state (DESS), balanced steady state free precession (bSSFP) and driven equilibrium Fourier transform (DEFT) but these techniques have not been well validated as yet in clinical studies (Crema, Roemer et al. 2011).

Compositional assessment techniques include T2 mapping, delayed gadolinium-enhanced MR imaging of cartilage (dGEMRIC), T1rho (T1 ρ) imaging, sodium (Na) imaging and diffusion-weighted imaging (Crema, Roemer et al. 2011). These imaging modalities aim to quantify changes in water content, collagen content and GAGs.

T2 mapping utilizes the interaction between water and surrounding macromolecules with increased interactions resulting in decreased T2 dependent changes in hydration and indirectly collagen concentration that can be objectively assessed in 2D either on colour or grey-scale maps using full thickness mean values, Z-score maps, laminar approaches, texture analysis and flattened cartilage relaxation time maps analysed with grey-level co-occurrence matrices (Burstein, Gray et al. 2009; Carballido-Gamio, Joseph et al. 2011; Crema, Roemer et al. 2011). The relaxation times of T1 and T2 are thus dependent on water content and indirectly the associated collagen network allowing imaging without contrast.

T2 mapping is essentially the pixel by pixel solving of the T2 relaxation curve and can be used to delineate collagen composition of cartilage as well as menisci, ligaments and tendons by utilizing special pulsed sequences (ultrashort echo time techniques) (Potter, Black et al. 2009). Early OA generates a more heterogenous T2 map than normal cartilage but should be interpreted with caution since T2 maps are affected by physical activity and there is no direct correlation between OA grade and T2 changes (Crema, Roemer et al. 2011). Additionally T2 artefacts are generated by the 'magic angle effect' whereby there is an artefactual increase in T2 signal when the ordered structure of collagen is orientated at 55

degrees to the magnetic field resulting in zero dipole-dipole interactions and a prolongation of T2 relaxation time. T2 also exhibits a non-monoexponential behaviour of T2 in cartilage which can make quantification of proton density difficult and has a long acquisition time (Burstein, Gray et al. 2009; Crema, Roemer et al. 2011). Further preventable errors can result from variations in voxel size, parameter selection, signal-to-noise ratio and receiver coil between institutions (Potter, Black et al. 2009).

T1ρ measures the spin-lattice relaxation time in the rotating frame and is similar to T2 relaxation except that an additional radiofrequency pulse is applied after the magnetization is tipped into the transverse plane with an exponential relationship of signal decay to the time constant T1ρ (Burstein, Gray et al. 2009). Experimental studies have shown that T1ρ may be more sensitive than T2 weighted MRI to proteoglycan depletion which is characteristically seen in early OA (Crema, Roemer et al. 2011). However T1ρ requires special pulsed sequences, multiple data sets and has low spatial resolution (Crema, Roemer et al. 2011). Comparison of T1ρ, T2 and dGEMRIC images with histological studies of proteoglycan distribution have shown no correlation, suggesting that other factors such as collagen fibre orientation and concentration as well as the presence of other macromolecules may contribute to variations in T1ρ (Burstein, Gray et al. 2009; Crema, Roemer et al. 2011). However its nonspecific sensitivity may provide a future tool for quantification of molecular changes in early OA.

The diffusion coefficient of water in cartilage correlates to the degree of hydration (Burstein, Gray et al. 2009). Since hydration increases with cartilage degeneration in early OA this is potentially an exploitable biomarker of both the collagen network and GAGs (Xia, Farquhar et al. 1995; Crema, Roemer et al. 2011). The movement of water molecules can be measured in a noninvasive manner without the use of contrast material using pulsed-gradient spin-echo (PGSE) by utilizing a pair of gradient pulses separated by a time interval to detect an irreversible loss of signal due to Brownian motion (Xia, Farquhar et al. 1995). Spatial resolution can be used to localize cartilage degradation in disease but monitors microscopic tissue damage rather than PG content and is more difficult in thin cartilage layers (Xia, Farquhar et al. 1995; Crema, Roemer et al. 2011).

Collagen structure changes in early OA but its concentration does not. Increased levels of degraded collagen have been observed in the superficial and middle zones (Burstein, Bashir et al. 2000). Measurement of collagen using experimental techniques include T2 relaxation times, magnetization transfer (MT) and quantum studies (Burstein, Bashir et al. 2000). T2 techniques are susceptible to the 'magic angle effect' (an artefact signal produced when tissues with an ordered collagen structure are placed at a certain angle to the magnetic field). Magnetization transfer delineates the interaction of water molecules and more slowly rotating molecules with collagen contributing to the majority of the effect and GAG to a lesser extent in cartilage (Burstein, Bashir et al. 2000).

The magnetization transfer in cartilage depends on both collagen structure and concentration with experimental pilot studies showing a variation in MT images in the form of saturation over full magnetization that corresponds to variations in collagen without changes to water or proteoglycan content (Bageac, Gray et al. 1999). However techniques are still experimental and subject to variation according to the parameters of the saturation and correlation to other imaging modalities (Burstein, Bashir et al. 2000). Multiple quantum studies again offer a potential technique for visualizing changes in macromolecules in early OA that result in a change in the protons or sodium associated with the proteoglycans (Morris and Freemont 1992).

MRI imaging techniques such as dGEMRIC and Na imaging specifically quantify changes in GAG concentration by exploiting the correlation of change in ionic concentration with GAG concentration since proteoglycans have substantial negative fixed charge (Burstein, Bashir et al. 2000; Xia, Zheng et al. 2008; Potter, Black et al. 2009; Crema, Roemer et al. 2011).

The dGEMRIC technique uses T1 mapping of an intravenously administered anionic contrast agent gadopentate dimeglumine (Gd-DTPA^{2-}) which allows quantitative assessment of GAG content. Time is needed to allow penetration of Gd-DTPA^{2-} through the full cartilage thickness. Hence it is called 'delayed' gadolinium enhanced MRI and can require a delay of an hour and a half from injection to the start of image acquisition (Crema, Roemer et al. 2011). The distribution of Gd-DTPA^{2-} will be high in areas where GAG content is low with resultant decreased T1. Since the concentration of Gd-DTPA^{2-} in the blood is time dependent, a state of equilibrium between GAG content and Gd-DTPA^{2-} is never reached and the T1 measurement after penetration of Gd-DTPA^{2-} is referred to as the dGEMRIC index which varies directly with GAG content (Crema, Roemer et al. 2011). There is a correlation between areas of low dGEMRIC index and cartilage lesions which also directly correlates to an increasing Kellgren/Lawrence radiographic severity grade (Williams, Sharma et al. 2005).

A low dGEMRIC index is associated with an increased risk of developing radiographic OA within 6 years (Owman, C.J et al. 2008). Potentially a reduced GAG content in cartilage may increase susceptibility to an increased loading stress on the collagen network resulting in increased mechanical shearing with subsequent fibrillation of the cartilage and resultant OA change (Owman, C.J et al. 2008). Furthermore dGEMRIC has also been applied to imaging of the meniscus and the dGEMRIC index has been shown to correlate with cartilage variations indicating that both may undergo a parallel degradative process (Krishnan, Shetty et al. 2007). The dGEMRIC index of the meniscus was not found to vary consistently with different zones of the meniscus and may be affected by vascular supply or steric hindrance (the size of atoms within collagen prevent certain chemical reactions) by the collagen matrix (Krishnan, Shetty et al. 2007).

The extracellular matrix has a negative fixed charge density due to the sulfate and carboxyl groups in the GAG molecule. Positive charged ions of sodium are therefore present in higher concentrations in cartilaginous interstitial fluid than in synovial fluid or bone (Felson, McLaughlin et al. 2003). Areas of cartilage where GAG depletion has occurred will therefore have a lower sodium ion concentration. Sodium MRI imaging measures the resonance frequency produced by Na's nuclear spin momentum and has the advantage in cartilage that sodium is naturally present with a higher concentration than the surrounding tissues (Felson, McLaughlin et al. 2003). Disadvantages of sodium imaging include the low spatial resolution compared to proton MR imaging with some spatial variation present in normal cartilage and the need for special hardware (Zanetti, Bruder et al. 2000).

Bone marrow lesions (BML) have been cited as a potential biomarker of structural deterioration in knee OA using sagittal short inversion time inversion-recovery (STIR), T1- and T2- weighted turbo spin-echo MR imaging (Zanetti, Bruder et al. 2000; Felson, McLaughlin et al. 2003; Link, Steinbach et al. 2003; Kijowski, Stanton et al. 2006). A natural history study by Felson et al. using a 1.5T MRI system showed that in the knee the presence of BML was a powerful risk factor for further structural deterioration (Felson, McLaughlin et al. 2003). In the medial compartment the presence of BMLs was found to correlate with an increased progression of medial compartment OA by a factor of six (Felson, McLaughlin et

al. 2003). Furthermore there was an association between frontal plane malalignment and BML. However other studies have shown that whilst BMLs are associated with OA they may not directly correlate with severity of Kellgren-Lawrence grading. Bone marrow lesions may instead correlate with a number of non-characteristic histological abnormalities including bone marrow necrosis, bone marrow fibrosis and trabecular abnormalities (Zanetti, Bruder et al. 2000; Link, Steinbach et al. 2003; Hayashi, Guermazi et al. 2011). Further MRI studies of the relation of BMLs to pain in OA have been more encouraging. Pain incidence and severity correlate to the presence and size of BMLs (Felson, Chaisson et al. 2001; Felson, Niu et al. 2007). Felson et al found that BMLs were present in 77.5% of patients with painful knees compared to 30% of patients with no knee pain (Felson, Chaisson et al. 2001; Felson, Niu et al. 2007).

Recently microCT has also been used, predominantly in animal models to define the nature of osteophytes and change in bone marrow volume in OA (Hayashi, Guermazi et al. 2011; Sampson, Beck et al. 2011). Such studies have reported that osteophyte size and localization may be better visualized using microCT. Increased bone volume is also observed in OA lesions (Sampson, Beck et al. 2011).

4. Ultrasound assessment in OA

Ultrasound (US) provides a cost-effective, real time, non-invasive multi-planar imaging modality in the assessment of OA and also to guide therapeutic injections (Moller, Bong et al. 2008). Ultrasound has the advantage over MRI and bone scintigraphy in that it is more readily available and non-invasive. However its main disadvantage is that it is operator dependent with a long learning curve (Iagnocco 2010). It is portable and therefore allows repeated assessment of subtle progression of joint pathology in both static and dynamic modes (Moller, Bong et al. 2008). Whilst CR changes such as JSN, subchondral sclerosis, marginal osteophytes and cysts are used to assess OA progression, in the hand these may be late findings. Thus US may provide a useful adjunct to the early assessment of subclinical manifestations of OA (Iagnocco 2010).

The recent development of high resolution high frequency transducers, multi-frequency probes, matrix probes and volumetric probes has expanded the application of US in the assessment of cartilage thickness, menisci, tendons, ligaments, joint capsule, synovial membrane, synovial fluid and bursae as well as to a lesser extent subchondral bone. Recent studies have indicated an association between synovial proliferation and BML with pain in OA making their assessment with US particularly attractive (Moller, Bong et al. 2008; Kortekaas, Kwok et al. 2010).

Anatomic sites most frequently assessed with US include the hand, the foot, the knee and hip joints both in terms of primary evaluation of early disease, therapeutic interventions and response to treatment (Walther, Harms et al. 2002; Kuroki, Nakagawa et al. 2008; Mancarella, Magnani et al. 2010). The anatomical site and type of tissue under investigation will determine the US technique used (Moller, Bong et al. 2008). Scanning protocols are tailored to specific joints with established guidelines ensuring standardization of images in two planes (Keen, Wakefield et al. 2009; Iagnocco 2010). For example, in the small joints of the hand, longitudinal and transverse scans in flexion for the dorsal aspects and in neutral to visualize the volar aspects are performed with a high frequency (more than 12 MHz) probe (Moller, Bong et al. 2008; Iagnocco 2010; Mancarella, Magnani et al. 2010; Wittoek, Carron et al. 2010). In order to visualize the weight bearing surfaces of the femoral condyles in the

knee, the scan is performed with the knee flexed in the supine position (Moller, Bong et al. 2008; Yoon, Kim et al. 2008). In the hip the leg is extended and externally rotated to allow visualization of the anterior surface of the femoral head using a lower frequency (8-12 MHz) probe (Backhaus, Burmester et al. 2001; Moller, Bong et al. 2008; Iagnocco 2010). Studies in the literature vary as to how the joint is positioned and which planes are scanned (Naredo, Acebes et al. 2008).

The shape and size of the probe also has a role in image acquisition with smaller hockey stick probes being more appropriate for the small joints of the hand and larger footprint probes more suited for knee and hip joints (Iagnocco 2010). Both grey-scale and Doppler scans provide complementary modalities for the thorough assessment of osteoarthritic joints (Iagnocco 2010). Using an initial grey-scale setting and by altering the probe frequency both superficial and deeper structures can be viewed in small joints such as in the hand and larger joints such as the hip (Iagnocco 2010; Mancarella, Magnani et al. 2010). Power Doppler settings allow the assessment of active inflammation, or at least to vascular hyperaemia in the synovium thus defining both disease state and response to therapy modalities (Iagnocco 2010; Mancarella, Magnani et al. 2010; Arrestier, Rosenberg et al. 2011). The application of US in the assessment of OA includes definition of the extent of changes in the cartilaginous matrix, changes in intra-articular and peri-articular soft tissues as well as assessment of changes to the bony cortex (Moller, Bong et al. 2008). Early disease progression is reflected in loss of sharpness of the superficial cartilaginous margin corresponding to micro-cleft formation and later loss of echogenicity (Moller, Bong et al. 2008; Iagnocco 2010). Diffuse thinning eventually progresses to cartilage loss and asymmetric JSN with good reproducibility and agreement between ultrasonographers and histological findings (Moller, Bong et al. 2008; Iagnocco 2010).

Bone changes in early OA include the presence of a hyperechoic signal in the area of joint capsule attachment (Moller, Bong et al. 2008). Later disease changes include the formation of osteophytes as cortical protrusions at the corresponding joint margin (Iagnocco 2010). In the hand osteophytes can be accompanied by cartilage erosions visualized as a step-down contour defect (Iagnocco 2010; Wittoek, Carron et al. 2010). Recent evidence has shown that US is more sensitive than CR for the detection of osteophytes and JSN in hand OA (Wakefield, Balint et al. 2005; Iagnocco 2010).

With reference to OA changes affecting intra-articular soft tissues, synovial thickening, joint effusion and increased vascularity can be detected using both grey-scale and Doppler modalities (Moller, Bong et al. 2008; Iagnocco 2010). Furthermore, increased synovial flow detected with Doppler modalities is also a sign of increased synovial vascularity which correlates well with corresponding histological changes (Backhaus, Burmester et al. 2001). The Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) definitions of synovial fluid and synovial hypertrophy applied in rheumatoid arthritis are also applicable to OA (Moller, Bong et al. 2008; Koutroumpas, Alexiou et al. 2010). Synovial thickening is defined as abnormal hypoechoic intra-articular material that is non-displaceable, poorly compressible and may exhibit power Doppler signal (PDS). Effusion is defined as abnormal intra-articular material that is hypoechoic or anechoic, displaceable and does not exhibit PDS (Koutroumpas, Alexiou et al. 2010). Synovial thickening is frequently found in inflamed OA joints and synovial fluid can be defined by its quantity and content with respect to US imaging in OA (Iagnocco 2010). It is unclear if any inflammation perceived is from OA or from complicating crystalline arthritis.

Specific US findings related to anatomical location of the joint under investigation have also been defined in the literature, with the majority of studies involving the joints of the hand (Walther, Harms et al. 2002; Kuroki, Nakagawa et al. 2008; Wittoek, Carron et al. 2010; Wittoek, Jans et al. 2010; Arrestier, Rosenberg et al. 2011). Several studies have also investigated the diagnostic accuracy of US compared to CR, CT and MRI in the hand (Keen, Wakefield et al. 2008; Moller, Bonel et al. 2009; Mancarella, Magnani et al. 2010).

Ultrasound is more sensitive than CR in detecting cartilage erosions in the hand which may provide a tool for allowing earlier identification of cartilage loss in joints (Wittoek, Carron et al. 2010). However longitudinal studies are required to validate the development of US detected cartilage erosions into CR detected erosions. Osteophytes are also detected with a higher sensitivity using US compared to CR due to its ability to assess the joint under investigation in multiple planes (Wakefield, Balint et al. 2005; Wittoek, Carron et al. 2010). By contrast, estimating JSN with US is dependent on the acoustic window since osteophytes can block adequate visualization and the central portion of the joint cannot be visualized with US (Wakefield, Balint et al. 2005). Evaluation of JSN is subjective with no validated criteria defined in the literature. Cartilage thickness may provide a surrogate marker of JSW since reduced cartilage thickness in the hand has been shown to correlate with JSN (McNally 2007). In order to improve near field resolution, increased sensitivity for detection of blood flow and minimize compression / obliteration of small quantities of effusion or synovial thickening, a lightly held probe with a generous amount of contact jelly reduces contact pressure (Koski, Saarakkala et al. 2006).

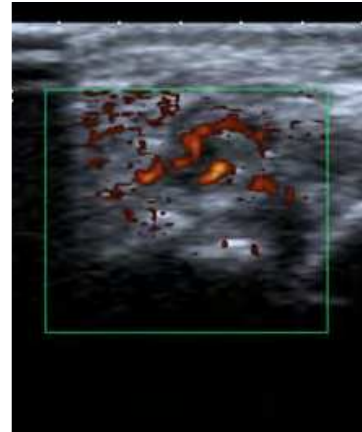
Effusion and PDS do not appear to be specific for cartilage erosion with effusion also found in 'normal' joints and conflicting results found in current studies (Chao, Wu et al. 2010; Kortekaas, Kwok et al. 2010; Mancarella, Magnani et al. 2010; Wittoek, Carron et al. 2010; Wittoek, Jans et al. 2010; Arrestier, Rosenberg et al. 2011). Subclinical inflammation has been reported in some studies with no correlation found with PDS or patients' reported pain levels but may indicate future disease progression (Kuroki, Nakagawa et al. 2008; Kortekaas, Kwok et al. 2010; Wittoek, Jans et al. 2010). Scanning of the sagittal (longitudinal) extensor and flexor sides is performed in relaxed finger extension with axial imaging used to view the metacarpophalangeal joints and coronal imaging used to view the interphalangeal joints (Koski, Saarakkala et al. 2006). Gentle flexion of the joints allows detection of intra-articular changes such as osteophytes and synovial thickening (Koski, Saarakkala et al. 2006) (Figure 5). Ultrasound shows good agreement with MRI for the assessment of cartilage erosion and grey-scale synovial thickening (Moller, Bonel et al. 2009). Osteophytes can produce a signal void on MRI due to the presence of densely packed calcium, making US more sensitive than CR and MRI (Moller, Bonel et al. 2009).

Similar techniques can be employed to image the small joints of the forefoot (Koski, Saarakkala et al. 2006). The extensor approach is used to probe the interphalangeal joints as well as the meta-tarsophalangeal joints to detect joint erosions and synovial thickening.

In the knee US probes can also be used arthroscopically to assess cartilage morphology as well as conventional scanning protocols to assess cartilage thickness in the weight bearing areas of the femoral condyles, protrusion of the medial meniscus in the knee and the presence of Baker's cysts (Kuroki, Nakagawa et al. 2008; Yoon, Kim et al. 2008; Iagnocco 2010). Alternative imaging protocols such as the longitudinal sagittal US scan may also provide visualization of a larger area of femoral condyle than the suprapatellar transverse axial scan (Yoon, Kim et al. 2008). Synovial thickening can also be detected but may not correspond to clinical response to intra-articular corticosteroid injections (Hattori, Takakura et al. 2005).



a. Plain radiograph of the hand demonstrating first carpometacarpal joint degenerative change



b. First carpometacarpal joint showing synovial thickening and increased vascularity on power Doppler imaging

Fig. 5. Plain x ray and ultrasound power Doppler signal

Validity of measurements of cartilage thickness in the knee using US has shown good reproducibility in normal to moderately damaged cartilage but is less accurate for severely damaged cartilage where the cartilage-soft tissue interfaces become less clear (Keen, Wakefield et al. 2008; Yoon, Kim et al. 2008). Ultrasound properties that can be exploited for assessing cartilage structure include the use of signal intensity which correlates to superficial cartilage integrity, echo duration which correlates to surface irregularity and the interval between signals that correlates to thickness (Kuroki, Nakagawa et al. 2008). High frequency pulsed echo US can be used to assess degeneration of the superficial collagen-rich cartilage zone. It is capable of detecting microstructural changes up to a depth of 500 μ m (Qvistgaard, Torp-Pedersen et al. 2006).

Hip ultrasound depends on patient size since there is a loss of resolution and poorer penetration of higher frequency probes at depth. Depending on patient size, sometimes only lower frequency curvilinear probes can be used (usually 5-8MHz) with significant loss of detail). In the hip the use of PDS has been found to correlate reliably with vascularity of synovial tissue (Backhaus, Burmester et al. 2001). Ultrasound assessment of femoral head shape, synovial profile, joint effusion and synovial thickening in OA has been shown to be reliable in trained US investigators (Yoon, Kim et al. 2005; Atchia, Birrell et al. 2007). The presence of an effusion or synovial thickening has been assessed by measuring the collum-capsule distance (distance between the neck of the femur and the hip capsule) and comparing it to the asymptomatic side (Atchia, Birrell et al. 2007). When compared with CR Kellgren scores there was a weak correlation to US scoring of osteophytes and femoral head shape (Atchia, Birrell et al. 2007). When associated with pain on activity, there is a highly significant association of global US hip joint evaluation when combined with US synovial thickening as a predictor of pain on activity (Atchia, Birrell et al. 2007).

In summary, there is a reasonable correlation between US measurements of cartilage thickness and histological findings for mild and moderate OA. In the hand US is more sensitive for the detection of osteophytosis but less so for cartilage erosions. In the knee US correlates well with MRI for the detection of effusion, synovial thickening and popliteal cysts but shows poor correlation with a clinical diagnosis of anserine tendinobursitis (Yoon, Kim et al. 2005). In the hip PDS correlates well to increased vascularity of synovial tissue. In

the foot and shoulder, there is good correlation between US and CR as well as clinical diagnosis of enthesitis and demonstration of bursitis over the medial aspect of the first metatarsophalangeal joint (Naredo, Acebes et al. 2008; Iagnocco 2010). Further work is still required to standardize definitions, scoring systems and validity (Iagnocco 2010).

5. Vibrational spectroscopy

There is no current validated tool for the diagnosis of symptomatic early OA prior to CR changes (Esmonde-White, Mandair et al. 2009). Chemical changes in synovial fluid and subchondral bone may provide biomarkers of early disease allowing for earlier intervention (Dehring, Crane et al. 2006; Williams and Spector 2008; Sofat 2009). Vibrational spectroscopy can provide detailed chemical information on the interactions between mineral and collagen matrix in cartilage, changes in subchondral bone, changes in the viscosity of synovial fluid and deposition of crystals such as basic calcium phosphate crystals (BCP) (Dehring, Crane et al. 2006).

Atoms in a molecule undergoing periodic motion while the molecule has a constant motion create a vibrational frequency which will depend on the quantity of energy absorbed during vibrational transitions and can produce a characteristic infrared spectra. All biological molecules have a unique spectra which can be measured using a variety of vibrational spectroscopic techniques, each with their own inherent advantages and disadvantages (Lambert, Whitman et al. 2006).

Both near infrared spectroscopy (NIR) and Fourier-transform infra-red (FTIR) spectroscopy have been utilized for the investigation of synovial fluid chemical composition in disease states but cannot identify individual components of synovial fluid (Esmonde-White, Mandair et al. 2009). FTIR uses automated pattern recognition but has the disadvantage that water interferes with certain parts of the spectra which can result in misinterpretation (Yavorsky, Hernandez-Santana et al. 2008). Raman spectroscopy provides a specific non-invasive, non-destructive and reagentless tool for the investigation of biological tissues (Esmonde-White, Mandair et al. 2009). Water does not interfere with Raman spectroscopy and unique spectra are available for biological molecules (Yavorsky, Hernandez-Santana et al. 2008). However it is expensive with fewer library spectra available (Yavorsky, Hernandez-Santana et al. 2008).

Synovial fluid aspirates provide an easy source of biomaterial for the investigation of changes in composition and viscosity in early OA (Esmonde-White, Mandair et al. 2009). Both NIR and FTIR can be used to identify early OA with a classification rate of greater than 95% using the overall chemical composition generated spectral pattern (Esmonde-White, Mandair et al. 2009). Background fluorescence especially from proteins can interfere with the spectra (Yavorsky, Hernandez-Santana et al. 2008). Further refinement with drop deposition to allow rough component separation and segregation of impurities in conjunction with Raman spectroscopy can improve the diagnostic potential of vibrational spectroscopy (Esmonde-White, Mandair et al. 2009). Correlation of spectral bands with Kellgren and Lawrence grades creates the potential of a future diagnostic tool (Esmonde-White, Mandair et al. 2009).

Crystals such as BCP and calcium pyrophosphate dihydrate (CPPD) are frequently reported in the early stages of OA before changes to subchondral bone are evident (Fuerst, Lammers et al. 2009). BCP crystals are small (1nm) and unlike CPPD (crystals 91-2µm) are not visible using light microscopy unless they clump together (Fuerst, Lammers et al. 2009). Raman

spectra can be used to distinguish between crystals and detect their presence in synovial fluid (Yavorsky, Hernandez-Santana et al. 2008).

Changes in cartilage and subchondral bone can also be detected with vibrational spectroscopy. FTIR has been used to correlate tissue damage with changes in the amide II and III envelopes (part of the spectra) as well as detecting spectral features of proteoglycans and collagen to a spatial resolution of 10µm and collagen degradation in OA knees (Dehring, Crane et al. 2006). Raman spectroscopy can also be used in a non-invasive fashion to investigate the subchondral bone under the non-mineralised layer of articular cartilage providing the potential for a future diagnostic tool in OA (Dehring, Crane et al. 2006).

6. Bone scans

Scintigraphy allows the assessment of the osseous physiology in human joints since it requires a living, metabolically functioning organism (Dye and Chew 1994). Whilst conventional radiography, CT scanning, MRI and ultrasound provide a structural assessment of a joint, bone scanning has the advantage of providing a physiological assessment (Dye and Chew 1994). The main disadvantages of bone scans are that the images are planar with superimposition of a 3D array into 2D and resolution is low for complex joints (Kim 2008).

The indications for performing a bone scan specifically in OA are limited, with scintigraphy used in a clinical setting to differentiate between pathologies. Historically, bone scans were requested to confirm or exclude a diagnosis of inflammatory arthritis, malignancy and fractures in one study (Duncan, Dorai-Raj et al. 1999). OA was the final diagnosis in 11% of scans. However, changes in periarticular uptake have been noted in patients with normal radiographic findings and an unstable bucket handle meniscal tear (Dye and Chew 1994). Potential future application is in the diagnosis of early OA prior to conventional radiographic changes.

Technetium-99m (Tc-99m) is the common gamma emitting radio-isotope used in bone scans. It is linked to methylene diphosphanate (MDP) which is taken up by metabolically active bone. Studies typically consist of a blood flow phase that reflects tissue perfusion, a blood pool phase that reflects vascularity and a final delayed static image phase that reflects a combination of blood supply and tracer extraction by metabolically active bone (Siegel, Donovan et al. 1976).

Newer applications such as single photon emission computed tomography (SPECT) have expanded the role of scintigraphy in bone imaging (Sarikaya, Sarikaya et al. 2001; Kim 2008; Papathanassiou, Bruna-Muraille et al. 2009). SPECT separates into sequential tomographic planes the metabolic activity thus improving image contrast and localization (Sarikaya, Sarikaya et al. 2001). Current clinical applications for SPECT in OA are limited due to the practicalities of low count rates and inefficient use of the camera field-of-view (Collier, Johnson et al. 1985). Bone SPECT has been used in the diagnosis of facet joint OA in the spine with studies showing that it may improve patient selection for therapeutic facet blocks (Holder, Machin et al. 1995; Dolan, Ryan et al. 1996). Conventional radiography and MRI are still the main modes of investigating the painful knee, SPECT has also been used to investigate chronic knee pain. SPECT was more sensitive than bone scintigraphy in detecting articular cartilage damage in the patellofemoral joint (Collier, Johnson et al. 1985). SPECT imaging correlates well with clinical scores and physical examination in patients with OA, even without abnormal radiographic findings which may indicate a future role in the diagnosis of early OA (Kim 2008).

Advances in image alignment software have allowed SPECT imaging to be fused to high resolution CT slices in the region of interest (Papathanassiou, Bruna-Muraille et al. 2009). Whilst technically challenging since patient position must be maintained, it has the advantage of combining high special structural information with highly sensitive functional information (Papathanassiou, Bruna-Muraille et al. 2009). The main disadvantage is the increased radiation dose to the patient of combining both CT and SPECT.

Various radiopharmaceuticals have been described in the literature under development in animals to allow imaging of cartilage as well as bone (Yu, Bartlett et al. 1988; Yu, Shaw et al. 1999). Other radiopharmaceuticals that target inflammation, osteophytes, cysts and sclerosis have also been described in a limited setting in the literature (Merrick 1992; Etchebehere, Etchebehere et al. 1998).

In positron emission spectroscopy (PET), 18-fluorodeoxyglucose (18-FDG) acts as a glucose analogue, taken up in cells within the body which have high glucose requirements. This includes brain and cardiac tissue as well as cells with high metabolic activity. Using CT imaging techniques, the resultant energy from the emitted positrons can be used to produce 3D functional imaging. When combined with CT scanning, the PET and CT images can be co-registered (merged), producing improved resolution and localization of focal of tracer uptake. PET-CT scanning demonstrates increased uptake in OA, (Elzinga, Laken et al. 2007; Omoumi, Mercier et al. 2009) however, the presence of increased of metabolic activity is not specific to this condition. Other isotopes such as 18-Fluoride (18-F) has a high affinity for bone. This isotope PET scan produces high quality bone images within 30 minutes of injection of the tracer (Omoumi, Mercier et al. 2009).

In summary, the current clinical applications of conventional bone scintigraphy in OA are limited to excluding differential diagnoses. Future applications of gamma emitting and positron emitting radiopharmaceuticals may allow imaging of anatomical and physiological changes in joints prior to conventional radiographic changes associated with early OA.

7. Implications of advances in imaging for therapies in OA

It is likely that if treatment interventions become targeted more towards BMLs e.g. with bisphosphonates, that MRI will play a central role in defining the nature and site of BMLs. There is also increasing evidence that synovial thickening is correlated strongly with pain in OA. Ultrasound is becoming increasingly accepted as a useful tool for detecting subclinical synovial thickening and may be used to target therapies to treat local inflammation e.g. corticosteroid injections. Although there are currently no DMOADs (disease-modifying OA drugs) that are effective in the long-term, it is possible that sensitive techniques such as dGEMRIC may be useful in quantifying structural change using novel therapies. In summary, developments in imaging have improved our understanding of OA immensely in recent years and may well play a pivotal role in guiding treatments for the future.

8. References

- Altman, R. D. and G. E. Gold (2007). "Atlas of individual radiographic features in osteoarthritis, revised." *Osteoarthritis and Cartilage* 15(Supplement A): A1-56.
- Amin, S., M. P. LaValley, et al. (2005). "The relationship between cartilage loss on magnetic resonance imaging and radiographic progression in men and women with knee osteoarthritis." *Arthritis and Rheumatism* 52(10): 3152-3159.

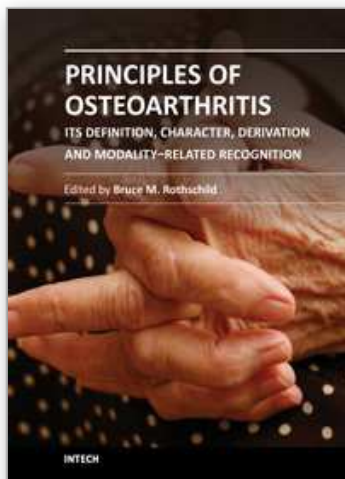
- Arrestier, S., C. Rosenberg, et al. (2011). "Ultrasound features of nonstructural lesions of the proximal and distal interphalangeal joints of the hands in patients with finger osteoarthritis." *Joint Bone Spine* 78(1): 65-69.
- Atchia, I., F. Birrell, et al. (2007). "A modular, flexible training strategy to achieve competence in diagnostic and interventional musculoskeletal ultrasound in patients with hip osteoarthritis." *Rheumatology* 46(10): 1583-1586.
- Backhaus, M., G.-R. Burmester, et al. (2001). "Guidelines for musculoskeletal ultrasound in rheumatology." *Ann Rheum Dis* 60: 641-649.
- Bageac, A. C., M. L. Gray, et al. (1999). "Development of an MRI surrogate for immunohistochemical staining of collagen damage in cartilage." *In 5th international conference on magnetic resonance microscopy. Heidelberg, Germany: Groupement ampere*. 17.
- Bagge, E., A. Bjelle, et al. (1991). "Osteoarthritis in the elderly: clinical and radiological findings in 79 and 85 year olds." *Annals of Rheumatology Disease* 50(8): 533-539.
- Buckland-Wright, C. (2006). "Which radiographic techniques should we use for research and clinical practice?" *Best Practice & Research Clinical Rheumatology* 20(1): 39-55.
- Buckland-Wright, C., D. G. Marfarlane, et al. (1995). "Accuracy and precision of joint space width measurements in standard and macroradiographs of osteoarthritic knees." *Annals of Rheumatology Disease* 54(11): 872-880.
- Buckland-Wright, J. C., D. G. MacFarlane, et al. (1995). "Quantitative microfocal radiography detects changes in OA knee joint space width in patients in a placebo controlled trial of NSAID therapy." *Journal of Rheumatology* 22(5): 937-943.
- Buckland-Wright, J. C., R. J. Ward, et al. (2004). "Reproducibility of the semi-flexed (metatarsophalangeal) radiographic knee position and automated measurements of medial tibiofemoral joint space width in a multicentre clinical trial of knee osteoarthritis." *Journal of Rheumatology* 31(8): 1588-1597.
- Burstein, D., A. Bashir, et al. (2000). "MRI techniques in early stages of cartilage disease." *Investigative Radiology* 35(10): 622-638.
- Burstein, D., M. L. Gray, et al. (2009). "Measures in molecular composition and structure in osteoarthritis." *Radiologic Clinics of North America* 2009(47): 675-686.
- Carballido-Gamio, J., G. B. Joseph, et al. (2011). "Longitudinal analysis of MRI T2 knee cartilage laminar organization in a subset of patients from the osteoarthritis initiative: A texture approach." *Magnetic Resonance in Medicine* 65(4): 1184-1194.
- Chan, W. P., M. P. Stevens, et al. (1991). "Osteoarthritis of the knee: comparison of radiography, CT, and MR imaging to assess extent and severity." *American Journal of roentgenology* 157(4): 799-806.
- Chao, J., C. Wu, et al. (2010). "Inflammatory characteristics on ultrasound predict poorer longterm response to intra-articular corticosteroid injections in knee osteoarthritis." *The Journal of rheumatology* 37: 650-655.
- Collier, B. D., R. P. Johnson, et al. (1985). "Chronic knee pain assessed by SPECT: comparison with other modalities." *Radiology* 157: 795-802.
- Crema, M. D., F. W. Roemer, et al. (2011). "Articular Cartilage in the Knee: Current MR Imaging Techniques and Applications in Clinical Practice and Research." *Radiographics* 31: 37-62.

- Dehring, K. A., N. J. Crane, et al. (2006). "Identifying chemical changes in subchondral bone taken from murine knee joints using Raman spectroscopy." *Applied Spectroscopy* 60(10): 1134.
- Dolan, A. L., P. J. Ryan, et al. (1996). "The value of SPECT scans in identifying back pain likely to benefit from facet joint injection." *British Journal of Rheumatology* 35: 1269-1273.
- Duncan, I., A. Dorai-Raj, et al. (1999). "The utility of bone scans in rheumatology." *Clinical Nuclear Medicine* 24(1): 9-14.
- Dye, S. F. and M. H. Chew (1994). "The use of scintigraphy to detect increased osseous metabolic activity about the knee." *Instructional Course Lectures* 43: 453-469.
- Elzinga, E. H., C. J. Laken, et al. (2007). "2-Deoxy-2-[F-18]fluoro-D-glucose joint uptake on positron emission tomography images: rheumatoid arthritis versus osteoarthritis." *Molecular Imaging and Biology* 9(6): 357-360.
- Esmonde-White, K. A., G. S. Mandair, et al. (2009). "Raman spectroscopy of synovial fluid as a tool for diagnosing osteoarthritis." *Journal of Biomedical Optics* 14(3): 034013.
- Etchebehere, E. C., M. Etchebehere, et al. (1998). "Orthopaedic pathology of the lower extremities: scintigraphic evaluation in the thigh, knee and leg." *Seminars in Nuclear Medicine* 28(1): 41-61.
- Felson, D. T., C. E. Chaisson, et al. (2001). "The association of bone marrow lesions with pain in knee osteoarthritis." *Annals of Internal Medicine* 134: 541-549.
- Felson, D. T., S. McLaughlin, et al. (2003). "Bone marrow edema and its relation to progression of knee osteoarthritis." *Annals of Internal Medicine* 139.
- Felson, D. T., J. B. Niu, et al. (2007). "Correlation of the development of knee pain with enlarging bone marrow lesions on magnetic resonance imaging." *Arthritis and Rheumatism* 56: 2986-2992.
- Fuerst, M., L. Lammers, et al. (2009). "Investigation of calcium crystals in OA knees." *Rheumatology International* 30(5): 623-631.
- Hattori, K., Y. Takakura, et al. (2005). "Quantitative ultrasound can assess the regeneration process of tissue-engineered cartilage using a complex between adherent bone marrow cells and a three dimensional scaffold." *Arthritis Research & Therapy* 7: R552-559.
- Hayashi, D., A. Guermazi, et al. (2011). "Osteoarthritis year 2010 in review: imaging." *Osteoarthritis and Cartilage*.
- Holder, L. E., J. L. Machin, et al. (1995). "Planar and high resolution SPECT bone imaging in the diagnosis of facet syndrome." *Journal of Nuclear Medicine* 36: 37-44.
- Hunter, D. J., G. H. Lo, et al. (2008). "The reliability of a new scoring system for knee osteoarthritis MRI and the validity of bone marrow lesion assessment: BLOKS (Boston Leeds osteoarthritis knee score)." *Annals of Rheumatology Disease* 67(2): 206-211.
- Iagnocco, A. (2010). "Imaging the joint in osteoarthritis: a place for ultrasound?" *Best Practice & Research Clinical Rheumatology* 24(1): 27-38.
- Keen, H. I., R. J. Wakefield, et al. (2009). "A systematic review of ultrasonography in osteoarthritis." *Annals of the Rheumatic Diseases* 68(5): 611-619.
- Keen, H. I., R. J. Wakefield, et al. (2008). "Can ultrasonography improve on radiographic assessment in osteoarthritis of the hands? A comparison between radiographic and

- ultrasonographic detected pathology." *Annals of the Rheumatic Diseases* 67(8): 1116-1120.
- Kellgren, J. and J. Lawrence (1957). "Radiological assessment of osteo-arthritis." *Annals of Rheumatology Disease* 16(4): 494-502.
- Kijowski, R., P. Stanton, et al. (2006). "Subchondral bone marrow edema in patients with degeneration of the articular cartilage of the knee joint." *Radiology* 238(3): 943-949.
- Kim, H. (2008). "Clinical value of 99mTc-methylene diphosphonate (MDP) bone single photon emission computed tomography (SPECT) in patients with knee osteoarthritis." *Osteoarthritis and Cartilage* 16(2): 212-218.
- Kornaat, P. R., R. Y. Ceulmans, et al. (2005). "MRI assessment of knee osteoarthritis: knee Osteoarthritis Scoring System (KOSS) inter-observer and intra-observer reproducibility of compartment-based scoring system." *Skeletal Radiology* 34(2): 95-102.
- Kortekaas, M. C., W. Y. Kwok, et al. (2010). "Pain in hand osteoarthritis is associated with inflammation: the value of ultrasound." *Annals of the Rheumatic Diseases* 69(7): 1367-1369.
- Koski, J. M., S. Saarakkala, et al. (2006). "Power Doppler ultrasonography and synovitis: correlating ultrasound imaging with histopathological findings and evaluating the performance of ultrasound equipments." *Annals of the Rheumatic Diseases* 65(12): 1590-1595.
- Koutroumpas, A. C., I. S. Alexiou, et al. (2010). "Comparison between clinical and ultrasonographic assessment in patients with erosive osteoarthritis of the hands." *Clinical Rheumatology* 29(5): 511-516.
- Krishnan, N., S. K. Shetty, et al. (2007). "Delayed gadolinium enhanced magnetic resonance imaging of the meniscus." *Arthritis and Rheumatism* 56(5): 1507-1511.
- Kuroki, H., Y. Nakagawa, et al. (2008). "Ultrasound properties of articular cartilage in the tibio-femoral joint in knee osteoarthritis: relation to clinical assessment (International Cartilage Repair Society grade)." *Arthritis Research & Therapy* 10(4): R78.
- Lambert, P. J., A. G. Whitman, et al. (2006). "Raman spectroscopy: the gateway into tomorrow's virology." *Virology Journal* 3: 51.
- Link, T. M., L. S. Steinbach, et al. (2003). "Osteoarthritis: MR imaging findings in different stages of disease and correlation with clinical findings." *Radiology* 226(2): 373-381.
- Mancarella, L., M. Magnani, et al. (2010). "Ultrasound-detected synovitis with power Doppler signal is associated with severe radiographic damage and reduced cartilage thickness in hand osteoarthritis." *Osteoarthritis and Cartilage* 18(10): 1263-1268.
- McNally, E. G. (2007). "Ultrasound of the small joints of the hands and feet: current status." *Skeletal Radiology* 37(2): 99-113.
- Merrick, M. V. (1992). "Investigating joint disease." *European journal of nuclear medicine and molecular imaging* 19(10): 894-901.
- Messent, E. A., R. J. Ward, et al. (2007). "Osteophytes, juxta-articular radiolucencies and cancellous bone changes in the proximal tibia of patients with knee osteoarthritis." *Osteoarthritis and Cartilage* 15(2): 179-186.

- Moller, B., H. Bonel, et al. (2009). "Measuring finger joint cartilage by ultrasound as a promising alternative to conventional radiographic imaging." *Arthritis and Rheumatism* 61: 435-441.
- Moller, I., D. Bong, et al. (2008). "Ultrasound in the study and monitoring of osteoarthritis." *Osteoarthritis and Cartilage* 16: S4-S7.
- Morris, G. A. and A. J. Freemont (1992). "Direct observation of the magnetization exchange dynamics responsible for magnetization transfer contrast in human cartilage in vitro." *Magnetic Resonance Medicine* 28: 97-104.
- Naredo, E., C. Acebes, et al. (2008). "Ultrasound validity in the measurement of knee cartilage thickness." *Annals of the Rheumatic Diseases* 68(8): 1322-1327.
- Omoumi, P., G. A. Mercier, et al. (2009). "CT arthrography, MR arthrography, PET, and scintigraphy in osteoarthritis." *Radiologic Clinics of North America* 47: 595-615.
- Owman, H., T. C.J, et al. (2008). "Association between findings on delayed gadolinium-enhanced magnetic resonance imaging of cartilage and future knee osteoarthritis." *Arthritis and Rheumatism* 58(6): 1727-1730.
- Papathanassiou, D., C. Bruna-Muraille, et al. (2009). "Single-photon emission computed tomography combined with computed tomography (SPECT/CT) in bone diseases." *Joint Bone Spine* 76(5): 474-480.
- Peterfy, C. G. and H. K. Genant (1996). "Emerging applications of magnetic resonance imaging in the evaluation of articular cartilage." *Radiologic Clinics of North America* 34(2): 195-213.
- Peterfy, C. G., A. Guermazi, et al. (2004). "Whole-organ magnetic resonance imaging score (WORMS) of the knee in osteoarthritis." *Osteoarthritis and Cartilage* 12(3): 177-190.
- Potter, H. G., B. R. Black, et al. (2009). "New techniques in articular cartilage imaging." *Clinics in Sports Medicine* 2009(28): 77-94.
- Qvistgaard, E., S. Torp-Pedersen, et al. (2006). "Reproducibility and inter-reader agreement of a scoring system for ultrasound evaluation of hip osteoarthritis." *Annals of the Rheumatic Diseases* 65(12): 1613-1619.
- Sampson, E. R., C. A. Beck, et al. (2011). "Establishment of an index with increased sensitivity for assessing murine arthritis." *Journal of Orthopedic Research* 29(8): 1145-1151.
- Sarikaya, I., A. Sarikaya, et al. (2001). "The role of single photon emission computed tomography in bone imaging." *Seminars in Nuclear Medicine* 31(1): 3-16.
- Siegel, B. A., R. L. Donovan, et al. (1976). "Skeletal uptake of ^{99m}Tc-diphosphanate in relation to local bone blood flow." *Radiology* 120: 121-123.
- Sofat, N. (2009). "Analysing the role of endogenous matrix molecules in the development of osteoarthritis." *International Journal of Experimental Pathology* 90: 463-479.
- Wakefield, R. J., P. V. Balint, et al. (2005). "Musculoskeletal ultrasound including definitions for ultrasonographic pathology." *Journal of Rheumatology* 32(12): 2485-2487.
- Walther, M., H. Harms, et al. (2002). "Synovial tissue of the hip at Power Doppler US: correlation between vascularity and Power Doppler US signal." *Radiology* 225: 225-231.
- Williams, A., L. Sharma, et al. (2005). "Delayed gadolinium-enhanced magnetic resonance imaging of cartilage in knee osteoarthritis: Findings at different radiographic stages of disease and relationship to malalignment." *Arthritis and Rheumatism* 52(11): 3528-3535.

- Williams, F. and T. Spector (2008). "Biomarkers in osteoarthritis." *Arthritis Research & Therapy* 10(1): 101.
- Wittoek, R., P. Carron, et al. (2010). "Structural and inflammatory sonographic findings in erosive and non-erosive osteoarthritis of the interphalangeal finger joints." *Annals of Rheumatology Disease* 69: 2173-2176.
- Wittoek, R., L. Jans, et al. (2010). "Reliability and construct validity of ultrasonography of soft tissue and destructive changes in erosive osteoarthritis of the interphalangeal finger joints: a comparison with MRI." *Annals of the Rheumatic Diseases* 70(2): 278-283.
- Xia, Y., T. Farquhar, et al. (1995). Self-diffusion monitors degraded cartilage." *Archives Of Biochemistry and Biophysics* 323(2): 323-328.
- Xia, Y., S. Zheng, et al. (2008). "Depth-dependent profiles of glycosaminoglycans in articular cartilage by μ MRI and histochemistry." *Journal of Magnetic Resonance Imaging* 28(1): 151-157.
- Yavorskyy, A., A. Hernandez-Santana, et al. (2008). "Detection of calcium phosphate crystals in the joint fluid of patients with osteoarthritis - analytical approaches and challenges." *Analyst* 133: 302-318.
- Yoon, C.-H., H.-S. Kim, et al. (2008). "Validity of the sonographic longitudinal sagittal image for assessment of the cartilage thickness in the knee osteoarthritis." *Clinical Rheumatology* 27(12): 1507-1516.
- Yoon, H. S., S. E. Kim, et al. (2005). "Correlation between ultrasonographic findings and the response to corticosteroid injection in pes anserinus tendinobursitis syndrome in knee osteoarthritis patients." *Journal of Korean Medical Science* 20: 109-112.
- Yu, S. W., S. M. Shaw, et al. (1999). "Radionuclide studies of articular cartilage in the early diagnosis of arthritis in the rabbit." *Annals of the Academy of Medicine, Singapore* 28(1): 44-48.
- Yu, W. K., J. M. Bartlett, et al. (1988). "Biodistribution of bis-[beta-(N, N-trimethylamino)ethyl]-selenide-75Se diiodide, a potential articular cartilage imaging agent." *International Journal of Radiation Applications and Instrumentation. Part B, Nuclear Medicine and Biology* 15(2): 229-230.
- Zanetti, M., E. Bruder, et al. (2000). "Bone marrow edema pattern in osteoarthritic knees: correlation between MR imaging and histologic findings." *Radiology* 200(215): 835-840.



Principles of Osteoarthritis- Its Definition, Character, Derivation and Modality-Related Recognition

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This volume addresses the nature of the most common form of arthritis in humans. If osteoarthritis is inevitable (only premature death prevents all of us from being afflicted), it seems essential to facilitate its recognition, prevention, options, and indications for treatment. Progress in understanding this disease has occurred with recognition that it is not simply a degenerative joint disease. Causative factors, such as joint malalignment, ligamentous abnormalities, overuse, and biomechanical and metabolic factors have been recognized as amenable to intervention; genetic factors, less so; with metabolic diseases, intermediate. Its diagnosis is based on recognition of overgrowth of bone at joint margins. This contrasts with overgrowth of bone at vertebral margins, which is not a symptomatic phenomenon and has been renamed spondylosis deformans. Osteoarthritis describes an abnormality of joints, but the severity does not necessarily produce pain. The patient and his/her symptoms need to be treated, not the x-ray.

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