Setting up distinctive outcome measures for each osteoarthritis phenotype

Jorge A. Roman-Blas, Lenny A. Mendoza-Torres, Raquel Largo and Gabriel Herrero-Beaumont

Abstract: Osteoarthritis (OA) is an evolving chronic joint disease with a huge global impact. Given the intricate nature of the etiopathogenesis and subsequent high heterogeneity in the clinical course of OA, it is crucial to discriminate between etiopathogenic endotypes and clinical phenotypes, especially in the early stages of the disease. In this sense, we propose that an OA phenotype should be properly assessed with a set of outcome measures including those specifically related to the main underlying pathophysiological mechanisms. Thus, each OA phenotype can be related to different and clinically meaningful outcomes. OA phenotyping would lead to an adequate patient stratification in well-designed clinical trials and the discovery of precise therapeutic approaches. A significant effort will be required in this field in light of inconclusive results of clinical trials of tissue-targeting agents for the treatment of OA.

Keywords: clinical trials, etiopathogenesis, osteoarthritis, outcome measures, phenotypes, therapeutic approaches

Received: 28 October 2019; revised manuscript accepted: 5 June 2020.

Introduction

Osteoarthritis (OA) is a very common and slowly progressive joint disease, which affects more than 300 million (15%) adults globally, particularly in aging populations. OA represents a leading cause of pain and chronic disability with a profound burden on the quality of life of patients and on public health systems. As aging, obesity and poor lifestyle increase in the world population, the burden of musculoskeletal diseases, particularly OA, rises greatly and could be even bigger than expected. As a matter of fact, musculoskeletal diseases are now the second most common cause of disability-adjusted life years (DALYs), and DALYs for OA increased by 104.9% from 1990 to 2016 worldwide. OA is also associated with increased rates of comorbidities, such as cardiovascular disease and diabetes mellitus, and an increased risk of cardiovascular disease-specific and all-cause mortality. In addition, the economic burden of OA is shown by high healthcare costs and high indirect costs.

Main etiopathogenic mechanisms in OA

Multiple pathophysiological mechanisms interacting in complex ways affect all joint structures, particularly articular cartilage, subchondral bone and synovial membrane at different time points throughout the long OA process. The imbalance between mechanical loading and its absorption by the articular cartilage causes damage in joint tissues. The predominance of catabolic over anabolic events leads to a progressive loss of glycosaminoglycan content and collagen network with a subsequent significant reduction of tensile strength and compliance. Main etiopathogenic processes include the degradation of cartilage extracellular matrix, increased high subchondral bone turnover and synovial inflammation. Overloading may drive these alterations on normal joint tissues, while in other circumstances they can be secondary to the action of average mechanical loading upon joint tissues with an altered structure. These early changes can occur due to genetic alterations, sex hormone deficiency, aging and other major factors such as metabolic imbalance and low-grade chronic systemic inflammation in the biology of join tissues.

Various types of cells present in joint tissues under mechanical stress overexpress receptors of the
innate immunity, namely toll-like receptors (TLRs). Tissue damage caused by overloading induce the release inside of the joint of a broad diversity of molecules, that is, hyaluronic acid, fibronectin fragments, small leucine-rich proteoglycans, collagen or cartilage oligomeric protein (COMP), which activate integrin receptors and the innate immune response, mainly the TLR2 and 4 mediated signalling pathways and complement system. On the other side, proinflammatory adipokines such as leptin, adiponectin, resistin and others are the effector molecules of joint damage caused by the interaction between metabolism imbalance and the immune system in OA. Not only does the association between OA and obesity occur by a direct overloading effect, but also by a chronic low-grade inflammation associated with obesity and metabolic syndrome. Furthermore, adipokines by their role in endothelial dysfunction and atherosclerosis may contribute to high mortality rates due to cardiovascular events in OA patients.

Therefore, mechanical stress, low-grade systemic inflammation and metabolic imbalance are main factors which play crucial roles on the onset and progression of OA. More importantly, these factors converge on the same etiopathogenic pathways whereby the chronic activation of innate immunity in chondrocytes, through TLR signalling, results in a robust activation of NF-κB, MAPK and PI3K dependent pathways. These signalling transduction cascades promote the production of pro-inflammatory cytokines, tissue-destructive enzymes and inflammatory-some components. The excess of glucose and/or lipids, the presence of crystals, as well as increased apoptosis also contribute to joint damage.

### Establishing OA phenotypes

Since OA is an evolving disease, the intricate nature of etiopathogenic events lead to a high heterogeneity in the clinical course and subsequent great difficulty on the development of an effective treatment for OA. In fact, although diverse candidate molecules for disease modifying OA drugs showed encouraging results in preclinical and early clinical studies, they fell short in achieving structural and clinical efficacy in phase III randomized clinical trials (RCTs). In this complex scenario, it is crucial to consider how to assess the efficacy of these drugs. What clinical symptoms or signs should be tracked to estimate the effects of candidate drugs? For instance, pain characteristics and severity over time can be chosen in knee OA. Notably, pain profile reflects the complexity of OA and its difficult assessment in RCTs. Indeed, the predominant joint tissue affected at a specific time expresses a particular type of pain in the early stages of OA, while in the advanced stages OA evolves towards a more uniform disease with persistent pain, and sometimes pain with neuropathic characteristics. Moreover, this picture becomes more complicated since silent periods have been observed during the OA process, which might explain the high rates of clinical improvement in some RCTs.

Based on very relevant molecular physiopathological mechanisms of the disease, and by differentiating aetiologies from risk factors, our group suggested to classify primary OA several years ago. Indeed, we proposed three OA subsets depending on the main underlying pathophysiological pathways: type I or genetically determined; type II, oestrogen hormone-dependent; and type III age-related. As a result of the interaction between these mechanisms and extra-articular risk factors in joint tissues, we further suggest four interchangeable clinical profiles –biomechanical, inflammatory, metabolic and osteoporotic may occur in OA patients during the early stages of the disease (Figure 1).

A significant effort has been also devoted in phenotyping OA for several other research groups. A total of 79 knee OA phenotypes were reported in the included studies of a recent systematic review. From such a variety of proposed phenotypes, which makes no sense at all, the authors identified six main clinical phenotypes: chronic pain, inflammatory, metabolic syndrome, bone and cartilage metabolism, mechanical overload and minimal joint disease. Their phenotype allocation was shown to be successful for 84% of cases with an overlap of 20%. Another systematic review identified that some characteristics such as pain sensitization, psychological distress, radiographic severity, body mass index (BMI), muscle strength, inflammation and comorbidities are associated with different clinical phenotypes in knee OA patients, whereas sex, obesity, other metabolic abnormalities, the pattern of cartilage damage and inflammation may determine distinct structural knee OA phenotypes.

Molecular biomarkers are expected to become useful tools to differentiate between subgroups of patients whose disease is triggered by specific main etiopathogenic mechanisms, proposed as ‘molecular endotypes’, and manifested by their
corresponding clinical phenotypes. Metabolomic studies in synovial fluid of human knees identified high inflammation in early and late OA, oxidative stress in late OA, or structural deterioration in early and late OA. Recently, a machine learning approach in a big dataset determined key variables that differentiate progression versus non-progression phenotypes in knee OA patients at 48 months. Baseline variables contributing to progression included bone marrow lesions, osteophytes, medial meniscal extrusion, and urine C-terminal cross-linked telopeptide type II collagen (uCTX-II), whereas the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, lateral meniscal extrusion and serum N-terminal pro-peptide of collagen IIA, were strongly associated with non-progression. Hence, the use of molecular biomarkers together with imaging, pain and function assessments may greatly help to identify distinct OA phenotypes, with the following progress in the design of more effective, stratified and individualized therapeutic strategies in OA.

At this point, it is crucial to distinguish phenotypes of outcomes. An OA phenotype is determined by either a single or combination of disease attributes that characterize a subgroup of patients sharing distinct underlying pathophysiological mechanisms. In turn, the outcome is defined as an event or measure in the study participants that is used to assess the effectiveness and/or safety of an intervention studied in clinical trials. Establishing different phenotypes by using the same outcomes would lead to erroneous interpretation having no practical utility. In this sense, we believe that each OA phenotype should be related to clinically meaningful outcomes, which will be different between OA phenotypes.

**Outcomes and endpoints according to knee OA phenotypes**

The identification of distinct profiles among OA patients will necessarily involve the use of a core set of outcome measures including clinical
variables, biological and imaging markers related to specific pathophysiological mechanisms involved in each clinical phenotype.

**Biomechanical OA**

The most important biomechanical contributors to the development and the progression of OA are overweight, joint malalignment, loss of meniscal function and ligament injury in the biomechanical phenotype. Thus, surrogates for mechanical stress such as weight and fat-free mass were strongly related to knee OA. Indeed, weight gain led to an increased progression of knee OA structural features, synovitis, patellofemoral bone marrow lesions (BMLs) and cartilage defects in overweight and obese women over 2.5 years. In contrast, more than 5% weight loss was associated with a slower increase in global cartilage T2 and deep layer cartilage T2 scores compared with stable weight after a follow up of 96 months. Furthermore, weight loss was also associated with improvements in the quality (increased proteoglycan content) and quantity (reduced thickness loss) on medial knee articular cartilage over 1 year.

Radiographic joint space width (JSW) or narrowing (JSN) is frequently used for OA diagnosis and

### Table 1. Outcome measurements for each OA phenotype

| OUTCOME MEASURES | OA PHENOTYPES |
|------------------|---------------|
|                  | Biomechanical | Osteoporotic | Metabolic | Inflammatory |
| **Conventional** | **Pain:**     | **Function:**| **BMI:**  | **MRI/US:** |
|                  | WOMAC-p       | WOAC-f       | KOOS-p    | Synovial inflammation |
|                  | KOOS-f        | HFP inflation |
| **Ongoing**      | MRI: Cartilage morphometry | MRI: Bone marrow lesions | MRI: Bone marrow lesions | MRIUS: Synovial inflammation |
|                  | X-ray: Malalignment | Osteophytes | Osteophytes | Joint effusion |
|                  | **Experimental** | **Bone scintigraphy:** | **Adipokine levels:** | **Biomarkers:** |
|                  | MRI: Biochemical alterations at joint tissues | SB texture | - Leptin levels | - s hs-CRP, sTLR4 |
|                  | MRI/US meniscal alterations | SB morphometry | - Omega-3 PUFA, DHA | - p, sf CD163, CD164 |
|                  | Biomarkers: | Subchondral BMD | **Fatty acid levels:** | **Carry over effect** |
|                  | uCTXII, sCOMP | SB remodelling | - HbA1c levels | ADA-criteria DM |
|                  | Muscle strength: | **Bone scintigraphy:** | **Metabolic syndrome** | Type 2 diabetes diagnostic criteria by the American Diabetes Association; BMI, bone mineral density; BMD, bone mass index; CT, computed tomography; CV, cardiovascular disease; DHA, docosahexaenoic acid; DXA, dual X-ray absorptiometry; HbA1c, hemoglobin A1c; HFP, Hoffa’s fat pad; hs-CRP, high sensitivity C-reactive protein; ICOAP, Intermittent and Constant Osteoarthritis Pain Questionnaire; JSN, joint space narrowing; JSW, joint space width; KOOS, Knee Injury and Osteoarthritis Outcome Score; KOOS-p, pain subscale of KOOS; KOOS-f, function subscale of KOOS; MRI, magnetic resonance imaging; OA, osteoarthritis; p,sf CD163, CD164, plasma and synovial fluid CD163 and CD164 levels; PET, positron emission tomography; PUFA, Polyunsaturated fatty acids; s,u CTXI, serum and urinary C-terminal telopeptide of type I collagen; SB, subchondral bone; sCOMP, serum cartilage oligomeric matrix protein; shsCRP, serum high-sensitivity C-reactive protein; sOsteocalcin, serum osteocalcin; SPECT, single-photon emission computed tomography; sTLR4, serum toll-like receptor 4; uCTXII, urinary C-terminal telopeptide of type II collagen; US, ultrasound; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; WOMAC-p, pain subscale of WOMAC. | - Hypertension |
|                  | - Quadriceps strength | **SPECT/CT, PET** | **Diabetes mellitus:** | - CV disease |
|                  | - Physical activity | **Biomarkers:** | - ADA-criteria DM | **Waist circumference** |
| **Carry over effect** | MRI/X ray: SB texture | s-u CTXI, s Osteocalcin | - HbA1c levels | - s hs-CRP, sTLR4 |
|                  | DXA: Subchondral BMD | | - Hypertension | - p, sf CD163, CD164 |
|                  | Bone scintigraphy: | SB remodelling | **Fatty acid levels:** | - CV disease |
|                  | SPECT/CT, PET | | - Omega-3 PUFA, DHA | **Waist circumference** |
|                  | Biomarkers: | | **Metabolic syndrome** | |
monitoring OA progression, and is still the only approved end point by regulatory bodies in clinical trials. However, the use of radiographic JSN exhibits some conspicuous limitations. It identifies patients with advanced OA who are more likely to be non-responsive to therapeutic interventions. It does not show correlation with the severity of clinical symptoms, being a poorly responsive endpoint that requires long and large clinical trials (2–4 years duration with about 1000 subjects) to determine therapy efficacy. Thus, radiographic JSN may impede drug development in OA.

On the other hand, only magnetic resonance imaging (MRI) currently provides a good assessment of all joint structures. MRI has displayed lesions in the tibiofemoral joint of middle aged and elderly people with radiographs not showing any OA feature, regardless of pain. Quantitative measurements of cartilage volume and thickness have been used as outcomes in intervention studies. Indeed, some systematic reviews have demonstrated that MRI biomarkers of OA hold concurrent and predictive validity, with good responsiveness and reliability. Data from a recent study with over 4 years of follow-up endorsed these previous results. Hence, the OARSI–FDA Working Group considers MRI as a suitable imaging tool to assess cartilage morphology in clinical trials assessing the development and progression of OA. In addition, MRI-assessed structural pathology has been also related with symptomatic knee OA. A 10.7 years follow-up study demonstrated that cartilage defects, BMLs and effusion-synovitis were associated with worse pain trajectories in older populations and knee OA patients. On the other hand, greater baseline pain, and fluctuating and persistent pain at the knee over 1 year predicted an increase of cartilage volume loss, incidence and progression of radiographic knee OA at 4 years follow-up.

Furthermore, a detailed analysis with cartilage segmentation in knee plates has reported subregional changes in different cohorts. Notably, cartilage thickening predominantly at the external subregion of medial femoral condyle was seen in individuals with pre-radiographic and radiographic knee OA (Kellgren/Lawrence stage 2). This finding may be consistent with cartilage swelling/hypertrophy described as a sign of early OA in vivo study. In turn, compositional MRI detects early biochemical alterations in joint tissues before morphologic changes can be seen in conventional MRI. As a matter of fact, local cartilage regions of interest had higher T2-values compared with the surrounding cartilage 4 years prior to lesion onset. Thus, MRI has become a valuable imaging modality for a better understanding of the natural history of OA and for the development of new therapies. Moreover, emerging hybrid imaging techniques including positron emission tomography (PET)/MRI and PET/computed tomography (CT) that evaluate joints with simultaneous assessment of morphological changes and metabolic activities show a great potential role in OA research.

The assessment of early OA changes in joint structures using dynamic imaging techniques also looks like an attractive approach to examine the outcome of joint loading. In this regard, the degree of ultrasound (US)-estimated medial meniscal subluxation correlated with radiographic medial tibiofemoral JSN, being remarkably higher in weight-bearing than in non-weight-bearing positions. Likewise, MRI studies showed that medial meniscal subluxation is significantly associated with cartilage volume loss, and both meniscal protrusion and meniscal root tears are very prevalent in patients with accelerated knee OA. In turn, malalignment has been strongly related with knee OA progression at 26-months follow-up. Frontal plane alignment was more strongly associated with tibiofemoral than patellofemoral OA worsening over 7 years. Nevertheless, patella alta correlated with the worsening of MRI-determined patellofemoral OA over 24 months. Malalignment and meniscal damage together may increase the risk of cartilage loss even more, likely due to the high dynamic load on local articular cartilage.

Biological markers aiming to detect very early OA changes in joint issues are being intensely studied. Both baseline urinary C-terminal telopeptide of type II collagen (uCTX-II) and urinary alpha isomerized version of collagen type I (uCTXIα) levels significantly predicted pain and structural worsening of knee OA over 48 months. High baseline serum cartilage oligomeric matrix protein (sCOMP) levels were associated with incident radiographic knee OA in two studies, one with an average 6.3 years follow-up and another with 10 years follow-up. In addition, a large scale meta-analysis described that uCTX-II levels are significantly associated with the risk of prevalence of hand, hip and knee OA progression and...
incidence of knee OA. A systematic review found strong evidence for uCTX-II level as a prognostic marker for knee OA progression and sCOMP level as a prognostic marker for incidence of knee and hip OA. These findings were confirmed by a longitudinal study that showed significant associations between uCTX-II and sCOMP levels and knee or hip OA progression at 5 years follow-up. However, a recent metaanalysis only revealed a moderate performance of sCOMP and uCTX-II for diagnosing knee or hip OA, although it concluded that sCOMP may predict OA progression. So far, none of the candidate biomarkers have shown to be sufficiently discriminative for diagnosis or prediction of progression in OA and have yet to be fully validated for acting as a surrogate outcome in OA.

Muscle strength also plays a relevant role in load distribution across a joint surface. Loss of quadriceps strength may reduce its shock-absorbing potential on the knee causing large dynamic loads on articular cartilage, and subsequent progressive cartilage degeneration. Indeed, quadriceps weakness increased the risk of worsening lateral patellofemoral cartilage damage at 7 years follow-up in women with or at risk of knee OA. In this regard, muscle torque may be used as a surrogate outcome for muscle capacity on protecting joints. The amount of physical activity, measured by a pedometer, was deleteriously related to knee OA progression at 2–5 years follow-up. Likewise, high and very low Physical Activity Scale for the Elderly (PASE) scores were associated with high progression of cartilage T2 measurements in asymptomatic middle-aged individuals over a period of 4 years. Furthermore, increasing levels of physical activity associated with high risk of knee OA have been observed in overweight and obese men after 96 months of follow-up. Long-term pain and function after treatment, known as the carry-over effect of an interventional agent, should be assessed. Remarkably, knee pain when using stairs has been described as the first symptom to appear in early OA, followed by pain when walking and standing. Furthermore, subjects who developed accelerated knee OA over 48 months apprised greater pain when walking and straightening the leg, and had difficulty in lying down compared with those who developed common knee OA. Subjects with the greatest functional impairment – WOMAC physical function scores between 40 and 68 – had an increased risk of undergoing total knee replacement over 30 months in a large cohort study of persons with or at high risk of symptomatic knee OA. In addition to X-rays, MRI, US, and potentially biological markers, these other outcome measurements may be useful options for conducting well-designed clinical trials in patients with biomechanical OA.

**Osteoporotic OA**

Greater prevalence of OA in women than men and the dramatic rise in OA prevalence among postmenopausal women, which are associated with the presence of oestrogen receptors in joint tissues, hint that OA is significantly related to sexual hormone status, particularly to oestrogen levels. Generalized involvement of joints with predominant node formation and signs of inflammation in interphalangeal joints of the hands have been described in postmenopausal women since the earliest studies of OA. A subset of middle-aged women who develop erosions associated with transient inflammation in the interphalangeal joints are characteristic of erosive OA. Lower levels of serum E2 were reported in postmenopausal women who developed radiographically defined knee OA. However, oestrogen replacement therapy has shown mixed results in OA, probably because of methodological flaws in the performed studies. Hence, oestrogen deficiency plays a conspicuous role in a distinctive OA, which develops in women during the early years following menopause.

In patients with this phenotype, increased remodelling and impaired structure of subchondral bone may play key roles in the development and progression of OA, responding to bone active drugs. These events can be assessed by imaging techniques such as digital X-ray, computerized tomography and MRI used in research studies, but technically difficult to handle at daily clinical practice. MRI studies have identified BMLs that are imaging features of OA with a characteristic signal pattern in subchondral bone. BMLs associated with OA correspond to fibrosis, necrosis, oedema and bleeding of fatty marrow as well as trabecular alterations on histopathology. BMLs, as well as cartilage defects and effusion-synovitis, were associated with worse pain trajectories over 10.7 years in older populations, particularly in those with radiographic knee OA. Notably, the size of BMLs significantly correlates with the progression of articular cartilage loss, the incidence of knee arthroplasty and pain fluctuations in patients with knee OA. Likewise, osteophytes
were independently associated with knee OA structural progression and the incidence of total knee replacement. Furthermore, in accord with the presence of osteophytes in MRI, OA can be classified in either hypertrophic or atrophic (osteoprotic) OA phenotypes. Therefore, BML volume and osteophytes arise as attractive potential outcomes for studying the development and progression of subchondral bone damage in OA and its response to therapeutic interventions.

In addition, subchondral trabecular bone texture has emerged as a promising imaging biomarker for knee OA. Changes at 12–18 months of MRI-assessed subchondral bone texture predicted radiographic knee OA progression at 36 months. Even radiographic subchondral trabecular bone texture predicted risk of radiographic and/or pain progression in individuals with knee OA at baseline and over 12 and 24 months. In contrast, the use of bone formation and resorption markers to assess subchondral bone turnover in OA has not been well established. So far, biomarkers such as type I collagen-degradation epitopes and osteocalcin have shown limited diagnostic potential.

The simultaneous use of dual X-ray absorptiometry (DXA), to assess subchondral bone mineral density (BMD) and bone scintigraphy to detect patients on high subchondral bone remodelling, arises as a reasonable approach in daily practice. In fact, a recent study showed that periarticular bone assessments including baseline and most rates of change in medial/lateral BMD and MRI-assessed trabecular morphometry in proximal tibia is associated with radiographic knee OA structural progression over 12–18 months. Likewise, baseline subchondral BMD positively predicted cartilage defect development at the medial tibial site. In turn, late-phase bone scintigraphy demonstrated that agent retention in the tibiofemoral compartment is associated with severity of knee symptoms. Furthermore, a (99m) Tc-DPD-SPECT/CT showed that elevated subchondral uptake is directly associated with the grade of cartilage lesions and with the Whole-Organ Magnetic Resonance Imaging Score (WORMS) sum in patients with knee OA. Scintigraphy would allow to assess the de novo rate of subchondral bone remodelling, thus acting as an early surrogate marker, whereas DXA would provide an index of accumulative effect therefore acting in some extent as a final outcome for subchondral bone status. Moreover, a study using a radioisotope with PET showed an increase of bone metabolism in the proximal femur of patients with symptomatic hip OA, suggesting that this method may detect early OA changes. However, several methodological issues in the study of OA subchondral bone should be addressed before these assessments may become suitable outcome measures for clinical trials in osteoporotic OA.

**Metabolic OA**

Metabolic syndrome components, high levels of proinflammatory adipokines, diabetes mellitus and cardiovascular events may notably contribute to the development and progression of joint damage in patients with metabolic OA. In this regard, metabolic syndrome was associated with hand OA, after adjustment for weight, whereas high abdominal circumference, hypertension, high fat consumption and self-reported diabetes mellitus were associated with early cartilage degradation measured with T2 relaxation times in knees of middle-aged subjects. Likewise, a recent study demonstrated that metabolic syndrome and low high-density lipoprotein (HDL) is related with medial tibial cartilage volume loss and increase of BML size during a mean follow-up period of 10.7 years. Both baseline leptin levels and change in leptin levels correlated with longitudinal cartilage thinning. Furthermore, baseline leptin levels were associated with the presence of osteophytes, synovitis and effusion, cartilage defects, BMLs and meniscal tears assessed by MRI 10 years later in middle-aged women. These findings suggest that leptin may play a relevant role in the maintenance of cartilage homeostasis, and thus hold great potential to become a valuable outcome measurement in metabolic OA. Furthermore, recent studies describe that serum leptin levels partially mediate the associations between osteoarthritis and adiposity, as assessed with BMI and percentage total body fat, as well as between knee OA and elevated BMI alone. Indeed, BMI has been shown to exert a major causal effect on the risk of OA, particularly at weight-bearing joints. Fatty acid levels have also been related to cartilage loss and synovitis. Indeed, a negative association was found between total omega-3 fatty acids or docosahexaenoic acid-specific omega-3 and patellofemoral cartilage loss. In contrast, omega-6 fatty acids and arachidonic acid were positively associated with synovitis. Diabetes mellitus has been described as a risk factor for OA progression and poor arthroplasty outcomes. Meta-analyses confirmed an association.
between diabetes mellitus and the development or presence of radiographic and symptomatic OA, although a recent systematic review concluded that little evidence supports this relationship. A longitudinal population-based study showed that diabetes mellitus predicts the development of severe OA undergoing hip or knee arthroplasty, and moreover, the probability of arthroplasty increased with the duration of diabetes mellitus. Accordingly, high haemoglobin A1c levels increased linearly with the risk of complications in total joint arthroplasty. Interestingly, medication-treated diabetes was not associated with the incidence of knee OA but independently reduced knee OA progression. High systolic blood pressure and pulse pressure were associated with increased incidence of radiographic knee OA, while treatment with ≥3 antihypertensive medications reduced it. Moreover, the presence of hypertension and diabetes mellitus was associated with bone loss at subchondral plate in knee OA.

Cardiovascular disease, particularly angina and congestive heart failure, was initially associated with prevalent OA in a population-based cross-sectional study. In a subsequent longitudinal analysis, OA was an independent predictor of cardiovascular disease, and, furthermore, the risk of cardiovascular disease was even higher among individuals with OA who underwent total joint replacements. On the other side, individuals with high cardiovascular risk were more likely to have OA-related arthroplasty up to a 30-year follow-up. In turn, the use of statins has been associated with a lower prevalence of generalized OA and with a more than 50% reduction in knee OA progression. Statin use was also associated with reduced risk of radiographic knee JSN progression in patients with nodal OA followed up annually over 8 years. The validation of these factors as outcomes would dramatically improve the detection of early stages of the disease, and thus modify its progression through appropriate therapeutic interventions in patients with metabolic OA.

**Inflammatory OA**

Severe local synovitis is developed by a subgroup of patients, in contrast of the chronic systemic low-grade inflammation seen in all subtypes of OA. Evaluation of synovial inflammation can be properly carried out by MRI and US. In fact, contrast-enhanced MRI offers a good assessment of the extent and degree of synovitis, whereas the presence of signal changes in Hoffa fat pad or joint effusion assessed on non-contrast-enhanced MRI can be considered as indirect markers of synovitis. MRI-detected synovial inflammation positively correlates with pain and radiographic progression in knee OA. Moreover, synovial tissue volume lessens following steroid therapy and rebounds in those whose pain relapses in knee OA. Histologic analysis of synovial biopsy specimens, as well as both contrast and non-contrast MRI studies of knee joints, have shown that mild-to-moderate synovial inflammation is associated with severe radiographic OA. Likewise, a further study demonstrated that contrast enhanced MRI-detected synovitis is strongly associated with radiographic severity and MRI-assessed widespread cartilage damage in knee OA.

Synovitis has been also associated with incident radiographic knee OA, specifically with a total synovitis score of 3 or higher on a 0–9 scale. Furthermore, effusion-synovitis and Hoffa-synovitis have been observed to strongly predict by 1–2 years the development of incident radiographic knee OA. This sense, a very recent study reported that effusion/synovitis preceded the development of accelerated knee OA by 2 years, boosting the chance for synovitis to become a prognostic outcome. Synovial hypertrophy, increased vascularity and synovial fluid can be also commonly detected with US in joints affected by OA. Signs of inflammation determined by US are more frequently seen in erosive OA hands than in nonerosive OA hands. Both US-assessed suprapatellar effusion and medial compartment synovitis were directly related with knee pain in motion, sitting and rest in patients with radiographic knee OA. Notably, US-detected effusion, as well as, severity of both radiographic damage and pain, were predictors of subsequent joint replacement over a 3-year follow-up. Thus, synovitis detected by US as an outcome measure also seems attractive for multicentre trials assessing OA in patients with inflammatory phenotypes. In turn, superolateral Hoffa’s fat pad (SHFP) oedema was associated with simultaneous cartilage damage, BMLs and osteophytes in lateral patella, and importantly predicted longitudinal patellar cartilage loss over 24 months. Hence, MRI-examined SHFP oedema may become an outcome measure for patellar OA.
Biomarkers that reflect systemic and synovial inflammation are being studied in OA. A meta-analysis found a significant association between serum levels of high sensitivity C-reactive protein (hs-CRP) and pain or discapacity in OA patients.\(^{135}\) Moreover, increased serum hs-CRP and IL-6 were associated with an increase in BML scores in patients with knee OA over 2 years.\(^{136,137}\) High plasma PGE2 and 15-HETE levels identified patients with symptomatic knee OA, and elevated levels of peripheral blood leukocyte IL-1\(\beta\), TNF\(\alpha\) and COX-2 gene expression determined a high risk of radiographic progression over 24 months in these patients.\(^{138}\) Similarly, plasma lipopolysaccharide binding protein and serum TLR4 were also associated with knee OA progression over 16–18 months.\(^{139}\) Synovial fluid (SF) biomarkers drive slightly higher expectations to reflect the local underlying molecular changes in knee OA. Indeed, SF IL-1\(\beta\) and IL-18 levels have been associated with OA severity and progression.\(^{140}\)

In the same way, high levels of inflammatory macrophages, CD163 and CD14, neutrophils, elastase and related markers (VEGF, MMP-3, TIMP-1, sICAM-1, sVCAM-1, and MCP-1) in SF and plasma were associated with an inflammatory subset of patients with knee OA that showed structural progression and severe pain.\(^{141,142}\) Nevertheless, as for other potential biomarkers, the role of inflammatory biomarkers for predicting structural damage in OA so far remains unclear, being necessary for more large scale, high-quality and homogenous studies. Hence, an appropriate assessment of synovitis features by MRI or US, particularly contrast-enhanced MRI, holds the potential for the development of useful outcomes and could be used in clinical trials of new drugs that target synovitis in OA patients with inflammatory phenotype. Finally, clinical trials in patients with inflammatory OA should also assess long-term pain and function after treatment (carry-over effect) of an interventional agent.\(^{61}\)

**Conclusion**

OA is an evolving chronic joint disease with a great global impact. The intricate nature of etiopathogenic events affecting all joint tissues lead to a high heterogeneity of the clinical course of OA. In this complex scenario, it becomes crucial to discriminate distinct etiopathogenic endotypes and clinical phenotypes, especially in the early stages of the disease. We propose establishing an OA phenotype that should comprise the usage of a set of distinctive outcome measures including those related to main pathophysiological mechanisms (Table 1). However, setting up OA phenotypes is highly challenging precisely because the complex etiopathogenesis and varied clinical manifestations throughout an evolving process can lead to the identification of multiple subsets of patients with no specific outcome measures and lacking clinical meaning. In this regard, the current proposal may contribute to better phenotyping of OA patients; therefore, it would lead to well-designed clinical trials and the discovery of precise therapeutic approaches for each OA phenotype. Hence, a significant effort will be required in this field, given the discordant results of clinical trials using tissue-targeting agents for the treatment of OA.

**Conflict of interest statement**

GH-B received grants from Novartis, Sandoz, Pfizer, Amgen, Mylan and Servier. GH-B and RL have a national patent on use of 6-shogaol for the treatment of osteoporosis and a national patent on use of osteostatin for the treatment of osteoarthritis. JAR-B and LAM-T report no conflict.
Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Instituto de Salud Carlos III, grants PI16/00065, PI16/00991, PI18/00261. This work is co-funded by Fondo Europeo de Desarrollo Regional (FEDER).

ORCID iDs
Jorge A. Roman-Blas https://orcid.org/0000-0003-1142-1946
Gabriel Herrero-Beaumont https://orcid.org/0000-0002-3241-991X

References
1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the global burden of disease study 2017. Lancet 2018; 392: 1789–1858.
2. Briggs AM, Woolf AD, Dreinhöfer K, et al. Reducing the global burden of musculoskeletal conditions. Bull World Health Organ 2018; 96: 366–368.
3. Calders P and Van Ginckel A. Presence of comorbidities and prognosis of clinical symptoms in knee and/or hip osteoarthritis: a systematic review and meta-analysis. Semin Arthritis Rheum 2018; 47: 805–813.
4. Kluzek S, Sanchez-Santos MT, Leyland KM, et al. Painful knee but not hand osteoarthritis is an independent predictor of mortality over 23 years follow-up of a population-based cohort of middle-aged women. Ann Rheum Dis 2016; 75: 1749–1756.
5. Zhao X, Shah D, Gandhi K, et al. Clinical, humanistic, and economic burden of osteoarthritis among noninstitutionalized adults in the United States. Osteoarthritis Cartilage 2019; 27: 1618–1626.
6. Castañeda S, Roman-Blas JA, Largo R, et al. Osteoarthritis: a progressive disease with changing phenotypes. Rheumatology (Oxford) 2014; 53: 1–3.
7. Jørgensen AEM, Kjær M and Heinemeier KM. The effect of aging and mechanical loading on the metabolism of articular cartilage. J Rheumatol 2017; 44: 410–417.
8. Francisco V, Ruiz-Fernández C, Pino J, et al. Adipokines: linking metabolic syndrome, the immune system, and arthritic diseases. Biochem Pharmacol 2019; 165: 196–206.
9. Herrero-Beaumont G, Pérez-Baos S, Sánchez-Pernaute O, et al. Targeting chronic innate inflammatory pathways, the main road to prevention of osteoarthritis progression. Biochem Pharmacol 2019; 165: 24–32.
10. Herrero-Beaumont G, Roman-Blas JA, Castañeda S, et al. Primary osteoarthritis no longer primary: three subsets with distinct etiological, clinical, and therapeutic characteristics. Semin Arthritis Rheum 2009; 39: 71–80.
11. Herrero-Beaumont G, Roman-Blas JA, Bruyère O, et al. Clinical settings in knee osteoarthritis: pathophysiology guides treatment. Maturitas 2017; 96: 54–57.
12. Dell’Isola A, Allan R, Smith SL, et al. Identification of clinical phenotypes in knee osteoarthritis: a systematic review of the literature. BMC Musculoskelet Disord 2016; 17: 425.
13. Dell’Isola A and Steultjens M. Classification of patients with knee osteoarthritis in clinical phenotypes: data from the osteoarthritis initiative. PLoS One 2018; 13: e0191045.
14. Deveza LA, Melo L, Yamato TP, et al. Knee osteoarthritis phenotypes and their relevance for outcomes: a systematic review. Osteoarthritis Cartilage 2017; 25: 1926–1941.
15. Mobasheri A, van Spil WE, Budd E, et al. Molecular taxonomy of osteoarthritis for patient stratification, disease management and drug development: biochemical markers associated with emerging clinical phenotypes and molecular endotypes. Curr Opin Rheumatol 2019; 31: 80–89.
16. Carlson AK, Rawle RA, Wallace CW, et al. Characterization of synovial fluid metabolomics phenotypes of cartilage morphological changes associated with osteoarthritis. Osteoarthritis Cartilage 2019; 27: 1174–1184.
17. Nelson AE, Fang F, Arbeeva L, et al. A machine learning approach to knee osteoarthritis phenotyping: data from the FNIH biomarkers consortium. Osteoarthritis Cartilage 2019; 27: 994–1001.
18. Visser AW, de Mutsert R, le Cessie S, et al. The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study. Ann Rheum Dis 2015; 74: 1842–1847.
19. Landsmeer MLA, de Vos BC, van der, Plas P, et al. Effect of weight change on progression of
knee OA structural features assessed by MRI in overweight and obese women. *Osteoarthritis Cartilage* 2018; 26: 1666–1674.

20. Gersing AS, Schwager BJ, Nevitt MC, *et al.* Weight loss regimen in obese and overweight individuals is associated with reduced cartilage degeneration: 96-month data from the osteoarthritis initiative. *Osteoarthritis Cartilage* 2019; 27: 863–870.

21. Anandacoomarasamy A, Leibman S, Smith G, *et al.* Weight loss in obese people has structure-modifying effects on medial but not on lateral knee articular cartilage. *Ann Rheum Dis* 2012; 71: 26–32.

22. Eckstein F, Kwoh CK and Link TM. Imaging research results from the osteoarthritis initiative (OAI): a review and lessons learned 10 years after start of enrolment. *Ann Rheum Dis* 2014; 73: 1289–1300.

23. Roemer FW, Kwoh CK, Hayashi D, *et al.* The role of radiography and MRI for eligibility assessment in DMOAD trials of knee OA. *Nat Rev Rheumatol* 2018; 14: 372–380.

24. Hayashi D, Roemer FW and Guermazi A. Recent advances in research imaging of osteoarthritis with focus on MRI, ultrasound and hybrid imaging. *Clin Exp Rheumatol* 2018; 36(Suppl. 114): 43–52.

25. Guermazi A, Niu J, Hayashi D, *et al.* Prevalence of abnormalities in knees detected by MRI in adults without knee osteoarthritis: population based observational study (Framingham Osteoarthritis Study). *BMJ* 2012; 345: e5339.

26. Hunter DJ, Zhang W, Conaghan PG, *et al.* Systematic review of the concurrent and predictive validity of MRI biomarkers in OA. *Osteoarthritis Cartilage* 2011; 19: 557–588.

27. Hunter DJ, Zhang W, Conaghan PG, *et al.* Responsiveness and reliability of MRI in knee osteoarthritis: a meta-analysis of published evidence. *Osteoarthritis Cartilage* 2011; 19: 589–605.

28. Wirth W, Hunter DJ, Nevitt MC, *et al.* Predictive and concurrent validity of cartilage thickness change as a marker of knee osteoarthritis progression: data from the osteoarthritis initiative. *Osteoarthritis Cartilage* 2017; 25: 2063–2071.

29. Conaghan PG, Hunter DJ, Maillefert JP, *et al.* Summary and recommendations of the OARSI FDA osteoarthritis assessment of structural change working group. *Osteoarthritis Cartilage* 2011; 19: 606–610.

30. Pan F, Tian J, Aitken D, *et al.* Predictors of pain severity trajectory in older adults: a 10.7-year follow-up study. *Osteoarthritis Cartilage* 2018; 26: 1619–1626.

31. Wang Y, Teichtahl AJ, Abram F, *et al.* Knee pain as a predictor of structural progression over 4 years: data from the osteoarthritis initiative, a prospective cohort study. *Arthritis Res Ther* 2018; 20: 250.

32. Pelletier JP, Raynauld JP, Berthiaume MJ, *et al.* Risk factors associated with the loss of cartilage volume on weight-bearing areas in knee osteoarthritis patients assessed by quantitative magnetic resonance imaging: a longitudinal study. *Arthritis Res Ther* 2007; 9: R74.

33. Eckstein F, Yang M, Guermazi A, *et al.* Reference values and Z-scores for subregional femorotibial cartilage thickness—results from a large population-based sample (Framingham) and comparison with the non-exposed osteoarthritis initiative reference cohort. *Osteoarthritis Cartilage* 2010; 18: 1275–1283.

34. Schaefer LF, Sury M, Yin M, *et al.* Quantitative measurement of medial femoral knee cartilage volume - analysis of the OA biomarkers consortium FNIH study cohort. *Osteoarthritis Cartilage* 2017; 25: 1107–1113.

35. Frobell RB, Nevitt MC, Hudelmaier M, *et al.* Femorotibial subchondral bone area and regional cartilage thickness: a cross-sectional description in healthy reference cases and various radiographic stages of osteoarthritis in 1,003 knees from the osteoarthritis initiative. *Arthritis Care Res (Hoboken)* 2010; 62: 1612–1623.

36. Calvo E, Palacios I, Delgado E, *et al.* Histopathological correlation of cartilage swelling detected by magnetic resonance imaging in early experimental osteoarthritis. *Osteoarthritis Cartilage* 2004; 12: 878–886.

37. Li X and Roemer FW. Compositional changes predict morphologic cartilage lesion development - are we one step closer to clinical translation of quantitative MRI? *Osteoarthritis Cartilage* 2019; 27: 723–725.

38. MacKay JW, Low SBL, Smith TO, *et al.* Systematic review and meta-analysis of the reliability and discriminative validity of cartilage compositional MRI in knee osteoarthritis. *Osteoarthritis Cartilage* 2018; 26: 1140–1152.

39. Kretzschmar M, Nevitt MC, Schwager BJ, *et al.* Spatial distribution and temporal progression of T2 relaxation time values in knee cartilage prior to the onset of cartilage lesions - data from
the osteoarthritis initiative (OAI). *Osteoarthritis Cartilage* 2019; 27: 737–745.

40. Acebes C, Romero FI, Contreras MA, et al. Dynamic ultrasound assessment of medial meniscal subluxation in knee osteoarthritis. *Rheumatology (Oxford)* 2013; 52: 1443–1447.

41. Naredo E, Cabero F, Palop MJ, et al. Ultrasonographic findings in knee osteoarthritis: a comparative study with clinical and radiographic assessment. *Osteoarthritis Cartilage* 2005; 13: 568–574.

42. Berthiaume MJ, Raynauld JP, Martel-Pelletier J, et al. Meniscal tear and extrusion are strongly associated with progression of symptomatic knee osteoarthritis as assessed by quantitative magnetic resonance imaging. *Ann Rheum Dis* 2005; 64: 556–563.

43. Foreman SC, Neumann J, Joseph GB, et al. Longitudinal MRI structural findings observed in accelerated knee osteoarthritis: data from the osteoarthritis initiative. *Skeletal Radiol* 2019; 48: 1949–1959.

44. Eckstein F, Wirth W, Hudelmaier M, et al. Patterns of femorotibial cartilage loss in knees with neutral, varus, and valgus alignment. *Arthritis Rheum* 2008; 59: 1563–1570.

45. Macri EM, Felson DT, Ziegler ML, et al. The association of frontal plane alignment to MRI-defined worsening of patellofemoral osteoarthritis: the MOST study. *Osteoarthritis Cartilage* 2019; 27: 459–467.

46. Haj-Mirzaian A, Guermazi A, Pishgar F, et al. Association of patella alta with worsening of patellofemoral osteoarthritis-related structural damage: data from the osteoarthritis initiative. *Osteoarthritis Cartilage* 2019; 27: 278–285.

47. Bennell KL, Bowles KA, Wang Y, et al. Higher dynamic medial knee load predicts greater cartilage loss over 12 months in medial knee osteoarthritis. *Ann Rheum Dis* 2011; 70: 1770–1774.

48. Kraus VB, Collins JE, Hargrove D, et al. Predictive validity of biochemical biomarkers in knee osteoarthritis: data from the FNIH OA Biomarkers Consortium. *Ann Rheum Dis* 2017; 76: 186–195.

49. Golightly YM, Marshall SW, Kraus VB, et al. Biomarkers of incident radiographic knee osteoarthritis: do they vary by chronic knee symptoms? *Arthritis Rheum* 2011; 63: 2276–2283.

50. Blumenfeld O, Williams FM, Hart DJ, et al. Association between cartilage and bone biomarkers and incidence of radiographic knee osteoarthritis (RKOA) in UK females: a prospective study. *Osteoarthritis Cartilage* 2013; 21: 923–929.

51. Valdes AM, Meulenbelt I, Chassaing E, et al. Large scale meta-analysis of urinary C-terminal telopeptide, serum cartilage oligomeric protein and matrix metalloprotease degraded type II collagen and their role in prevalence, incidence and progression of osteoarthritis. *Osteoarthritis Cartilage* 2014; 22: 683–689.

52. Hosnijeh FS, Runhaar J, van Meurs JB, et al. Biomarkers for osteoarthritis: can they be used for risk assessment? A systematic review. *Maturitas* 2015; 82: 36–49.

53. Hosnijeh FS, Siebuhr AS, Uitterlinden AG, et al. Association between biomarkers of tissue inflammation and progression of osteoarthritis: evidence from the Rotterdam study cohort. *Arthritis Res Ther* 2016; 18: 81.

54. Hao HQ, Zhang JF, He QQ, et al. Cartilage oligomeric matrix protein, C-terminal cross-linking telopeptide of type II collagen, and matrix metalloproteinase-3 as biomarkers for knee and hip osteoarthritis (OA) diagnosis: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 2019; 27: 726–736.

55. Hosnijeh FS, Biemer-Zeinsstra SM and Bay-Jensen AC. Osteoarthritis year in review 2018: biomarkers (biochemical markers). *Osteoarthritis Cartilage* 2019; 27: 412–423.

56. Bennell KL, Wrigley TV, Hunt MA, et al. Update on the role of muscle in the genesis and management of knee osteoarthritis. *Rheum Dis Clin North Am* 2013; 39: 145–176.

57. Culvenor AG, Segal NA, Guermazi A, et al. Sex-specific influence of quadriceps weakness on worsening patellofemoral and tibiofemoral cartilage damage: a prospective cohort study. *Arthritis Care Res (Hoboken)* 2019; 71: 1360–1365.

58. Doré DA, Winzenberg TM, Ding C, et al. The association between objectively measured physical activity and knee structural change using MRI. *Ann Rheum Dis* 2013; 72: 1170–1175.

59. Lin W, Alizai H, Joseph GB, et al. Physical activity in relation to knee cartilage T2 progression measured with 3 T MRI over a period of 4 years: data from the osteoarthritis initiative. *Osteoarthritis Cartilage* 2013; 21: 1558–1566.

60. Soutakbar H, Lamb SE and Silman AJ. The different influence of high levels of physical activity on the incidence of knee OA in
overweight and obese men and women—a gender-specific analysis. Osteoarthritis Cartilage 2019; 27: 1430–1436.

61. Navarro-Sarabia F, Coronel P, Collantes E, et al. A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. Ann Rheum Dis 2011; 70: 1957–1962.

62. Hensor EM, Dube B, Kingsbury SR, et al. Toward a clinical definition of early osteoarthritis: onset of patient-reported knee pain begins on stairs. Data from the osteoarthritis initiative. Arthritis Care Res (Hoboken) 2015; 67: 40–47.

63. Davis J, Eaton CB, Lo GH, et al. Knee symptoms among adults at risk for accelerated knee osteoarthritis: data from the osteoarthritis initiative. Clin Rheumatol 2017; 36: 1083–1089.

64. Wise BL, Niu J, Felson DT, et al. Functional impairment is a risk factor for knee replacement in the multicenter osteoarthritis study. Clin Orthop Relat Res 2015; 473: 2505–2513.

65. Srikanth VK, Fryer JL, Zhai G, et al. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. Osteoarthritis Cartilage 2005; 13: 769–781.

66. Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum 1998; 41: 778–799.

67. Wood P. Age and the rheumatic diseases. In: Bennett PH and Wood PH (eds) Population studies of the rheumatic diseases. 4th ed. Amsterdam: Excerpta Medica, 1982, pp. 26–37.

68. Nadkar MY, Samant RS, Vaidya SS, et al. Relationship between osteoarthritis of knee and menopause. J Assoc Physicians India 1999; 47: 1161–1163.

69. Prieto-Alhambra D, Judge A, Javaid MK, et al. Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. Ann Rheum Dis 2014; 73: 1659–1664.

70. Ushiyama T, Ueyama H, Inoue K, et al. Expression of genes for estrogen receptors alpha and beta in human articular chondrocytes. Osteoarthritis Cartilage 1999; 7: 560–566.

71. Braidman IP, Hainey L, Batra G, et al. Localization of estrogen receptor beta protein expression in adult human bone. J Bone Miner Res 2001; 16: 214–220.

72. Dietrich W, Haitel A, Holzer G, et al. Estrogen receptor-beta is the predominant estrogen receptor subtype in normal human synovia. J Soc Gynecol Invest 2006; 13: 512–517.

73. Sciore P, Frank CB and Hart DA. Identification of sex hormone receptors in human and rabbit ligaments of the knee by reverse transcription-polymerase chain reaction: evidence that receptors are present in tissue from both male and female subjects. J Orthop Res 1998; 16: 604–610.

74. Kahlert S, Grohé C, Karas RH, et al. Effects of estrogen on skeletal myoblast growth. Biochem Biophys Res Commun 1997; 232: 373–378.

75. Roman-Blas JA, Castañeda S, Largo R, et al. Osteoarthritis associated with estrogen deficiency. Arthritis Res Ther 2009; 11: 241

76. Kellgren JH and Moore R. Generalized osteoarthritis and Heberden’s nodes. Br Med J 1952; 1: 181–187.

77. Felson DT and Nevitt MC. The effects of estrogen on osteoarthritis. Curr Opin Rheumatol 1998; 10: 269–272.

78. Punzi L, Ramonda R and Sfriso P. Erosive osteoarthritis. Best Pract Res Clin Rheumatol 2004; 18: 739–758.

79. Sowers MR, McConnell D, Jannausch M, et al. Estradiol and its metabolites and their association with knee osteoarthritis. Arthritis Rheum 2006; 54: 2481–2487.

80. Herrero-Beaumont G, Roman-Blas JA, Largo R, et al. Bone mineral density and joint cartilage: four clinical settings of a complex relationship in osteoarthritis. Ann Rheum Dis 2011; 70: 1523–1525.

81. Xu L, Hayashi D, Roemer FW, et al. Magnetic resonance imaging of subchondral bone marrow lesions in association with osteoarthritis. Semin Arthritis Rheum 2012; 42: 105–118.

82. Barr AJ, Campbell TM, Hopkinson D, et al. A systematic review of the relationship between subchondral bone features, pain and structural pathology in peripheral joint osteoarthritis. Arthritis Res Ther 2015; 17: 228.

83. Yu D, Xu J, Liu F, et al. Subchondral bone changes and the impacts on joint pain and articular cartilage degeneration in osteoarthritis. Clin Exp Rheumatol 2016; 34: 929–934.

84. Driban JB, Price L, Lo GH, et al. Evaluation of bone marrow lesion volume as a knee osteoarthritis biomarker—longitudinal relationships with pain and structural changes:
data from the osteoarthritis initiative. *Arthritis Res Ther* 2013; 15: R112.

85. MacKay JW, Kapoor G, Driban JB, *et al.* Association of subchondral bone texture on magnetic resonance imaging with radiographic knee osteoarthritis progression: data from the osteoarthritis initiative Bone Ancillary Study. *Eur Radiol* 2018; 28: 4687–4695.

86. Kraus VB, Collins JE, Charles HC, *et al.* Predictive validity of radiographic trabecular bone texture in knee osteoarthritis: the Osteoarthritis Research Society International/Foundation for the National Institutes of Health Osteoarthritis Biomarkers Consortium. *Arthritis Rheumatol* 2018; 70: 80–87.

87. Bihlet AR, Byrjalsen I, Bay-Jensen AC, *et al.* Associations between biomarkers of bone and cartilage turnover, gender, pain categories and radiographic severity in knee osteoarthritis. *Arthritis Res Ther* 2019; 21: 203.

88. Roman-Blas JA, Castañeda S, Largo R, *et al.* An OA phenotype may obtain major benefit from bone-acting agents. *Semin Arthritis Rheum* 2014; 43: 421–428.

89. Lo GH, Schneider E, Driban JB, *et al.* Periarticular bone predicts knee osteoarthritis progression: data from the osteoarthritis initiative. *Semin Arthritis Rheum* 2018; 48: 155–161.

90. Doré D, Quinn S, Ding C, *et al.* Subchondral bone and cartilage damage: a prospective study in older adults. *Arthritis Rheumatol* 2010; 62: 1967–1973.

91. Kraus VB, McDaniel G, Worrell TW, *et al.* Association of bone scintigraphic abnormalities with knee malalignment and pain. *Ann Rheum Dis* 2009; 68: 1673–1679.

92. Maas O, Joseph GB, Sommer G, *et al.* Association between cartilage degeneration and subchondral bone remodeling in patients with knee osteoarthritis comparing MRI and (99m) Tc-DPD-SPECT/CT. *Osteoarthritis Cartilage* 2015; 23: 1713–1720.

93. Temmerman OP, Raijmakers PG, Kloet R, *et al.* In vivo measurements of blood flow and bone metabolism in osteoarthritis. *Rheumatol Int* 2013; 33: 959–963.

94. Jungmann PM, Kraus MS, Alizai H, *et al.* Association of metabolic risk factors with cartilage degradation assessed by T2 relaxation time at the knee: data from the osteoarthritis initiative. *Arthritis Care Res (Hoboken)* 2013; 65: 1942–1950.

95. Pan F, Tian J, Mattap SM, *et al.* Association between metabolic syndrome and knee structural change on MRI. *Rheumatology (Oxford)* 2020; 59: 185–193.

96. Stannus OP, Cao Y, Antony B, *et al.* Cross-sectional and longitudinal associations between circulating leptin and knee cartilage thickness in older adults. *Ann Rheum Dis* 2015; 74: 82–88.

97. Karvonen-Gutierrez CA, Harlow SD, Jacobson J, *et al.* The relationship between longitudinal serum leptin measures and measures of magnetic resonance imaging-assessed knee joint damage in a population of mid-life women. *Ann Rheum Dis* 2014; 73: 883–889.

98. Kroon FPB, Veenbrink AI, de Mutsert R, *et al.* The role of leptin and adiponectin as mediators in the relationship between adiposity and hand and knee osteoarthritis. *Osteoarthritis Cartilage* 2019; 27: 1761–1767.

99. Fowler-Brown A, Kim DH, Shi L, *et al.* The mediating effect of leptin on the relationship between body weight and knee osteoarthritis in older adults. *Arthritis Rheumatol* 2015; 67: 169–175.

100. Hindy G, Åkesson KE, Melander O, *et al.* Cardiometabolic polygenic risk scores and osteoarthritis outcomes: a Mendelian Randomization Study using data from the Malmö Diet and Cancer Study and the UK Biobank. *Arthritis Rheumatol* 2019; 71: 925–934.

101. Funck-Brentano T, Nethander M, Movérare-Skritic S, *et al.* Causal factors for knee, hip, and hand osteoarthritis: a Mendelian Randomization Study in the UK Biobank. *Arthritis Rheumatol* 2019; 71: 1634–1641.

102. Baker KR, Matthan NR, Lichtenstein AH, *et al.* Association of plasma n-6 and n-3 polyunsaturated fatty acids with synovitis in the knee: the MOST study. *Osteoarthritis Cartilage* 2012; 20: 382–387.

103. Veronese N, Cooper C, Register J-Y, *et al.* Type 2 diabetes mellitus and osteoarthritis. *Semin Arthritis Rheum* 2019; 49: 9–19.

104. Williams MF, London DA, Husni EM, *et al.* Type 2 diabetes and osteoarthritis: a systematic review and meta-analysis. *J Diabetes Complications* 2016; 30: 944–950.

105. Louati K, Vidal C, Berenbaum F, *et al.* Association between diabetes mellitus and osteoarthritis: systematic literature review and meta-analysis. *RMD Open* 2015; 1: e000077.

106. Dawson LP, Fairley JL, Papandony MC, *et al.* Is abnormal glucose tolerance or diabetes a risk factor for knee, hip, or hand osteoarthritis? A systematic review. *Semin Arthritis Rheum* 2018; 48: 176–189.
107. Schett G, Kleyer A, Perricone C, et al. Diabetes is an independent predictor for severe osteoarthritis: results from a longitudinal cohort study. *Diabetes Care* 2013; 36: 403–409.

108. Harris AH, Bowe TR, Gupta S, et al. Hemoglobin A1C as a marker for surgical risk in diabetic patients undergoing total joint arthroplasty. *J Arthroplasty* 2013; 28(Suppl. 8): 25–29.

109. Shirinsky IV and Shirinsky VS. Effects of medication-treated diabetes on incidence and progression of knee osteoarthritis: a longitudinal analysis of the osteoarthritis initiative data. *Rheumatol Int* 2017; 37: 983–991.

110. Lo GH, McAlindon TE, Katz JN, et al. Systolic and pulse pressure associate with incident knee osteoarthritis: data from the osteoarthritis initiative. *Clin Rheumatol* 2017; 36: 2121–2128.

111. Wen CY, Chen Y, Tang HL, et al. Bone loss at subchondral plate in knee osteoarthritis patients with hypertension and type 2 diabetes mellitus. *Osteoarthritis Cartilage* 2013; 21: 1716–1723.

112. Rahman MM, Kopec JA, Cibere J, et al. The relationship between osteoarthritis and cardiovascular disease in a population health survey: a cross-sectional study. *BMJ Open* 2013; 3: e002624.

113. Rahman MM, Kopec JA, Anis AH, et al. Risk of cardiovascular disease in patients with osteoarthritis: a prospective longitudinal study. *Arthritis Care Res (Hoboken)* 2013; 65: 1951–1958.

114. Kadam UT, Holmberg A, Blagojevic M, et al. Risk factors for cardiovascular disease and future osteoarthritis-related arthroplasty: a population-based cohort study in men and women from Malmö, Sweden. *Scand J Rheumatol* 2011; 40: 478–485.

115. Valdes AM, Zhang W, Muir K, et al. Use of statins is associated with a lower prevalence of generalised osteoarthritis. *Ann Rheum Dis* 2014; 73: 943–945.

116. Clockaerts S, Van Osch GJ, Bastiaansen-Jenniskens YM, et al. Statin use is associated with reduced incidence and progression of knee osteoarthritis in the Rotterdam study. *Ann Rheum Dis* 2012; 71: 642–647.

117. Haj-Mirzaian A, Mohajer B, Guermazi A, et al. Statin use and knee osteoarthritis outcome measures according to the presence of Heberden nodes: results from the osteoarthritis initiative. *Radiology* 2019; 293: 396–404.

118. Wang X, Hunter DJ, Jin X, et al. The importance of synovial inflammation in osteoarthritis: current evidence from imaging assessments and clinical trials. *Osteoarthritis Cartilage* 2018; 26: 165–174.

119. Mathiesen A and Conaghan PG. Synovitis in osteoarthritis: current understanding with therapeutic implications. *Arthritis Res Ther* 2017; 19: 18.

120. Wang X, Blizzard L, Halliday A, et al. Association between MRI-detected knee joint regional effusion-synovitis and structural changes in older adults: a cohort study. *Ann Rheum Dis* 2016; 75: 519–525.

121. Collins JE, Losina E, Nevitt MC, et al. Semiquantitative imaging biomarkers of knee osteoarthritis progression: data from the Foundation for the National Institutes of Health Osteoarthritis Biomarkers Consortium. *Arthritis Rheumatol* 2016; 68: 2422–2431.

122. O’Neill TW, Parkes MJ, Maricar N, et al. Synovial tissue volume: a treatment target in knee osteoarthritis (OA). *Ann Rheum Dis* 2016; 75: 84–90.

123. Krasnokutsky S, Belitskaya-Lévy I, Bencardino J, et al. Quantitative magnetic resonance imaging evidence of synovial proliferation is associated with radiographic severity of knee osteoarthritis. *Arthritis Rheum* 2011; 63: 2983–2991.

124. Guermazi A, Hayashi D, Roemer FW, et al. Synovitis in knee osteoarthritis assessed by contrast-enhanced magnetic resonance imaging (MRI) is associated with radiographic tibiofemoral osteoarthritis and MRI-detected widespread cartilage damage: the MOST study. *J Rheumatol* 2014; 41: 501–508.

125. Felson DT, Niu J, Neogi T, et al. Synovitis and the risk of knee osteoarthritis: the MOST Study. *Osteoarthritis Cartilage* 2016; 24: 458–464.

126. Atukorala I, Kwoh CK, Guermazi A, et al. Synovitis in knee osteoarthritis: a precursor of disease? *Ann Rheum Dis* 2016; 75: 390–395.

127. Roemer FW, Kwoh CK, Hannon MJ, et al. What comes first? Multitissue involvement leading to radiographic osteoarthritis: magnetic resonance imaging-based trajectory analysis over four years in the osteoarthritis initiative. *Arthritis Rheumatol* 2015; 67: 2085–2096.

128. Harkey MS, Davis JE, Lu B, et al. Early pre-radiographic structural pathology precedes the onset of accelerated knee osteoarthritis. *BMC Musculoskelet Disord* 2019; 20: 241.

129. Keen HI, Wakefield R and Conaghan PG. Optimising ultrasonography in rheumatology. *Clin Exp Rheumatol* 2014; 32(S Suppl. 85): S13–16.
130. Kortekaas MC, Kwok W-Y, Reijnierse M, et al. Brief report: association of inflammation with development of erosions in patients with hand osteoarthritis: a prospective ultrasonography study. *Arthritis Rheumatol* 2016; 68: 392–397.

131. Wu PT, Shao CJ, Wu KC, et al. Pain in patients with equal radiographic grades of osteoarthritis in both knees: the value of gray scale ultrasound. *Osteoarthritis Cartilage* 2012; 20: 1507–1513.

132. Chan KK, Sit RW, Wu RW, et al. Clinical, radiological and ultrasonographic findings related to knee pain in osteoarthritis. *PLoS One* 2014; 9: e92901.

133. Conaghan PG, D’Agostino MA, Le Bars M, et al. Clinical and ultrasonographic predictors of joint replacement for knee osteoarthritis: results from a large, 3-year, prospective EULAR study. *Ann Rheum Dis* 2010; 69: 644–647.

134. Haj-Mirzaian A, Guermazi A, Hafezi-Nejad N, et al. Superolateral Hoffa’s fat pad (SHFP) oedema and patellar cartilage volume loss: quantitative analysis using longitudinal data from the Foundation for the National Institute of Health (FNIH) Osteoarthritis Biomarkers Consortium. *Eur Radiol* 2018; 28: 4134–4145.

135. Jin X, Beguerie JR, Zhang W, et al. Circulating C reactive protein in osteoarthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2015; 74: 703–710.

136. Zhu Z, Jin X, Wang B, et al. Cross-sectional and longitudinal associations between serum levels of high-sensitivity C-reactive protein, knee bone marrow lesions, and knee pain in patients with knee osteoarthritis. *Arthritis Care Res (Hoboken)* 2016; 68: 1471–1477.

137. Zhu Z, Otahal P, Wang B, et al. Cross-sectional and longitudinal associations between serum inflammatory cytokines and knee bone marrow lesions in patients with knee osteoarthritis. *Osteoarthritis Cartilage* 2017; 25: 499–505.

138. Attur M, Krasnokutsky S, Statnikov A, et al. Low-grade inflammation in symptomatic knee osteoarthritis: prognostic value of inflammatory plasma lipids and peripheral blood leukocyte biomarkers. *Arthritis Rheumatol* 2015; 67: 2905–2915.

139. Huang ZY, Perry E, Huebner JL, et al. Biomarkers of inflammation - LBP and TLR-predict progression of knee osteoarthritis in the DOXY clinical trial. *Osteoarthritis Cartilage* 2018; 26: 1658–1665.

140. Denoble AE, Huffman KM, Stabler TV, et al. Uric acid is a danger signal of increasing risk for osteoarthritis through inflammasome activation. *Proc Natl Acad Sci USA* 2011; 108: 2088–2093.

141. Daghestani HN, Pieper CF and Kraus VB. Soluble macrophage biomarkers indicate inflammatory phenotypes in patients with knee osteoarthritis. *Arthritis Rheumatol* 2015; 67: 956–965.

142. Haraden CA, Huebner JL, Hsueh MF, et al. Synovial fluid biomarkers associated with osteoarthritis severity reflect macrophage and neutrophil related inflammation. *Arthritis Res Ther* 2019; 21: 146.

143. Emery CA, Whittaker JL, Mahmoudian A, et al. Establishing outcome measures in early knee osteoarthritis. *Nat Rev Rheumatol* 2019; 15: 438–448.

144. Smith TO, Hawker GA, Hunter DJ, et al. The OMERACT-OARSI core domain set for measurement in clinical trials of hip and/or knee osteoarthritis. *J Rheumatol* 2019; 46: 981–989.

145. Roemer FW, Collins J, Kwoh CK, et al. MRI-based screening for structural definition of eligibility in clinical DMOAD trials: rapid osteoarthritis MRI eligibility score (ROAMES). *Osteoarthritis Cartilage* 2020; 28: 71–81.

146. Driban JB, McAlindon TE, Amin M, et al. Risk factors can classify individuals who develop accelerated knee osteoarthritis: data from the osteoarthritis initiative. *J Orthop Res* 2018; 36: 876–880.