

New horizons in osteoarthritis

Leonardo Punzi, Francesca Oliviero, Roberta Ramonda

Rheumatology Unit, Department of Clinical and Experimental Rheumatology, University of Padova, Italy

Correspondence:

Leonardo Punzi

MD, PhD

Rheumatology Unit

Department of Clinical and Experimental Rheumatology

University of Padova

Via Giustiniani

235128 Padova

Italy

punzireu@unipd.it

Summary

Osteoarthritis (OA), also known as degenerative joint disease, is the most frequent chronic musculoskeletal disease and the leading cause of disability in elderly persons. There are currently at least 27 million persons afflicted with OA in the United States, and the annual cost to society in medical care and wage loss is expected to reach nearly \$100 billion dollars by 2020, with consequent increased spending on its diagnosis and treatment, side effect prevention, and loss of productivity. Despite this enormous burden, many aspects of OA are still unknown, with implications not only in terms of diagnosis and assessment but also with regard to therapy. Awareness of this state of affairs has attracted many researchers to this field, making OA one of the most actively studied sectors of rheumatology. Although some clinicians are unaware of recent advances, there is a large body of publications indicating that much has been achieved. Major progress has been made in formulating better definitions of risk factors, in particular in indicating the responsibility of biomechanical and genetic factors, and, with regard to pathogenesis, underlining the role of subchondral bone, cytokines and proteinases. Assessment of OA activity and its progression has been improved with the advent of biomarkers and new imaging procedures, in particular sonography and magnetic resonance imaging (MRI), but also of better clinical instruments, including more reliable patient questionnaires. Information from ongoing studies may improve the to some extent incomplete definition of OA phenotypes. Finally, promising new horizons have been opened up even with regard to the treatment of OA, which is still for the most part unsatisfactory except for surgical replacement therapy. Numerous new substances have been formulated and the findings of trials studying their effects are encouraging, although much has yet to be done.

Key words: osteoarthritis; cartilage; biomechanics; cytokines; proteinases; biomarkers; IL-1; therapy

Introduction

Osteoarthritis (OA) is the most frequent chronic musculoskeletal disease and is undoubtedly by far the most common cause limiting the daily activities of the elderly population [1]. There are currently at least 27 million persons afflicted with OA in the United States, costing the economy approximately \$60 billion annually [2, 3]. The annual cost to society in medical care and wage loss due to arthritis is expected to reach nearly \$100 billion dollars by 2020, with consequent increased spending on diagnosis and therapy, side effect prevention and lost earnings. At present, approximately 40% of adults aged over 70 suffer from OA of the knee, of these 80% suffer from limitation in movement and 25% are impaired in carrying out their daily activities [4]. It is also important to underline the synergistic effects of other conditions coexisting with OA, in particular obesity and cardiovascular diseases [5, 6].

Despite this enormous burden, OA has not received adequate attention from civil authorities and clinicians, including rheumatologists themselves. An increasing number of researchers have, nevertheless, been attracted to this in some respects “unpopular” field. The reason for this incongruence may at least in part be explained by the presence in the past of a series of misconceptions such as an epidemiologic approach for the most part focussing on the patient’s radiographic profile rather than on clinical characteristics and phenotypes, excessive attendance to traditional radiographic signs, which in this case often become evident only late in the disease’s progression, inadequate exchanges between basic researchers and clinicians on scientific findings and patients’ needs, and limited therapeutic alternatives that have frequently proved disappointing. Awareness of these inconsistencies may perhaps facilitate the search for untried paths aiming to uncover new data clarifying unresolved questions such as the role of risk factors, fostering early diagnosis even in the pre-radiological phase, identifying reliable disease activity indices and, finally, verifying new therapies. Some of these objectives are close to attainment, as demonstrated by numerous findings published in the literature and outlined in this review.

Risk factors

OA, classified as primary or idiopathic, usually develops without known cause. An increasing body of evidence suggests that some risk factors such as genetic predisposition, age, obesity, female sex, greater bone density, joint laxity, and excessive mechanical loading may play a part in its development. Although age is the most important risk factor in OA it is still unclear whether it should be considered an ageing process or a “true” disease, since the former occurs in all members of the population while the latter affects only a limited subset [7, 8]. In addition, despite the fact that almost all elderly people show radiographic findings of OA, the number of subjects who actually complain of symptoms directly related to the disease is much lower [9, 10]. Heberden’s nodes are, for example, a case in point, as few patients complain about their bony hand outgrowths despite the frequency with which radiographic alterations of these bone swellings are noted in the general population. Some investigators have recently voiced conjecture regarding the role of genetic factors in determining longevity and the predisposition to age-associated diseases including OA [11], while others speculate that some environmental factors, in particular mechanical factors, may accelerate and accentuate these processes [12].

Genetic predisposition

Genetic predisposition may have an effect on OA in a variety of ways, by e.g. influencing susceptibility to the disease, age at onset, progression, subtype and, probably, response to treatment. Identifying susceptibility genes may be useful in helping to explain the disease’s mechanisms, since it may uncover the primary biological events causing OA [13].

The familial aggregation of clinical and radiographic features of OA was first demonstrated in the 1940s by the classical studies carried out on Heberden’s nodes, and has since been confirmed, with regard to hand and knee OA, by several community-based studies [14–17]. A recent analysis of x-ray features of hand and knee OA in twins recruited from a healthy population demonstrated that genetic factors accounted for between 39% and 65% of the variation in liability to disease at these two sites [18].

With regard to the most important susceptibility genes recently identified, frizzle-related protein 3 (FRZB) [19] and asporin (ASPN) [20] are particularly interesting. Studies carried out in the UK have reported that two single nucleotide polymorphisms (SNP) of FRZB increase the risk of knee and hip OA in Caucasian women but not in men [21, 22]. SNP’s role was not confirmed in a Spanish population, in which another SNP tended to be more frequent in patients with clinical disease in multiple joints, and specifically in women with hip OA [23, 24]. With regard to ASPN, its association with knee or hip OA has been observed in the Japanese [20], but not in European populations [25–28].

Many of the gene defects affecting the formation of the cartilage matrix and patterning of skeletal elements during development result in a variety of congenital cartilage dysplasias with Mendelian inheritance, though occur-

ring only very rarely [29]. Interestingly, OA is most often site-specific in individuals with skeletal dysplasias. Mutations in the type II collagen gene (COL2A1), for example, cause spondyloepiphyseal dysplasia congenita. Although this cartilage-specific collagen is the most abundant component of articular cartilage in all joints, the OA phenotype of the disease is site-specific [30]. Hip OA is very severe, spine and knee OA is moderately severe, but the hand is normal. Mutations in COMP (cartilage oligomeric matrix protein), another abundant component of articular/epiphyseal cartilage, cause early, severe OA but the spine and peripheral joints are unaffected [31]. The adverse effects of joint malalignment and congruity in these patients may contribute to the possible loss of articular cartilage and in some cases early OA onset [29–31].

Genetic predisposition may also influence the type of reactivity of some innate functions involved in the inflammatory response. Botha-Scheepers et al. have demonstrated that joint space narrowing (JSN) was present 24 months after baseline in 33.7% of symptomatic patients with knee OA [32]. After stimulation of whole blood samples with lipopolysaccharide (LPS) it was found that patients in the highest quartile of tumour necrosis factor (TNF) α production had a sixfold increased risk while patients in the highest quartile of interleukin (IL)-10 production had a fourfold increased risk of JSN progression, as compared, in both cases, with values in patients in the lowest quartile [32]. No significant associations were found between variations in IL-1 β and IL-1Ra production and JSN progression. The innate capacity to produce TNF α and IL-10 upon LPS stimulation is thus associated with radiological progression of knee OA, even over a relatively short follow-up period of 2 years. Another study by the same group produced similar results. In the Genetics of Osteoarthritis and Progression (GARP) study, the role of the C-reactive protein (CRP) gene in hand OA (HOA) was evaluated by determining serum levels of CRP using a high sensitivity (hs) method and assessing genetic variations of the CRP gene by genotyping five tagging SNPs [33]. A haplotype of the CRP gene, linked to a high basal hsCRP level, was associated with severe HOA, indicating that innate high basal serum-hsCRP levels may influence OA onset and severity [33].

Another interesting study by Stern et al. supports the hypothesis of a genetic association between erosive hand OA (EHOA), a severe subtype of hand OA, and an SNP on gene encoding IL-1 β [35].

Biomechanical reactivity

Biomechanics is the term commonly used in OA to define the biochemical reaction to mechanical stimuli, a process considered crucial for the disease’s modern pathogenesis. Joint structures are organised for functions essentially related to joint motion, including load transfer across the joint. Thus, while “normal” loading is useful and necessary to stimulate physiological changes of joint structures, “abnormal” loading, especially during activity, may accelerate the disease’s onset and progression [36, 37]. The biological events induced by mechanical factors may destabilise the normal coupling of degradation and synthesis of articular

cartilage chondrocytes, extracellular matrix and subchondral bone. Several studies have demonstrated that some mechanical joint derangements due to meniscectomy or anterior cruciate ligament injuries may dramatically increase the incidence and progression of knee OA [36, 37]. However, just as with age, these events occur only in some subjects who are probably predisposed. Clarifying the relationship between mechanical injuries and the development of articular cartilage abnormalities can be considered one of the major challenges facing modern rheumatological research.

Chondrocytes are programmed to respond to direct biomechanical perturbation and act as “mechanosensors” by means of specific sensitive receptors, many of which bind to extracellular matrix (ECM) components [38, 39] (fig. 1). The best studied are the integrins, which act as receptors for fibronectin (FN), and type II collagen fragments [38–40]. Activation of these receptors can stimulate the production of inflammatory cytokines, chemokines, and matrix-degrading proteinases, mainly metalloproteinases (MMP)s [40]. In a physiological setting integrins modulate cell /ECM signalling, which is essential in regulating growth and differentiation as well as in maintaining cartilage homeostasis. Abnormal integrin expression during disease activity may alter cell /ECM signalling and modify chondrocyte synthesis activity with subsequent imbalance of destructive or catabolic cytokines over regulatory factors and/or anti-inflammatory or anabolic cytokines [41]. “Abnormal” mechanical loading stimulates depletion of proteoglycans, damages the collagen network and reduces the synthesis of cartilage matrix proteins [42]. In response to traumatic injury global gene expression is activated, resulting in increased expression of inflammatory mediators, including that of cytokines and proteinases [38–42].

Cytokines, growth factors and metalloproteinases

Cytokines, involved in cell-cell interactions, are hormone-like proteins that regulate the intensity and duration of the immune response [43]. Cytokines and growth factors involved in OA may be released from different cellular sources, such as chondrocytes, synovial cells or osteocytes.

It is almost certain that cytokines are involved in OA development and progression, and that blocking cytokines is useful in protecting cartilage from damage [44–46].

IL-1 and TNF are the most important and best studied cytokines in OA. IL-1, released either by the synovium [47] or the chondrocytes [48], could stimulate the latter to produce most or all of the proteinases involved in cartilage destruction [49, 50]. TNF α and IL-1 may also inhibit the synthesis of proteoglycans and type II collagen [51, 52]. Chondrocytes in OA cartilage express IL-1, IL-1 β converting enzyme (caspase-1) and type 1 IL-1 receptor (IL-1RI) [38]. In turn, IL-1 synthesised by chondrocytes may be able to induce the expression of MMPs and aggrecanases [51, 52], the synthesis of prostaglandin E2 (PGE2) [53, 54] and the production of nitric oxide (NO) via inducible NO synthetase (iNOS, or NOS2) [48,55, 56]. IL-1 β also induces other proinflammatory cytokines such as IL-6, leukaemia inhibitory factor (LIF), IL-17, and IL-18 and chemokines, including IL-8 [38, 57]. IL-6 plays an important role in influencing cartilage metabolism. When Guerne et al. analysed the effects of IL-6 on proteoglycan synthesis by human articular chondrocytes in the presence of sIL-6R [58], they found that sIL-6R potentiates the inhibitory effect of IL-6 on proteoglycan synthesis by articular chondrocytes, but the overall effect of IL-6 + IL-6sR is moderate compared to that of IL-1 [58].

Table 1. MOST RELEVANT BIOMARKERS IN OSTEOARTHRITIS

Tissue of origin	Specimen	Markers of Synthesis	Markers of Degradation
Bone	Serum	PINP, P1CP, bone-specific ALP, osteocalcin	PYD, DPD, NTX-I, CTX-I, ICTP, BSP, cathepsin K
	Synovial fluid	ND	BSP
	Urine	HP	CTX-I, DPD, PYD, NTX-I
Cartilage	Serum	CS846, CS383, CS704, P1ICP, P1ANP, P1IHNP, YKL-40, TIMPs	CPF, K5SD4, K5ANP1, Coll 2-I, Coll2-1NO2, COL3-34m, COL 2-14N1, CTX-II, 2B4, COMP, MMPs
	Synovial fluid	CS846, CS383, CS704, P1ICP, P1ANP, YKL-40, TIMPs	CPF, K5SD4, K5ANP1, COL3-34m, COL 2-14N1, CTX-II, COMP, MMPs
	Urine	ND	CTX-II, HELIX-II, TINE
	Synovial membrane	ND	ND
Synovial membrane	Serum	P1CP, P1IHNP, HA, YKL-40, COMP, MMPs, TIMPs, Cytokines	PYD, Glc-Gal-PYD, CTX-I, NTX-I
	Synovial fluid	P1CP, P1IHNP, YKL-40, COMP, MMPs, TIMPs, cytokines	PYD
	Urine	ND	CTX-II, Glc-Gal-PYD, PYD

PINP: collagen I amino-terminal propeptide; P1CP: Procollagen I carboxyterminal propeptide; ALP: alkaline phosphatase; PYD: pyridinoline; DPD: deoxy-PYD; NTX-I: N-terminal cross-linking telopeptide of type I collagen; CTX-I: C-terminal cross-linking telopeptide of type I collagen; ICTP: carboxy-terminal telopeptide of type I collagen; BSP: bone sialoprotein; CS846: chondroitin sulphate epitope 846; CS383: chondroitin sulphate epitope 383; CS704: chondroitin sulphate epitope 704; P1ICP: procollagen type I carboxy-terminal propeptide; P1ANP: N-propeptide of type IIA procollagen; P1IHNP: N-propeptide of type IIB procollagen; TIMP: tissue inhibitor metalloproteinase; K5SD4: keratan sulphate epitope S04; K5ANP1: keratan sulphate epitope ANP1; Coll 2-I: α 1(I) collagen; Coll2-1NO2: related form of Coll2-I; Coll3-34m: type III collagen denaturation product; Coll2-14n1: type II collagen denaturation product; CTX-II: C-terminal crosslinking telopeptide of type II collagen; COMP: cartilage oligomeric matrix protein; MMP: metalloproteinase; HELIX-II: type II collagen helical peptide I; TINE: collagen type II neopeptide; HA: hyaluronan; Glc-Gal-PYD: glucosyl-galactosylpyridinoline; P1IHNP: type III collagen N-propeptide.

Table 1
Most relevant biomarkers in osteoarthritis.

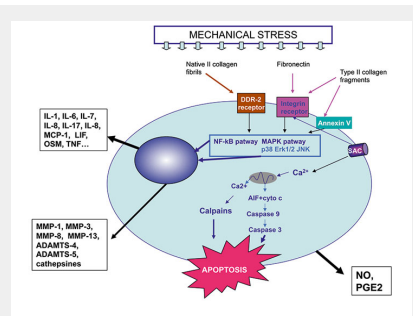


Figure 1
Chondrocyte changes induced by mechanical stress. Chondrocytes can respond to direct biomechanical perturbation by increasing expression of inflammatory mediators, including cytokines and proteinases, and stress response factors. Chondrocytes have receptors for responding to mechanical stimulation (mechanoreceptors), many of which are also receptors for extracellular matrix (ECM) components, including: integrins, a receptor for fibronectin and type II collagen fragments; discoidin domain receptor-2 (DDR-2), a receptor of native II collagen fibrils; annexin-V, a receptor of collagen II fragments. All these receptors interact with intracellular signaling molecules to transduce mechanical signals into biochemical responses which lead to a production of number of proinflammatory substances, including cytokines, proteolytic enzymes, NO and PGE2. The most important among these intracellular signal cascades are NF- κ B and MAPK

pathways. The MAPK family, which include p38, Erk 1 and 2, and JNK, is of critical importance for cell survival, cell differentiation, and chondrogenesis. Other interesting ways stimulated by mechanical forces are the stretch-activated ion channels (SACs), which are believed to respond to membrane tension, interacting with integrins and leading to an elevation of intracellular calcium. This may stimulate mitochondria to release AIF and cytochrome c, which in turn activate pro-caspases 9 and 3 to produce caspase 9 and caspase 3, involved in chondrocyte apoptosis. To this process may also contribute calpains, a family of proteolytic enzymes stimulated by the rise in cytoplasmic calcium from the ERG and mitochondria.

Cytokines involved in cartilage metabolism can be grouped into three categories: catabolic cytokines, which include IL-1 β , TNF α , IL-17, and IL-18; inhibitory cytokines, which include IL-4, IL-10, IL-11, IL-13, IL-1 receptor antagonist, and interferon- γ ; and anabolic cytokines, which comprise insulin-like growth factor 1, TGF β 1, TGF β 2, TGF β 3, fibroblast growth factor (FGF)-2, FGF-4, FGF-8, BMP-2, BMP-4, BMP-6, BMP-7, BMP-9, and BMP-13 [46].

Cytokines synergise with one another in normal joint tissues in maintaining a perfectly balanced network [59]. An imbalance in this system could have important implications for the pathogenesis of most arthropathies, including OA [60, 61]. In this context the role of subchondral bone region, in combination with or independently of the synovial membrane, which represents the most abundant source of cytokines in OA, seems increasingly relevant [62, 63].

As underlined above, the most relevant destructive effects of cytokines on the cartilage are mediated by MMPs, including ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) [64–68]. Among the members of the MMP family relevant roles are played by MMP-13, involved in the degradation of collagen type II in OA cartilage [67], and by ADAMTS4 and ADAMTS5, believed to be key proteases in the degradation of aggrecans [69, 70].

Adipokines

The term “adipokine” is generally applied to biologically active substances found in the adipocytes of white adipose tissue (WAT), although they may be synthesised at other sites too [71]. Adipokines include a variety of pro-inflammatory peptides or cytokines which contribute to the “low-grade inflammatory state” of obese subjects [72, 73]. The best known of this family are leptin, adiponectin and resistin. Leptin is a 16 kDa non-glycosylated peptide hormone belonging to the class I cytokine superfamily chiefly produced by adipocytes [74]. Leptin can be considered a cytokine-like hormone with pleiotropic actions exerting biological influences by binding to its receptors [75]. Leptin is able to modulate cells involved in immune/inflammatory reactions, including monocytes/macrophages, neutrophils, dendritic cells and T-cells [76]. Leptin production is much higher in OA human cartilage than in normal cartilage [77]. The finding that administration of exogenous leptin increases IGF1 and TGF β 1 production by rat knee-joint cartilage has suggested that high circulating leptin levels in obese individuals may protect cartilage from degeneration [77]. Under pathological conditions, however, control of matrix homeostasis by chondrocytes in the joint is lost. In cultured human and murine chondrocytes, NOS2 activation by IL-1 is increased by leptin via a mechanism involving JAK2, PI3K, MEK1 and p38 [78]. It has recently been demonstrated that leptin is also able to induce synthesis of relevant MMPs involved in cartilage damage, such as MMP9 and MMP13 [79].

Adiponectin is produced largely by WAT and has structural homology with collagens VIII and X and complement factor C1q [80]. Adiponectin acts via two receptors, one (AdipoR1) found predominantly in skeletal muscle and the

other (AdipoR2) in the liver [81]. Adiponectin has a wide range of effects in immune and inflammatory diseases and exerts relevant actions on innate and adaptive immunity [71]. In contrast to a “protective” role against obesity and vascular diseases, it seems that in skeletal joints adiponectin may be proinflammatory and involved in matrix degradation [79]. Chondrocytes present functional adiponectin receptors, activation of which leads to the induction of NOS2 via a signalling pathway involving PI3 kinase; and adiponectin-treated chondrocytes similarly increase IL-6, TNF and MCP1 (monocyte chemotactic protein 1) synthesis [82].

Resistin is a dimeric protein that received its name from its apparent induction of insulin resistance in mice, thus providing a possible link between obesity and insulin resistance [83]. Levels of both resistin and leptin are elevated in obese individuals. Resistin is produced by WAT and monocyte/macrophages, but also by cartilage itself, and is a very powerful proinflammatory cytokine, increasing production of IL-1, TNF- α , and various chemokines [84]. Following traumatic joint injury, resistin levels are increased, causing matrix degradation and release of inflammatory cytokines from articular cartilage [85].

Serum levels of adiponectin and resistin were recently measured in 48 women with erosive HOA (EHOA), 27 with non-EHOA and 20 without HOA as controls [86]. Adiponectin but not resistin were significantly higher in EHOA than in non-EHOA or healthy controls. Both adiponectin and resistin neither correlated with the levels of CRP nor were related to Body Mass Index, thus suggesting that adiponectin may play a role in the pathophysiology of the erosive subset of HOA [86].

Subchondral bone

An increasing body of evidence shows that subchondral bone is actively involved in the pathogenesis of OA through several possible mechanisms, including a defect in its role as a shock absorber; abnormal osteocyte function; increased production of bone-derived products, cytokines, and MMPs [38, 62, 63]. It is still unclear whether changes occurring in subchondral bone precede or follow OA onset. In any case, it is possible that a crucial role is played by the vascular invasion of bone marrow tissue into this region [87]. In agreement with this, it has been seen that concentrations of some inflammatory cytokines such as IL-1, TNF and IL-6 are significantly upregulated, supporting the hypothesis that vascularised subchondral plates may increase the synthesis of cytokines and proteolytic enzymes, thereby contributing to the degradation of adjacent hyaline cartilage [88].

The importance of angiogenesis in OA has recently been discussed in detail [89]. Angiogenesis and inflammation are closely integrated processes in OA and may affect disease progression and pain. Angiogenesis may promote chondrocyte hypertrophy and endochondral ossification, contributing to radiographic changes in the joint. In association with inflammation it may sensitise nerves and thus increase pain. Innervation may also accompany vascularisation of the articular cartilage, where compressive forces and hypoxia may stimulate these new nerves.

Several experiments have demonstrated that inadequate fluid flow round osteocytes may result in osteocyte apoptosis, attraction of osteoclasts and excavation of the nonviable bone [90, 91]. In some cases partial or total collapse of subchondral bone may take place, as can be seen in avascular necrosis (AVN) [87, 92]. Subchondral bone ischaemia may be crucial to OA development in several ways, first of all by blocking the nutrient and oxygen supply, usually furnished by the dense subchondral vasculature in close proximity to the cartilage, and via microchannels that penetrate the subchondral mineralisation zone, permitting communication between bone and cartilage [87].

These events at the subchondral bone level are clearly demonstrated by high resolution magnetic resonance imaging (MRI) of the joints. Bright areas of subchondral bone on MRI, commonly observed in both early and established OA and in individuals with painful joints [93], probably correspond to areas of bone marrow-like oedema lesions (BMLOL), occurring idiopathically or in response to bone trauma [93]. Longitudinal studies have shown that BMLOL are an important risk factor for structural deterioration in knee OA [94–96]. It has recently been shown that subchondral cysts, characteristic of established and severe OA, develop in preexisting regions of subchondral BMLOL [97]. While BMLOL's origin is unknown, it may be secondary to ischaemic episodes perhaps exacerbated by reperfusion injuries [98, 99].

Biomarkers

Molecular markers in OA have been the object of growing attention due to their potential usefulness in formulating early diagnosis, in assessing disease activity and severity and in evaluating drug effects [100]. In this respect, biochemical markers or biomarkers are ideal, as they are non-invasive and inexpensive measures [101]. The NIH-funded Biomarkers Network, a multidisciplinary group interested in the development and validation of biomarkers, has recently proposed the “Burden of Disease, Investigative, Prognostic, Efficacy of Intervention and Diagnostic” (BIPED) biomarker classification [102]. It may be concluded, however, that although a great number of substances are continually proposed, only a few can be considered true OA “disease markers” [100–108].

Until now no biomarkers appear to have been able to assist in OA disease diagnosis in the preradiological stages, but with the recent introduction of highly sensitive (hs) immunoassays, a growing number of studies have suggested that CRP may be a marker of OA activity and severity [106]. It would seem that higher CRP levels may predict worse disease outcomes over the next four years [109].

It has been observed that serum hsCRP levels are higher in patients with EHOA than in non-EHOA patients [110]. This probably reflects disease activity rather than subtype, since hsCRP levels correlate with clinical activity scores [110]. As MMPs are particularly involved in cartilage degradation, their levels or activities have been investigated in an attempt to obtain information concerning OA severity or progression [111]. The most abundant MMP both in serum and SF is MMP-3 [111, 112]. It has been

hypothesised that pro-matrix MMP-3 acts as a marker for posttraumatic cartilage degradation [113, 114].

The molecular markers most useful in identifying cartilage synthesis or degradation originate from different articular sources such as cartilage, bone and synovial tissue [101, 102]. Serum hyaluronan (HA), a marker of synovial proliferation and hyperactivity, appears to reflect OA progression [115, 116]. Other interesting biochemical markers are serum keratin sulphate (KS), COMP, YKL-40, and urinary C-terminal crosslinking telopeptides of collagen types I and II (uCTX-II) [106]. COMP concentrations in synovial lavage fluids as well as in serum are an early indicator of radiographic progression at follow-up [117–119]. It has also been seen that COMP is the most sensitive test for identifying subjects affected with the genetic form of premature OA [120, 121]. In the ECHODIAH study, performed by French investigators to determine whether systemic markers of bone, cartilage, and synovium can predict structural progression of hip OA, 10 markers were evaluated: N-propeptides of collagen types I and III, COMP, YKL-40, HA, MMP-1 and MMP-3, CRP and urinary C-terminal crosslinking telopeptides of collagen types I and II (uCTX-II) [122]. Combined measurements of uCTX-II and sHA were found to be the best predictor of structural progression in hip OA [122]. Coll 2-1 and Coll 2-1 NO₂, new serum biochemical markers, have recently been used to study oxidative-related type II collagen network degradation in patients with OA and RA [123]. No relationship was found between radiological OA severity and serum levels of these markers, but, interestingly, Coll 2-1NO₂ was correlated with CRP in the sera of OA and RA patients [123]. Coll 2-1, Coll 2-1NO₂ and myeloperoxidase (MPO) were all higher in the serum of patients with EHOA than in that of non-EHOA subjects, although only the rise in MPO was significant [124]. In another study, Col 2-3/4C epitope levels were higher in the EHOA patients than in the nodal non-EHOA subjects and controls [125].

Phenotyping osteoarthritis

In their daily practice clinicians are no doubt frustrated by the bulk of basic research activities concerning OA compared with the few products really available for their patients. The task of clearly defining markers that can be used for early preradiological diagnoses and assessment of disease activity or progression is, on the other hand, quite arduous in the absence of a well-established clinical definition. It must be said that much effort continues to be expended in improving the quality of clinical observation.

In this context an important step was taken by the American College of Rheumatology in establishing criteria for diagnosis and classification of OA with emphasis on the role of pain [126]. Since that time constant advances have been made in the assessment of symptoms and signs, facilitating early diagnoses and, at times, identification of a subtype or variant not yet detectable by means of radiographic or laboratory findings. EHOA, for example, can be identified by assessment of clinical features even before x-ray identification is possible. In fact, this subtype of hand OA is characterised clinically by frequent inflammatory episodes at times persisting for years and, at times, involving

several joints simultaneously [127]. By contrast, flares of nodal HOA occur chiefly at the onset of each joint's involvement, in a "stuttering" onset polyarthropathy of distal interphalangeal (DIP)s and proximal interphalangeal (PIP)s resembling a "monoarthritis multiplex" [127]. Typically, the patient develops discomfort followed by swelling of a single interphalangeal joint, later involving another IP joint and then another, producing the "stuttering onset" of polyarthrosis of distal and proximal IP joints. Instability and ankylosis of IP joints are, moreover, almost always a feature only of EHOA [128]. Since EHOA is commonly detected by MRI [129], in future the criteria defining EHOA will probably also include specific clinical features in addition to erosion [130].

In keeping with the idea that the modern approach to OA should include adequate evaluation of affected patients, advancement in disease assessment has been obtained by the use of reliable questionnaires, in particular those evaluating quality of life, function pain and radiographic progression [131–133]. Under the auspices of the OARSI (Osteoarthritis Research Society International) and the OMERACT (Outcome Measures in Rheumatology Clinical Trials) initiative, an international working group was recently set up to define the theoretical requirements for total joint replacement in knee and hip OA for use by clinical trials evaluating potential disease-modifying drugs [134]. It was their decision that the domains of pain, physical function and joint structure on x-rays would be combined as a surrogate measure of outcome [135, 136].

High scores on self-reported health-related quality of life (HRQOL) questionnaires have been found to be associated with higher odds of visiting a physician, using analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs), and having had arthroplasty [137]. The relationship between mental health and physical disability is a complex problem particular to OA. It has been demonstrated that the depression commonly found in older persons is associated with functional disability [138], and that depression and pain are more important predictors of disability than radiographic evidence of degenerative joint alterations in patients with hip or knee OA [139]. It has also been observed that treatment for depression, e.g. antidepressants and/or psychotherapy, may reduce pain and improve functional status and quality of life in older patients with OA [140].

It is to be hoped that the availability of these new tools will help to differentiate OA subtypes and improve health professionals' attitude to their patients.

Future therapeutic strategies

One of the most frequent complaints by clinicians treating OA patients is their frustration with the ineffectiveness of the therapeutic tools that are available. As underlined by recent recommendations, one of the reasons for this state of affairs is probably the lack of a global OA management strategy [141–145]. There is no doubt that, with respect to other rheumatic diseases, pharmacological treatment of OA is the least satisfactory. Advances in surgical treatment are much more evident, with regard not only to joint replacement but also to tissue engineering, so-called "biosurgery"

[146–147]. These have been linked to space-filling materials, also known as scaffolds, capable of regenerating or repairing cartilage [148]. Cell transplantation has not yet been attempted in the treatment of OA.

Just as in other types of arthritis, and bearing in mind the importance of genetic predisposition, even gene therapy could be a powerful tool for the future. However, it is unlikely that in future strategies modification of relevant gene mutations can be used to treat OA. A more realistic approach may be to try modifying the synovium or subchondral bone to enhance synthesis of the cartilaginous matrix, inhibit its breakdown, or a combination of the two [149–151]. Unfortunately, all the results currently available concern either animal models or in vitro studies, since no human clinical gene therapy trials have been implemented.

A number of ongoing trials are exploring the use of anti-cytokine therapy. Three strategies currently targeting the activities of catabolic cytokines include: inhibiting the proteinases that degrade cartilage matrix proteins [152], suppressing cytokine-induced signalling pathways [153, 154] and inhibiting chondrocyte apoptosis using inducible NO synthase or caspase inhibitors [155]. As several proteinases involved in OA share overlapping substrate specificities and structural epitopes, some proteinase inhibitors appear to be effective in both animal models and human clinical trials [156]. Krezski et al. have, however, recently reported that PG-116800, the MMP inhibitor, is not only ineffective in modifying the matrix structure in OA patients but seems to provoke numerous musculoskeletal adverse effects [157]. Strategies to suppress cytokine-induced signalling pathways include: cytokine neutralisation, receptor blockade, inhibition of cytokine processing, inhibition of cytokine synthesis or action, and combined therapies [44, 158].

In ongoing trials drug administration is primarily through oral and infusion therapy and is only rarely intra-articular. It is possible that some factors may limit the efficacy of anti-cytokine drugs administered by this latter pathway, including a shorter half-life. This is probably the reason why anakinra, the IL-1 receptor antagonist, was found to be effective in modifying disease progression in animal models [159, 160] and in a 12-week open-label study on symptomatic human knee OA [161], but caused no statistical improvement over placebo after one month in a follow-up controlled trial [162]. In a prospective randomised controlled trial autologous interleukin-1 receptor antagonists were however found to improve function and symptoms in OA patients compared to placebo [163].

The intra-articular pathway has in any case proven to be a satisfactory tool for patients and physicians alike, as demonstrated by the fact that, together with hyaluronate derivatives, it has won worldwide popularity [164–168]. Many pharmaceutical companies are in fact anxious to accelerate research in this area, as demonstrated by the many interesting products now being tested in animals and in phase I human trials.

Funding / potential competing interests

No funding; no competing interests.

References

- Verbrugge LM, Patrick DL. Seven chronic conditions: their impact on US adults' activity levels and use of medical services. *Am J Public Health*. 1995;85:173–82.
- Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum*. 2008;1:26–35.
- Elders MJ. The increasing impact of arthritis on Public Health. *J Rheumatol*. 2000;27:6–8.
- World Health Organisation and the Bone and Joint Decade 2001. Available at <http://www.boneandjointdecade.org>
- Corti MC, Guralnik JM, Sartori L, Baggio G, Manzato E, Pezzotti P, et al. The impact of cardiovascular and osteoarticular diseases on disability in older men and women: rationale, design and sample characteristics of the PRO.VA (Progetto veneto Anziani) Study. *J Am Geriatr Soc*. 2002;50:1535–40.
- Calza S, Decarli A, Ferraroni M. Obesity and prevalence of chronic diseases in the 1999–2000 Italian National Health Survey. *BMC Public Health*. 2008;8:140–9.
- Forbes WF. General concepts of the association of ageing and disease. In "Osteoarthritis. Public Health implications for an ageing population". Hamerman D, Ed. Johns Hopkins University Press, Baltimore and London, 1997, pp 3–14.
- Crepaldi G, Punzi L. Aging and osteoarthritis. *Aging Clin Exp Res*. 2003;15:355–8.
- Bagge E, Bjelle A, Edén S, Svanborg A. Clinical and radiological findings in 79 and 85 year olds. *Ann Rheum Dis*. 1991;50:535–9.
- Corti MC, Rigon C. Epidemiology of osteoarthritis: prevalence, risk factors and functional impact. *Aging Clin Exp Res*. 2003;15:359–63.
- Hamerman D. Ageing and the musculoskeletal system. *Ann Rheum Dis*. 1997;56:578–85.
- Kirkwood TBL. What is the relationship between osteoarthritis and ageing? *Baillière's Clin Rheumatol*. 1997;11:683–93.
- Ikegawa S. New gene associations in osteoarthritis: what do they provide, and where are we going? *Curr Opin Rheumatol*. 2007;19:429–34.
- Stecher RM. Heberden's nodes: heredity in hypertrophic arthritis of the finger joints. *Am J Med Sci*. 1941;210:801–9.
- Kellgren JH, Lawrence JS, Bier F. Genetic factors in generalised osteoarthritis. *Ann Rheum Dis*. 1963;22:237–55.
- Felson DT, Couropmitree NN, Chaisson CE, Hannan MT, Zhang Y, McAlindon TE, et al. Evidence for a Mendelian gene in a segregation analysis of generalized radiographic osteoarthritis: the Framingham study. *Arthritis Rheum*. 1998;41:1064–71.
- Hirsch R, Lethbridge-Cejku M, Hanson R, Scott WW Jr, Reichle R, Plato CC, et al. Familial aggregation of osteoarthritis: data from the Baltimore Longitudinal Study on Aging. *Arthritis Rheum*. 1998;41:1227–32.
- Spector TD, Cicuttini F, Baker J, Loughlin J, Hart D. Genetic influences on osteoarthritis in women: a twin study. *BMJ*. 1996;312:940–3.
- Loughlin J, Dowling B, Chapman K, Marcelline L, Mustafa Z, Southam L, et al. Functional variants within the secreted frizzled-related protein 3 gene are associated with hip osteoarthritis in females. *Proc Natl Acad Sci USA*. 2004;101:9757–62.
- Kizawa H, Kou I, Iida A, Sudo A, Miyamoto Y, Fukuda A, et al. An aspartic acid repeat polymorphism in asporin inhibits chondrogenesis and increases susceptibility to osteoarthritis. *Nat Genet*. 2005;37:138–44.
- Valdes AM, Loughlin J, Oene MV, Chapman K, Surdulescu GL, Doherty M, et al. Sex and ethnic differences in the association of ASPN, CALM1, COL2A1, COMP, and FRZB with genetic susceptibility to osteoarthritis of the knee. *Arthritis Rheum*. 2007;56:137–46.
- Lane NE, Lian K, Nevitt MC, Zmuda JM, Lui L, Li J, et al. Frizzled-related protein variants are risk factors for hip osteoarthritis. *Arthritis Rheum*. 2006;54:1246–54.
- Rodriguez-Lopez J, Pombo-Suarez M, Liz M, Gomez-Reino JJ, Gonzalez A. Further evidence of the role of frizzled-related protein gene polymorphisms in osteoarthritis. *Ann Rheum Dis*. 2007;66:1052–5.
- Snelling S, Ferreira A, Loughlin J. Allelic expression analysis suggests that cisacting polymorphism of FRZB expression does not contribute to osteoarthritis susceptibility. *Osteoarthritis Cartilage*. 2007;15:90–2.
- Mustafa Z, Dowling B, Chapman K, Sinsheimer JS, Carr A, Loughlin J. Investigating the aspartic acid (D) repeat of asporin as a risk factor for osteoarthritis in a UK Caucasian population. *Arthritis Rheum*. 2005;52:3502–6.
- Kaliakatsos M, Tzetis M, Kanavakis E, Fytily P, Chouliaras G, Karachalios T, et al. Asporin and knee osteoarthritis in patients of Greek origin. *Osteoarthritis Cartilage*. 2006;14:609–11.
- Rodriguez-Lopez J, Pombo-Suarez M, Liz M, Gomez-Reino JJ, Gonzalez A. Lack of association of a variable number of aspartic acid residues in the asporin gene with osteoarthritis susceptibility: case-control studies in Spanish Caucasians. *Arthritis Res Ther*. 2006; 8:R55.
- Valdes AM, Loughlin J, Oene MV, Chapman K, Surdulescu GL, Doherty M, et al. Sex and ethnic differences in the association of ASPN, CALM1, COL2A1, COMP, and FRZB with genetic susceptibility to osteoarthritis of the knee. *Arthritis Rheum*. 2007;56:137–46.
- Li Y, Xu L, Olsen BR. Lessons from genetic forms of osteoarthritis for the pathogenesis of the disease. *Osteoarthritis Cartilage*. 2007;15:1101–5.
- Superti-Furga A, Unger S. Nosology and classification of genetic skeletal disorders: 2006 revision. *Am J Med Genet A*. 2007;143:1–18.
- Ikegawa S. Genetic analysis of skeletal dysplasia: recent advances and perspectives in the postgenome-sequence era. *J Hum Genet*. 2006;51:581–6.
- Botha-Scheepers S, Watt I, Slagboom E, de Craen AJM, Meulenbelt I, Rosendaal FR, et al. Innate production of tumour necrosis factor α and interleukin 10 is associated with radiological progression of knee osteoarthritis. *Ann Rheum Dis*. 2008;67:1165–9.
- Bos SD, Suchiman HE, Kloppenburg M, Houwing-Duistermaat JJ, le Graverand MP, Seymour AB, et al. Allelic Variation at the C-Reactive Protein Gene Associates to Both Hand Osteoarthritis Severity and Serum High Sensitive CRP Levels in the GARP Study. *Ann Rheum Dis*. 2008;67:877–9.
- Valdes AM, Loughlin J, Timms KM, van Meurs JJ, Southam L, Wilson SG, et al. Genome-wide association scan identifies a prostaglandin-endoperoxide synthase 2 variant in risk of knee osteoarthritis. *Am J Hum Gen*. 2008;82:1231–40.
- Stern AG, de Carvalho MR, Buck GA, Adler RA, Rao TP, Disler D, et al. I-NODAL Network. Association of erosive hand osteoarthritis with a single nucleotide polymorphism on the gene encoding interleukin-1 beta. *Osteoarthritis Cartilage*. 2003;11:394–402.
- Felson DT. The epidemiology of knee osteoarthritis: results from the Framingham Osteoarthritis Study. *Semin Arthritis Rheum*. 1990;20:42–50.
- Englund M, Lohmander LS. Risk factors for symptomatic knee osteoarthritis fifteen to twenty-two years after meniscectomy. *Arthritis Rheum*. 2004;50:2811–9.
- Goldring MB, Goldring SR. Osteoarthritis. *J Cell Physiol*. 2007;213:626–34.
- Millward-Sadler SJ, Salter DM. Integrin-dependent signal cascades in chondrocyte mechanotransduction. *Ann Biomed Eng*. 2004;32:435–46.
- Kurz B, Lemke AK, Fay J, Pufe T, Grodzinsky AJ, Schunke M. Pathomechanisms of cartilage destruction by mechanical injury. *Ann Anat*. 2005;187:473–85.
- Iannone F, Lapadula G. The pathophysiology of osteoarthritis. *Aging Clin Exp Res*. 2003;15: 364–72.
- Fitzgerald JB, Jin M, Dean D, Wood DJ, Zheng MH, Grodzinsky AJ. Mechanical compression of cartilage explants induces multiple time-dependent gene expression patterns and involves intracellular calcium and cyclic AMP. *J Biol Chem*. 2004;279:19502–11.
- Dayer J-M. The process of identifying and understanding cytokines: from basic studies to treating rheumatic diseases. *Best Pract Res Clin Rheumatol*. 2004;18:31–45.
- Goldring MB, Otero M, Tsuchimochi K, Ijiri K, Li Y. Defining the roles of inflammatory and anabolic cytokines in cartilage metabolism. *Ann Rheum Dis*. 2008;67(suppl III):iii75–82.

- 45 Goldring MB. Anticytokine therapy for osteoarthritis. *Expert Opin Biol Ther.* 2001;1:17–29.
- 46 Zigang GE, Hu Y, Heng BC, Yang Z, Ouyang H, Lee EH, Cao T. Osteoarthritis and Therapy. *Arthritis Rheum.* 2006;55:493–500.
- 47 Meats JE, McGuire MB, Russell RG. Human synovium releases a factor which stimulates chondrocyte production of PGE and plasminogen activator. *Nature.* 1980;286:891–2.
- 48 Melchiorri C, Meliconi R, Frizziero L, Silvestri T, Pulsatelli L, Mazzetti I, et al. Enhanced and coordinated in vivo expression of inflammatory cytokines and nitric oxide synthase by chondrocytes from patients with osteoarthritis. *Arthritis Rheum.* 1998;41:2165–74.
- 49 Tetlow LC, Adlam DJ, Woolley DE. Matrix metalloproteinase and proinflammatory cytokine production by chondrocytes of human osteoarthritic cartilage. *Arthritis Rheum.* 2001;44:585–94.
- 50 Wu W, Billingham RC, Pidoux I, Antoniou J, Zukor D, Tanzer M, et al. Sites of collagenase cleavage and denaturation of type II collagen in aging and osteoarthritic articular cartilage and their relationship to the distribution of matrix metalloproteinase 1 and matrix metalloproteinase 13. *Arthritis Rheum.* 2002;46:2087–94.
- 51 Goldring MB, Birkhead J, Sandell LJ, Kimura T, Krane SM. Interleukin 1 suppresses expression of cartilage-specific types II and IX collagens and increases types I and III collagens in human chondrocytes. *J Clin Invest.* 1988;82:2026–37.
- 52 Reginato AM, Sanz-Rodriguez C, Diaz A, Dharmavaram RM, Jimenez SA. Transcriptional modulation of cartilage-specific collagen gene expression by interferon gamma and tumour necrosis factor in cultured human chondrocytes. *Biochem J.* 1993;294:761–9.
- 53 Goldring MB, Suen LF, Yamin R, Lai WF. Regulation of collagen gene expression by prostaglandins and interleukin-1 β in cultured chondrocytes and fibroblasts. *Am J Ther.* 1996;3:9–16.
- 54 Miyamoto M, Ito H, Mukai S, Kobayashi T, Yamamoto H, Kobayashi M et al. Simultaneous stimulation of EP2 and EP4 is essential to the effect of prostaglandin E2 in chondrocyte differentiation. *Osteoarthritis Cartilage* 2003;11:644–52.
- 55 Taskiran D, Stefanovic-Racic M, Georgescu H, Evans C: Nitric oxide mediates suppression of cartilage proteoglycan synthesis by interleukin-1. *Biochem Biophys Res Commun.* 1994;200:142–8.
- 56 Goldring MB, Berenbaum F. The regulation of chondrocyte function by proinflammatory mediators: Prostaglandins and nitric oxide. *Clin Orthop.* 2004;427:S37–S46.
- 57 Goldring SR, Goldring MB. The role of cytokines in cartilage matrix degeneration in osteoarthritis. *Clin Orthop.* 2004;423:S27–S36.
- 58 Guerne PA, Desgeorges A, Jaspar JM, Relic B, Peter R, Hoffmeyer P, Dayer JM. Effects of IL-6 and its soluble receptor on proteoglycan synthesis and NO release by human articular chondrocytes: comparison with IL-1. Modulation by dexamethasone. *Matrix Biol.* 1999;18:253–60.
- 59 Pelletier JP, Martel-Pelletier J, Abramson SB: Osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets. *Arthritis Rheum.* 2001;44:1237–47.
- 60 Bertazzolo N, Punzi L, Stefani MP, Cesaro G, Pianon M, Finco B, Todesco S. Interrelationships between interleukin (IL)-1, IL-6 and IL-8 in synovial fluid of various arthropathies. *Agents Actions.* 1994;41:90–2.
- 61 Punzi L, Calò L, Plebani M. Clinical significance of cytokine determination in synovial fluid. *Crit Rev Clin Lab Sci.* 2002;39:63–88.
- 62 Hulejova H, Baresova V, Klezl Z, Polanska M, Adam M, Senolt L. Increased level of cytokines and matrix metalloproteinases in osteoarthritic subchondral bone. *Cytokine.* 2007;38:151–6.
- 63 Martel-Pelletier J, Lajeunesse D, Pelletier J-P. Subchondral bone and osteoarthritis progression: a very significant role. In "Osteoarthritis, Inflammation and Degradation: A Continuum" J. Buckwalter, M. Lotz and J-F Lotz Eds. IOS Press 2007, pp 206-18.
- 64 Tetlow LC, Adlam DJ, Woolley DE. Matrix metalloproteinase and proinflammatory cytokine production by chondrocytes of human osteoarthritic cartilage: associations with degenerative changes. *Arthritis Rheum.* 2001;44:585–94.
- 65 Arner EC. Aggrecanase-mediated cartilage degradation. *Curr Opin Pharmacol.* 2002;2:322–9.
- 66 Rengel Y, Ospelt C, Gay S. Proteinases in the joint: clinical relevance of proteinases in joint destruction. *Arthritis Res Ther.* 2007;9:221.
- 67 Murphy G, Nagase H: Reappraising metalloproteinases in rheumatoid arthritis and osteoarthritis: destruction or repair? *Nat Clin Pract Rheumatol.* 2008;4:128–35.
- 68 Plaas A, Osborn B, Yoshihara Y, Bai Y, Bloom T, Nelson F, Mikecz K, Sandy JD. Aggrecanolytic in human osteoarthritis: confocal localization and biochemical characterization of ADAMTS5-hyaluronan complexes in articular cartilages. *Osteoarthritis Cartilage.* 2007;15:719–34.
- 69 Glasson SS, Askew R, Sheppard B, Carito B, Blanchet T, Ma HL, et al. Deletion of active ADAMTS5 prevents cartilage degradation in a murine model of osteoarthritis. *Nature.* 2005;434:644–8.
- 70 Stanton H, Rogerson FM, East CJ, Golub SB, Lawlor KE, Meeker CT, et al. ADAMTS5 is the major aggrecanase in mouse cartilage in vivo and in vitro. *Nature.* 2005;434:648–52.
- 71 Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nature Rev Immunol.* 2006;6:772–83.
- 72 Fantuzzi G. Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol.* 2006;115:911–9.
- 73 Dayer JM, Chicheportiche R, Juge-Aubry C, Meier C. Adipose tissue has anti-inflammatory properties. *Ann NY Acad Sci.* 2006;1069:444–53.
- 74 Matarese G, Moschos S, Mantzoros CS. Leptin in immunology. *J Immunol.* 2005;174:3137–42.
- 75 Fruhbeck G. Intracellular signalling pathways activated by leptin. *Biochem J.* 2006;393:7–20.
- 76 Lam QL, Lu L. Role of leptin in immunity. *Cellul & Molecul Immunol.* 2007;4:1–13.
- 77 Dumond H, Presle N, Terlain B, Mainard D, Loeuille D, Netter P, et al. Evidence for a key role of leptin in osteoarthritis. *Arthritis Rheum.* 2003;48:3118–29.
- 78 Otero M, Lago R, Lago F, Reino JJ, Gualillo O. Signalling pathway involved in nitric oxide synthase type II activation in chondrocytes: synergistic effect of leptin with interleukin-1. *Arthritis Res Ther.* 2005;7:R581–91.
- 79 Lago F, Dieguez C, Gómez-Reino J, Gualillo O. Adipokines as emerging mediators of immune response and inflammation. *Nature Clin Pract Rheumatol.* 2007;3:716–24.
- 80 Oh DK, Ciaraldi T, Henry RR. Adiponectin in health and disease. *Diabetes Obes Metab.* 2007;9:282–9.
- 81 Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. *Endocr Rev.* 2005;26:439–51.
- 82 Lago R, Gomez R, Otero M, Lago F, Gallego R, Dieguez C, et al. A new player in cartilage homeostasis: adiponectin induces nitric oxide synthase type II and pro-inflammatory cytokines in chondrocytes. *Osteoarthritis Cartilage.* 2008;16:1101–9.
- 83 Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, et al. The hormone resistin links obesity to diabetes. *Nature.* 2001;409:307–12.
- 84 Lee JH, Ort T, Ma K, Picha K, Carton J, Marsters PA, et al. Resistin is elevated following traumatic joint injury and causes matrix degradation and release of inflammatory cytokines from articular cartilage in vitro. *Osteoarthritis Cartilage.* 2009;17:613–20.
- 85 Sandell LJ. Obesity and osteoarthritis. Is the leptin the link? *Arthritis Rheum.* 2009;60:2858–60.
- 86 Filková M, Lisková M, Hulejová H, Haluzík M, Gatterová J, Pavelková A, et al. Increased serum adiponectin levels in female patients with erosive compared with non-erosive osteoarthritis *Ann Rheum Dis.* 2009;68:295–6.
- 87 Findlay DM. Vascular pathology in osteoarthritis. *Rheumatology.* 2007;46:1763–8.
- 88 Hulejová H, Baresova V, Klézl Z, Polanska M, Adam A, Senolt L. Increased level of cytokines and matrix metalloproteinases in osteoarthritic subchondral bone. *Cytokine.* 2007;38:151–6.
- 89 Bonnet CS, Walsh DA. Osteoarthritis, angiogenesis and inflammation. *Rheumatology. (Oxford).* 2005;44:7–16.
- 90 Noble B. Bone microdamage and cell apoptosis. *Eur Cell Mater.* 2003;6:46–55.

- 91 Aguirre JI, Plotkin LI, Stewart SA, Weinstein RS, Parfitt AM, Manolagas SC, et al. Osteocyte apoptosis is induced by weightlessness in mice and precedes osteoclast recruitment and bone loss. *J Bone Miner Res.* 2006;21:605–15.
- 92 Arnett TR, Gibbons DC, Utting JC, Orriss IR, Hoebertz A, Rosendaal M, et al. Hypoxia is a major stimulator of osteoclast formation and bone resorption. *J Cell Physiol.* 2003;196:2–8.
- 93 Mandalia V, Fogg AJ, Chari R, Murray J, Beale A, Henson JH. Bone bruising of the knee. *Clin Radiol.* 2005;60:627–36.
- 94 Felson DT, McLaughlin S, Goggins J, LaValley MP, Gale ME, Totterman S, et al. Bone marrow edema and its relation to progression of knee osteoarthritis. *Ann Intern Med.* 2003;139:330–6.
- 95 Hunter DJ, Zhang Y, Niu J, Goggins J, Amin S, LaValley MP, et al. Increase in bone marrow lesions associated with cartilage loss: a longitudinal magnetic resonance imaging study of knee osteoarthritis. *Arthritis Rheum.* 2006;54:1529–35.
- 96 Zhai G, Blizzard L, Srikanth V, Ding C, Cooley H, Cicuttini F, et al. Correlates of knee pain in older adults: Tasmanian Older Adult Cohort Study. *Arthritis Rheum.* 2006;55:264–71.
- 97 Carrino JA, Blum J, Parellada JA, Schweitzer ME, Morrison WB. MRI of bone marrow edema-like signal in the pathogenesis of subchondral cysts. *Osteoarthritis Cartilage.* 2006;14:1081–5.
- 98 Winet H, Hsieh A, Bao JY. Approaches to study of ischemia in bone. *J Biomed Mater Res.* 1998;43:410–21.
- 99 Otter MW, Qin YX, Rubin CT, McLeod KJ. Does bone perfusion/reperfusion initiate bone remodeling and the stress fracture syndrome? *Med Hypotheses.* 1999;53:363–8.
- 100 Punzi L, Oliviero F, Plebani M. New biochemical insights into the pathogenesis of osteoarthritis and the role of laboratory investigations in clinical assessment. *Crit Rev Clin Lab Sci.* 2005;42:279–309.
- 101 Lohmander LS. The role of molecular markers in monitor breakdown and repair. In: Reginster J-Y, Henrotin Y, Martel-Pelletier J and Pelletier J-P eds. *Experimental and clinical aspects of osteoarthritis.* Springer-Verlag, Heidelberg, 1999:296–311.
- 102 Bauer DC, Hunter DJ, Abramson SB, Attur M, Corr M, Felson D, et al. Classification of osteoarthritis biomarkers: a proposed approach. *Osteoarthritis Cartilage.* 2006;14:723–7.
- 103 Altman RD, Lozada CJ. Laboratory findings in osteoarthritis. In: Moskowitz RW, Howell DS, Altman RD, Buckwalter JA, Goldberg VM eds. *Osteoarthritis.* Saunders Philadelphia, 3rd edition 2001:273–91.
- 104 Thonar EJ, Manicourt DH. Noninvasive markers in osteoarthritis. In: Moskowitz RW, Howell DS, Altman RD, Buckwalter JA, Goldberg VM eds. *Osteoarthritis.* Saunders Philadelphia, 3rd edition 2001:293–313.
- 105 Punzi L, Oliviero F, Ramonda R, Valvason C, Sfriso P, Todesco S. Laboratory investigations in osteoarthritis. *Aging Clin Exp Res.* 2003;15:373–9.
- 106 Punzi L, Oliviero F, Ramonda R, Valvason C, Todesco S. Laboratory findings in osteoarthritis. *Semin Arthritis Rheum.* 2005;34/2S:58–61.
- 107 Punzi L, Oliviero F, Sfriso P. Biomarkers of matrix fragments, inflammation markers in osteoarthritis. In *Osteoarthritis, Inflammation and Degradation: A continuum.* J.Buckwalter, M.Lotz and Stolz J-F Eds. IOS Press Amsterdam. 2007;267–79.
- 108 Dayer E, Dayer J-M, Roux-Lombard P. Primer: the practical use of biological markers of rheumatic and systemic inflammatory diseases. *Nature Clinical Practice Rheumatology.* 2007;3:512–20.
- 109 Spector TD, Hart DJ, Nandra D, Doyle DV, Mackillop N, Gallimore JR, et al. Low-level increases in serum C-reactive protein are present in early osteoarthritis of the knee and predict progressive disease. *Arthritis Rheum.* 1997;40:723–7.
- 110 Punzi L, Ramonda R, Oliviero F, Sfriso P, Mussap M, Plebani P, et al. Value of C-reactive protein determination in erosive osteoarthritis *Ann Rheum Dis.* 2005;64:965–7.
- 111 Vignon E, Balblanc JC, Mathieu P, Louisot P, Richard M. Metalloprotease activity, phospholipase A2 activity and cytokine concentration in osteoarthritis synovial fluids. *Osteoarthritis Cartilage.* 1993;1:115–20.
- 112 Ribbens C, Andre B, Kaye O, Kaiser MJ, Bonnet V, Jaspas JM, et al. Synovial fluid matrix metalloproteinase-3 levels are increased in inflammatory arthritides whether erosive or not. *Rheumatology.* (Oxford) 2000;39:1357–65.
- 113 Garnero P, Mazières B, Gueguen A, Abbal M, Berdahl L, Lequesne M, et al. Cross-sectional association of 10 molecular markers of bone cartilage, and synovium with disease activity and radiological joint damage in patients with hip osteoarthritis: the ECHODIAH cohort. *J Rheumatol.* 2005;32:697–703.
- 114 Bobacz K, Maier R, Fialka C, Ekhart H, Woloszczuk W, Geyer G, et al. Is pro-matrix metalloproteinase-3 a marker for posttraumatic cartilage degradation? *Osteoarthritis Cartilage.* 2003;11:665–72.
- 115 Goldberg RL, Huff JP, Lenz ME, Glickman P, Katz R, Thonar EJ. Elevated plasma levels of hyaluronate in patients with osteoarthritis and rheumatoid arthritis. *Arthritis Rheum.* 1991;34:799–807.
- 116 Sharif M, George E, Shepstone L, Knudson W, Thonar EJ, Cushnaghan J, et al. Serum hyaluronic acid level as a predictor of disease progression in osteoarthritis of the knee. *Arthritis Rheum.* 1995;38:760–7.
- 117 Sharif M, Saxne T, Shepstone L, et al. Relationship between serum cartilage oligomeric matrix protein levels and disease progression in osteoarthritis of the knee joint. *Br J Rheumatol.* 1995;34:306–10.
- 118 Conrozier T, Saxne T, Fan CS, et al. Serum concentrations of cartilage oligomeric matrix protein and bone sialoprotein in hip osteoarthritis: a one year prospective study. *Ann Rheum Dis.* 1998;57:527–32.
- 119 Dragomir AD, Kraus VB, Renner JB, Luta G, Clark A, Vilim V, Hochberg MC, Helmick CG, Jordan JM. Serum cartilage oligomeric matrix protein and clinical signs and symptoms of potential pre-radiographic hip and knee pathology. *Osteoarthritis Cartilage.* 2002;10:707–13.
- 120 Bleasel JF, Poole AR, Heinegard D, Saxne T, Holderbaum D, Ionescu M, et al. Changes in serum cartilage marker levels indicate altered cartilage metabolism in families with the osteoarthritis-related type II collagen gene COL2A1 mutation. *Arthritis Rheum.* 1999;42:39–45.
- 121 Williams FM, Andrew T, Saxne T, Heinegard D, Spector TD, MacGregor AJ. The heritable determinants of cartilage oligomeric matrix protein. *Arthritis Rheum.* 2006;54:2147–51.
- 122 Mazières B, Garnero P, Guéguen A, Abbal M, Berdahl L, Lequesne M, et al. Molecular markers of cartilage breakdown and synovitis at baseline as predictors of structural progression of hip osteoarthritis. The ECHODIAH Cohort. *Ann Rheum Dis.* 2006;65:354–9.
- 123 Deberg M, Labasse A, Christgau S, Cloos P, Bang Henriksen D, et al. New serum biochemical markers (Coll 2-1 and Coll 2-INO2) for studying oxidative-related type II collagen network degradation in patients with osteoarthritis and rheumatoid arthritis. *Osteoarthritis Cartilage.* 2005;13:258–65.
- 124 Ramonda R, Deberg M, Campana C, Frigato M, Bosselot A, Henrotin Y, Punzi L. Coll 2-1, Coll 2-INO2 in erosive and non-erosive osteoarthritis of the hand. *Osteoarthritis Cartilage.* 2008;16(suppl 4):S56.
- 125 Silvestri T, Pulsatelli L, Dolzani P, Punzi L, Meliconi R. Analysis of cartilage biomarkers in erosive and non-erosive osteoarthritis of the hand. *Osteoarthritis Cartilage.* 2004;12:843–5.
- 126 Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis of the knee. *Arthritis Rheum.* 1986;29:1039–49.
- 127 Punzi L, Ramonda R, Sfriso P. Erosive osteoarthritis. *Best Pract Res Clin Rheumatol.* 2004;5:739–58.
- 128 Zhang W, Doherty M, Leeb BF, Alekseeva L, Arden NK, Bijlsma JW, et al; ESCISIT EULAR evidence-based recommendations for the diagnosis of hand osteoarthritis: report of a task force of ESCISIT. *Ann Rheum Dis.* 2009;68:8–17.
- 129 Tan AL, Grainger AJ, Tanner SF, et al. A high-resolution magnetic resonance imaging study of distal interphalangeal joint arthropathy in psoriatic arthritis and osteoarthritis. Are they the same? *Arthritis Rheum.* 2006;54:1328–33.
- 130 Punzi L, Ramonda R. Phenotyping erosive osteoarthritis of the hand. *Osteoarthritis Cartilage.* 2008;16(Suppl 4):S10.
- 131 Salaffi F, Carotti M, Grassi W. Health-related quality of life in patients with hip or knee osteoarthritis: comparison of generic and disease-specific instruments. *Clin Rheumatol.* 2005;24:29–37.
- 132 Salaffi F, Leardini G, Canesi B, Mannoni A, Fioravanti A, Caporali R, et al. Reliability and validity of the Western Ontario and McMaster

- Universities (WOMAC) Osteoarthritis Index in Italian patients with osteoarthritis of the knee. *Osteoarthritis Cartilage*. 2003;11:551–60.
- 133 Punzi L, Ramonda R. Importance of self-reported health-related quality of life in identifying the needs of elderly people with osteoarthritis. *Aging Clin Exp Res*. 2005;17:253–4.
- 134 Hawker GA, Stewart L, French MR, Cibere J, Jordan JM, March L, et al. Understanding the pain experience in hip and knee osteoarthritis. An OARSI/OMERACT initiative. *Osteoarthritis Cartilage*. 2008;16:415–22.
- 135 Gossec L, Hawker GA, Davis AM, Maillefert JF, Lohmander S, Altman R, et al. OMERACT/OARSI initiative to define states of severity and indication for joint replacement in hip and knee osteoarthritis. An OMERACT 8 Special Interest Group. *J Rheumatol*. 2007;34:1432–5.
- 136 Maillefert JF, Kloppenburg M, Fernandes L, Punzi L, Günther KP, Martin Mola E, et al. Multi-language translation and cross-cultural adaptation of the OARSI/OMERACT measure of intermittent and constant osteoarthritis pain (ICOAP). *Osteoarthritis Cartilage*. 2009;17:1293–6.
- 137 Dominick KL, Ahern FM, Gold CH, Heller DA. Health-related quality of life and health service use among older adults with osteoarthritis. *Arthritis Rheum*. 2004;51:326–31.
- 138 Wells KB, Steward A, Hays RD, Burnam MA, Rogers W, Daniels M, et al. The functioning and well-being of depressed patients: results from the Medical Outcomes Study. *JAMA*. 1989;262:914–9.
- 139 Creamer P, Lethbridge-Cejku M, Hochberg MC. Factors associated with functional impairment in symptomatic knee osteoarthritis. *Rheumatology*. (Oxford) 2000;39:959–67.
- 140 Lin EH, Katon W, Von Korff M, Tang L, Williams JW Jr, Kroenke K, et al. Effect of improving depression care on pain and functional outcomes among older adults with arthritis. *JAMA*. 2003;290:2428–34.
- 141 Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JWJ, Dieppe P, et al. EULAR recommendations 2003: an evidence based medicine approach to knee osteoarthritis. Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCSIT). *Ann Rheum Dis*. 2003;62:1145–55.
- 142 Zhang W, Doherty M, Arden N, Bannwarth B, Bijlsma J, Gunther KP, et al. EULAR evidence based recommendations for the management of hip osteoarthritis - report of a task force of the EULAR standing committee for international clinical studies including therapeutics (ESCSIT). *Ann Rheum Dis*. 2005;64:5:669–81.
- 143 Zhang W, Doherty M, Leeb BF, Alekseeva L, Arden N, Bijlsma J, et al. EULAR evidence based recommendations for the management of hand osteoarthritis - report of a task force of the EULAR standing committee for international clinical studies including therapeutics (ESCSIT) *Ann Rheum Dis*. 2007;66:377–88.
- 144 Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis Cartilage*. 2007;15:981–1000.
- 145 Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage*. 2008;16:137–62.
- 146 Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N Engl J Med*. 1994;331:889–95.
- 147 Almaraz AJ, Athanasiou KA. Design characteristics for the tissue engineering of cartilaginous tissues. *Ann Biomed Eng*. 2004;32:2–17.
- 148 Hui JH, Chen F, Thambyah A, Lee EH. Treatment of chondral lesions in advanced osteochondritis dissecans: a comparative study of the efficacy of chondrocytes, mesenchymal stem cells, periosteal graft, and mosaicplasty (osteochondral autograft) in animal models. *J Pediatr Orthop*. 2004;24:427–33.
- 149 Nixon AJ, Haupt JL, Frisbie DD, Morisset SS, McIlwraith CW, Robbins PD, et al. Gene-mediated restoration of cartilage matrix by combination insulin-like growth factor-I/interleukin-1 receptor antagonist therapy. *Gene Ther*. 2005;12:177–86.
- 150 Evans CH, Gouze JN, Gouze E, Robbins PD, Ghivizzani SC. Osteoarthritis gene therapy. *Gene Ther*. 2004;11:379–89.
- 151 Hannon GJ. RNA interference. *Nature*. 2002;418:244–51.
- 152 Tu G, Xu W, Huang H, Li S. Progress in the development of matrix metalloproteinase inhibitors. *Curr Med Chem*. 2008;15:1388–95.
- 153 Ho LJ, Lin LC, Hung LF, Wang SJ, Lee CH, Chang DM, et al. Retinoic acid blocks pro-inflammatory cytokine-induced matrix metalloproteinase production by down-regulating JNK-AP-1 signaling in human chondrocytes. *Biochem Pharmacol*. 2005;70:200–8.
- 154 Finckh A, Gabay C. At the horizon of innovative therapy in rheumatology: new biologic agents. *Curr Opin Rheumatol*. 2008;20:269–75.
- 155 Berenbaum F. New horizons and perspective in the treatment of osteoarthritis. *Arthritis Res Ther* 2008;10(Suppl2):S1–7.
- 156 Bursavich MG, Gilbert AM, Lombardi S, Georgiadis KE, Reifenberg E, Flanneryb CR, et al. Synthesis and evaluation of aryl thioxothiazolidinone inhibitors of ADAMTS-5 (Aggrecanase-2). *Bioorg Medicin Chem Lett* 2007;17:1185–8.
- 157 Krzeski P, Buckland-Wright C, Balint G, Cline GA, Stoner K, Lyon R, et al. Development of musculoskeletal toxicity without clear benefit after administration of PG 116800, a matrix metalloproteinase inhibitor, to patients with knee osteoarthritis: a randomized, 12 month, double-blind, placebo-controlled study. *Arthritis Res Ther*. 2007;9:R109.
- 158 Chevalier X, Mugnier B, Bouvenot G. Targeted anti-cytokine therapies for osteoarthritis. *Bull Acad Natl Med*. 2006;190:1411–20.
- 159 Caron JP, Fernandes JC, Martel-Pelletier J, Tardif G, Mineau F, Geng C, et al. Chondroprotective effect of intraarticular injections of interleukin-1 receptor antagonist in experimental osteoarthritis: Suppression of collagenase-1 expression. *Arthritis Rheum*. 1996;39:1535–44.
- 160 Zhang X, Mao Z, Yu C. Suppression of early experimental osteoarthritis by gene transfer of interleukin-1 receptor antagonist and interleukin-10. *J Orthop Res*. 2004;22:742–50.
- 161 Chevalier X, Giraudeau B, Conrozier T, Marliere J, Kiefer P, Goupille P. Safety study of intraarticular injection of interleukin 1 receptor antagonist in patients with painful knee osteoarthritis: a multicenter study. *J Rheumatol*. 2005;32:1317–23.
- 162 Chevalier X, Goupille P, Beaulieu AD, Burch FX, Bensen WG, Conrozier T, et al. Intraarticular injection of anakinra in osteoarthritis of the knee: a multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum*. 2009;61:344–52.
- 163 Yang KG, Raijmakers NJH, van Arkel ERA, Caron JJ, Rijk PC, Willems WJ, et al. Autologous interleukin-1 receptor antagonist improves function and symptoms in osteoarthritis when compared to placebo in a prospective randomized controlled trial. *Osteoarthritis Cartilage*. 2008;16:498–505.
- 164 Brzusek D, Petron D. Treating knee osteoarthritis with intra-articular hyaluronans. *Curr Med Res Opin*. 2008;24:3307–22.
- 165 Punzi L. The complexity of the mechanisms of action of hyaluronan in joint diseases. *Clin Exp Rheumatol*. 2001;19:242–6.
- 166 Goldberg, VM; Buckwalter, JA. Hyaluronans in the treatment of osteoarthritis of the knee: evidence for disease-modifying activity. *Osteoarthritis Cartilage*. 2005;13:216–24.
- 167 Bellamy, N; Campbell, J; Robinson, V; Gee, T; Bourne, R; Wells, G. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev*. 2006 CD005321.
- 168 Strauss EJ, Hart JA, Miller MD, Altman RD, Rosen JE. Hyaluronic acid viscosupplementation and osteoarthritis: current uses and future directions. *Am J Sports Med*. 2009;37:1636:44.