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Pre-Osteoarthritis: Definition and Diagnosis of an Elusive Clinical Entity

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Abstract

Objective. An attempt to define pre-osteoarthritis (OA) versus early OA and definitive osteoarthritis. *Methods*. A group of specialists in the field of cartilage science and treatment was formed to consider the nature of OA onset and its possible diagnosis. *Results*. Late-stage OA, necessitating total joint replacement, is the end stage of a biological process, with many previous earlier stages. Early-stage OA has been defined and involves structural changes identified by arthroscopy or radiography. The group argued that before the "early-stage OA" there must exist a stage where cellular processes, due to the presence of risk factors, have kicked into action but have not yet resulted in structural changes. The group suggested that this stage could be called "pre-osteoarthritis" (pre-OA). *Conclusions*. The group suggests that defining points of initiation for OA in the knee could be defined, for example, by traumatic episodes or surgical meniscectomy. Such events may set in motion metabolic processes that could be diagnosed by modern MRI protocols or arthroscopy including probing techniques before structural changes of early OA have developed. Preventive measures should preferably be applied at this pre-OA stage in order to stop the projected OA "epidemic."

Keywords

epidemiology, general, posttraumatic arthritis, diagnosis, diagnostics

Introduction

Osteoarthritis (OA) is a degenerative joint disorder of huge proportions. It affects primarily the large weight-bearing joints in the hip and the knee. In recent decades, a shift has taken place so that OA of the knee now is the most common manifestation of the disease. On a global basis, about 1.5 million patients are treated annually for end-stage disease by total knee arthroplasty (TKA) and many times the patients suffer from the disease but have not yet reached the indication for TKA. In the coming decades a 4- to 6-fold increase in the number of TKAs is anticipated. In order to influence this oncoming epidemic, preventive measures need to be applied at the earliest possible stage. In this article, we discuss what this early stage can be and how it can be identified.

Background

A group of specialists in the field of cartilage science and treatment was formed to consider the nature of OA onset and its treatment.

The group concluded that OA is a disease of multifactorial origin, beginning as a preclinical condition that can become very advanced before it becomes symptomatic, due to the avascular and noninnervated nature of cartilage. We considered OA as difficult to define unless it is considered as a continuum that reflects organ failure, the organ being an articular joint.

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We further considered that OA can be classified by causation in four principle groups. These groups are formed by answers to two questions: Is the cause of the arthritis principally congenital or acquired? Is the cause principally biological or biomechanical?

1. The *congenital-biological* group includes entities such as inherited disorders of epiphyseal growth, collagen structure, and proteoglycan (PG) synthesis. GDF5 gene abnormality, for example, carries a 1.8× risk of OA and is currently not treatable.[1]
2. The *congenital-biomechanical* group include hip dysplasia, osteochondritis dissecans, varus or valgus knee alignment, and rare conditions such as dysplasia epiphysealis hemimelica.
3. The *acquired-biological* examples include damage to an articular surface from sepsis and rheumatoid arthritis.
4. The *acquired-biomechanical* disorders, finally, is certainly the largest group. The largest single factor is chondral or osteochondral trauma. The other common example in this group is anterior cruciate ligament deficiency.

Ligament instability unfortunately seems to lead to OA whether it is treated surgically or not. Normal homeostasis is disrupted, and biological mechanisms play an important part, although secondary to the biomechanical problem.

Meniscal injury with partial or total meniscectomy alters knee kinematics, which significantly increases the risk of OA.[2-5]

Other common examples include fractures leading to shortening, malunion of long bones, or intra-articular fractures.

Chronic overload is thought to lead to subchondral stiffening as a cause of arthritis.[6] This may also relate to parathyroid and calcitonin activity causing high remodeling rates.[7,8] In this context, obesity could also be considered as a principally biomechanical problem, although there are also theories of important biological mechanisms through the action of leptins on both articular bone and cartilage. Acid diet has also been a candidate, but a recent review negates this effect.[9]

Staging

It is generally recognized that OA disease is a condition of slow biologic progression and the time frame from a known initiation point is on the order of 10 to 20 years. During this long time period the disease passes through a number of stages. The *end stage* of the disease is often counted as the time when a TKA is indicated and is relatively well defined. The point of onset, however, is often difficult to establish.

Luyten *et al*.[10] have established an *early-stage* OA and have delineated how this stage of the disease should be defined. According to them, early OA is defined by three criteria:

- Knee pain
- Radiographic findings according to Kellgren-Lawrence <2
- At least one of
- A: "Arthroscopy": International Cartilage Repair Society (ICRS) I-IV in two compartments or ICRS II-IV in one compartment
- B: MR-findings as defined by Whole-Organ Magnetic Resonance Imaging Score (WORMS) 3-6[11] or BLOKS (Boston Leeds Osteoarthritis Knee Score)[12] or bone marrow lesions.

By definition, hence, "early OA" involves symptoms where patients seek medical advice because of pain. At that point a clinical diagnosis is established, and the rationale of Luyten *et al*.[10] is that patients at this stage can be very different and react differently to a variety of treatments. In order to be able to compare different studies and different modes of treatment applied, a distinct definition of the patient material is beneficial.

The defining signs of "early OA" involve structural changes in the cartilage. Even subtle ICRS I changes, or WORMS changes on MRI, involve degradation of extracellular matrix (ECM) and osteophyte formation. A weight-bearing knee x-ray stadium Kellgren-Lawrence 1 involves structural changes along the joint line. Such changes take time to develop, and hence, it follows that the disease has been established for a long time on the cellular level before early OA can be diagnosed. This is a preclinical stage where the patient is symptom free and functions well but is in a stage where cellular processes have started and often act relentlessly to destroy the joint. This is a stage that we propose could be called "pre-osteoarthritis" (pre-OA) and this is the stage where possible curing interventions can best be applied.

Our question is whether this theoretical entity really exists and whether it can be identified?

Does Pre-OA Exist?

It is generally agreed that OA is not a mechanical but rather a biological process.[13,14] This process may well be driven by mechanics, that is, trauma[15] or meniscectomy,[5] but the actual breakdown of cartilage is caused by cells in the joint, predominantly the chondrocytes in the affected cartilage area. These cells start to express a different biosynthetic pattern that induces the production of metalloproteases and collagenases, which, in turn, break down the ECM.[16,17] Joints are subject to enormous loads, often many times body

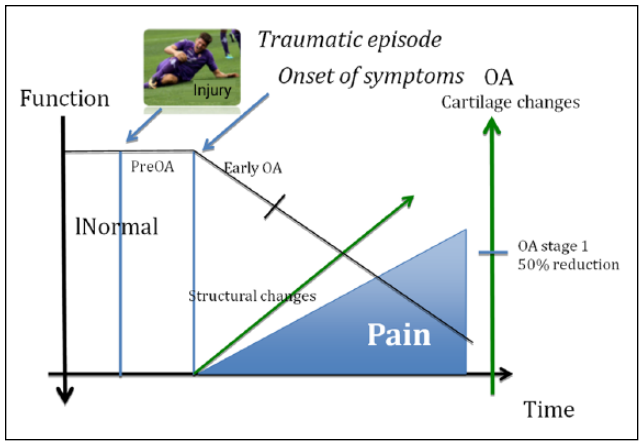

Figure 1. Self-explanatory diagram of a suggested position of Pre-OA in the development of osteoarthritis (OA).

weight. In order to accommodate these loads, the actual "work" of the cartilage is carried by the ECM and the biology of the cartilage is left to a minute portion, less than <1% to 2% or 300 to 400 cells/mm^3. This is on the order of 1/1000th of the number of cells in parenchymatous organs and hence the "biology" of cartilage is very slow. This would explain the poor healing capacity and also the very slow development of OA (see **Fig. 1**).

For this reason, pre-OA as defined by us, from a philosophical point of view, "must" exist, representing the long transition from normal, healthy cartilage to osteoarthritic cartilage. Indeed, it appears reasonable that a long phase should exist where cellular enzymatic processes have started but not yet reached clinical, that is, symptomatic, relevance. Thus, the question is if there is a broad threshold phase or a thin transition zone where pure healthy cartilage transforms into diseased cartilage that often is called degenerative cartilage. Is degenerative cartilage also osteoarthritic cartilage? Probably, degenerative cartilage is sometimes traumatized cartilage but not yet OA cartilage or might also be that it will never become an OA cartilage. Due to changes in the morphology, OA may develop in some of those joints while others remain in a degenerative state, which could also be a stage of pre-OA.

A possible model for this situation is the meniscectomy. It is known that such a procedure will lead to OA in, possibly, all cases if they are followed long enough.[18,19] Consequently, meniscectomy could be modelled as a hypothetical point of onset.[20,21] Patients are often symptom-free for many years despite the fact that the cell activities are altered by the changed environment.

Another possible model is trauma. Traumatic episodes sometimes result in chondral fractures, where full-thickness pieces of cartilage are torn loose resulting in a defect in the cartilage down to intact subchondral bone. Such defects do not heal in animals[22] or in humans.[23-25]

In this context, Buckwalter emphasizes three stages:

- Stage 1, where there is no structural damage but influence on the cellular level
- Stage 2, where cartilage is disrupted down to but not through subchondral bone
- Stage 3, which is an osteochondral fracture

Such a delineation appears appealing. Stage 2 corresponds to the major trauma where cartilage is torn and where, in the absence of bleeding, healing is improbable. Instead, rapid deterioration of joint function ensues. Stage 1, where chondrocytes express a different panel of degrading enzymes, results in a slower destruction of the joint. Such trauma is common among farmers and forestry workers, who have a high probability of getting knee OA.[26-28]

Stage 1 may also represent the situation after meniscectomy, where "microtrauma" is inflicted on the cartilage on a daily basis. Stage 3 corresponds to the artificial situation where blood is drawn through microfracturing.

Mechanobiology

The response of cartilage tissue to mechanical loading can be either anabolic or catabolic, depending on the magnitude, type, and duration of the load. Physiologic levels of loading are likely beneficial and can influence positively the biochemical composition, for example, PG content, of the tissue[29,30] and result in temporary changes in cartilage thickness.[30,31] If the level of loading is intensive and repetitive, however, the homeostasis of the tissue can be disturbed, with surface fibrillation, chondrocyte proliferation, PG depletion, and increased expression of biomarkers MMPs and COMP.[25,32] The immediate changes to the chondrocytes and cartilage matrix, which follow injurious mechanical loading, have been investigated using application of blunt, impact loads to cartilage and osteochondral disks *in vitro*.[33,34] From these studies, it is clear that the injury results in both necrotic and apoptotic cell death.[35,36] Furthermore, it has been shown that antioxidants can reduce the magnitude of cell death,[37,38] implying that the mechanically triggered production of reactive oxygen radicals, perhaps mediated by the expression of pro-inflammatory cytokines, are important in the early events of cartilage destruction.

Trauma and meniscectomy are examples of episodes that precisely mark the point in time after which OA begins to develop. At some point during this long development of the disease (10-20 years), pre-OA must, by definition, exist. The question is: Can it be diagnosed? When is the cartilage at a point of no return, if indeed such a return is possible? Could one, with treatment, slow down or halt a progression of cartilage degeneration and return it to a healthier state?

Table 1. Primary Candidates as Instruments for the Diagnosis of Pre-OA.

Diagnostic Tool	Current Feasibility	Remarks
Biomarkers	Developmental stage; none currently available for clinical use	Intensive research and breakthroughs are expected
MRI-T2 mapping	Currently in clinical use	
dGEMRIC	Currently in clinical use; has shown prognostic power of OA	Difficult standardization
Arthroscopy+ probing	Still developmental	Probing by ultrasound, NIR, or mechanics assess subsurface structures

OA = osteoarthritis; MRI = magnetic resonance imaging; dGEMRIC = delayed gadolinium enhanced MRI of cartilage; NIR = near-infrared.

Diagnosis of Pre-OA

A number of different modes of assessment of joints are available (**Table 1**).

Clinical history is always of importance. In the case of possible pre-OA, a history of knee trauma is of interest. Such trauma could be of a single-occurrence nature or iterative as, for example, in soccer players.[39] These authors found a higher incidence of OA in elite soccer players even in the absence of (known) trauma. It might be that pain is absent[40] or less pronounced in the pre-OA stage.

Physical examination is part of any patient workup. A varus alignment due to OA precludes a normal standing x-ray. A varus alignment, however, could be due to a malunited fracture, which is highly indicative of possible pre-OA.[41]

Ordinary *radiology* in the supine position is not an accepted mode of examining the possibly osteoarthritic knee. Instead, radiographs should be obtained in the standing, weight-bearing position.[42] These should be normal, that is, without joint space narrowing. In fact, Cotofana *et al*.[43] found an interesting increase in joint space with osteophytes indicative of early OA. Basically, however, standard radiography is regarded as an insensitive diagnostic and monitoring tool and is not sensitive enough to detect pre-OA or early stages of OA.[44]

Biomarkers

The ECM components of cartilage uphold the structural integrity and mechanical properties of articular cartilage and are composed of two types of major building blocks, the collagen fibers and PGs.[45] The most abundant matrix protein in the articular cartilage is type II collagen, which forms the bulk of the collagen fibril network. The collagens constitute two thirds of the dry weight, and in addition to type II collagen, Types I, III, V, VI, IX, X, and XI are also present. The PGs constitute around 30% of the tissue. The PGs are aggregating or nonaggregating wherein the nonaggregating types are keratan sulfate, chondroitin sulfate, and dermatan sulfate. The predominant aggregating PG (aggrecan) makes up 95% of the total PG mass of articular cartilage.[46] Cartilage matrix also contains a variety of small leucine-rich repeated PGs that maintain the tissue integrity and modulate metabolism: decorin, biglycan, fibromodulin, and lumicin.[47] Cartilage oligomeric protein (COMP) is a pentamer with binding regions to types I, II, and IX collagen and is believed to play a role in fibril formation and maintenance of cartilage ECM.[48] The ECM matrix structure is affected in OA and matrix components are released into the synovial fluid and subsequently into the bloodstream. Biomarkers for OA have been based on the hypothesis that remnants from the ECM undergoing breakdown could be found and detected in synovial fluid, blood, or urine.

A biomarker is then defined as a biological molecule found in blood or other body fluids and in tissue samples that is reflecting normal biological processes, pathogenic processes, or responses to therapeutic intervention.[49] Due to the increasing clinical challenge in OA a lot of effort has been put into development of biochemical markers that have the capacity to diagnose early-stage OA, predict OA progression, and assess therapeutic response. The ability to detect early-stage OA could result in improved management of patients with combined preventative measures and lifestyle changes. Many biological markers available today appear to be sufficiently characterized for the study of progressive OA, but few have been identified for the diagnosis of the early stage of the disease.

The search for OA biomarkers have been focused on two categories (a) inflammation and (b) early molecular events.

Inflammatory Markers. Traumatic injury to the joint triggers an inflammatory response that could be detected in elevated levels of C-reactive protein (CRP) as detected by high-sensitivity assays. The increase in CRP levels is probably preceding the release of other OA indicators, such as molecular markers of matrix breakdown, and could be observed well before clinical disease. Furthermore, inflammation directly affects synovial cells and chondrocytes, causing them to produce cytokines including interleukins and catabolic agents like proteases that will interfere with repair and accelerate cartilage breakdown. An interesting hypothesis has been postulated, describing that inflammation is maintained by fragments of cartilage breakdown that trigger the innate

response.[50] The members of the small leucine-rich PGs (see above) target the classic complement pathway and cause its enhanced activation.[51] Complexes of COMP and the C3b component of the complement pathway have also been demonstrated in the synovial fluid of patients with OA, thus demonstrating a local activation of the innate immune response in the joint.[52]

ECM Molecular Breakdown. When cartilage fibrillation causes cartilage swelling, it can be observed by MR. The underlying molecular events are poorly understood but early changes at the molecular level are present including turnover of aggrecan, cartilage intermediate layer protein 1 (CIlP-1), COMP, and fibronectin.

The aggrecanases (ADAMTS 4 and 5) causes breakdown of aggrecan that liberates the major part of the molecule (containing heavily negatively charged chondroitin sulfate chains) from cartilage. These glycosaminoglycan chains are the key contributors to the maintenance of the fixed charge density and osmotic environment of cartilage, which are responsible for the water-retaining and mechanical proper ties of the tissue.[53,54]

In a recent summary, inflammatory/immunological markers were among the relatively "best"-performing markers with regard to burden, prognostic power, and/or treatment efficacy.[55] Furthermore, a summary of current biomarkers under investigation is given in a recent review.[56]

Although the rationale behind biochemical markers seems clear, breakthroughs in the biochemical marker in pre-OA disease are limited so far. In an attempt to solve the biomarker problem in OA disease, the National Institutes of Health–funded OA Biomarkers Network defined biomarkers according to the "BIPED" biomarker classification (which stands for Burden of Disease, Investigative, Prognostic, Efficacy of Intervention[57]). A systemic review in 2010 on serum and urinary biochemical markers for knee and hip OA concluded that no biomarkers published until that year were sufficiently discriminating to allow diagnosis and prognosis of OA in individual or limited numbers of patients. Furthermore, none of the markers could function as primary outcome parameters in clinical trials. More research on molecular validation and origin(s) and metabolism of biochemical markers was therefore deemed necessary.[58]

Computed Tomography

Contrast-enhanced computed tomography (CECT), analogously to delayed gadolinium enhanced MRI of cartilage (dGEMRIC),[59-61] allows us to evaluate the intrinsic ionic distribution in cartilage.[62] This distribution is known to correlate with tissue PG content, and thereby also with mechanical properties of the tissue.[63] In the first *in vivo* studies, intra-articular injection of the negative contrast agent has been applied, indicating the feasibility of this minimally invasive approach.[64,65] Comparison of both immediate and delayed, for example, at 45 minutes, imaging after injection allows evaluation of the diffusion of contrast agent in cartilage.[65] Diffusion parameters may provide quantitative indices that sensitively reflect early compositional changes in cartilage.

Even in the case of peripheral joints, such as knee, the radiation dose for a patient in *multiple CT imaging* must be minimized. This necessitates the optimization of imaging protocols. Positive contrast agents could provide a higher contrast for cartilage imaging[66] and can be administered by intravenous injection. However, positive contrast agents are not in general use in x-ray diagnostics due to their toxicity. Optical coherence tomography (OCT) provides an additional intra-articular imaging modality to diagnose minute degenerative changes, especially in the superficial cartilage, including high-resolution quantitative analysis of surface roughness.[67,68]

Magnetic Resonance Imaging

MRI, being a multiplanar diagnostic tool, is an excellent modality for evaluation of patients with OA of knee joint. It accurately defines the extent of bony and soft tissue changes in the knee joint. MRI allows the evaluation of subchondral bone, which is a richly innervated structure that is considered to be important in the occurrence of pain and the structural progression of OA.[69,70] Joint effusion is best detected on fat-suppressed proton-density or T2-weighted fast-spin echo MRI sequences.

MRI can provide accurate and reproducible data on a series of cartilage measures, such as volume, thickness, and denuded cartilage area.[71] Cartilage defects range from focal blistering and surface irregularities to deep ulceration and full-thickness cartilage wear with exposure of subchondral bone.[72]

Quantitative MR imaging techniques and quantitative MR biomarkers can detect early degeneration of articular cartilage, mainly represented by an increasing water content, collagen disruption, and PG loss. T2 mapping, T1rho mapping, dGEMRIC, and diffusion-weighted imaging (DWI) are applicable on most clinical 1.5-T and 3-T MR scanners. Currently, the knowledge concerning the correlation of clinical and MR findings is limited, and a standard of reference is difficult to define. Nevertheless, modern imaging techniques can help detect early signs of cartilage degeneration and joint deterioration.

Delayed Gadolinium-Enhanced MRI of Cartilage. dGEMRIC is a quantitative cartilage MR imaging technique that correlates with the PG content of articular cartilage and is able to provide a direct measure of the GAG content. It requires the application of a negatively charged intravenous contrast

agent (Gd-DTPA2−). The negatively charged Gd-DTPA2− molecule penetrates cartilage in an inverse relationship to the concentration of negatively charged GAG side chains of PG. A depletion of GAG content in degenerated cartilage results in an accumulation of the paramagnetic gadolinium ions, following the principle of electroneutrality.[73] About 45 to 120 minutes after contrast administration, postcontrast MRI is performed. Additionally, an exercise period is required after contrast agent application, which influences the distribution of the contrast agent. Usually, T1 relaxation time measurements pre (T1) and post contrast application (T1-Gd) are used to determine the contrast agent concentration in cartilage. Very exciting correlations between dGEMRIC and ensuing radiographic developments of OA 5 years later have been reported.[60]

T1rho Relaxation Time. T1rho values have been shown to increase with GAG (PG) content loss of the ECM of hyaline cartilage, with increases in bulk water and with cartilage softening, while being less dependent on collagen disruption. T1rho relaxation time measurements do not require contrast agent injections.[74]

T2 and T2 Relaxation.* T2 measurements do not require contrast agent injections and higher and more heterogeneous T2 values are thought to characterize collagen deterioration and increasing water contents. T2 values still vary significantly between different acquisition methods and MR scanners. T2* has shorter imaging times and the possibility of 3D acquisition and thereby providing greater spatial resolution. In contrast to T2 mapping, T2* mapping uses a gradient echo (GE) pulse sequence and includes both T2 relaxation and coherent dephasing effects.[75]

Diffusion-Weighted Imaging and Diffusion Tensor Imaging. Diffusion-weighted imaging can probe water mobility in articular cartilage. Water molecules diffuse in the space surrounding the ECM of the cartilage. In cartilage with an intact collagen network water mobility is restricted. The increased mobility of water in a deteriorated ECM, representing early cartilage degeneration, can be assessed by DWI. Therefore, by measuring the molecular movements of water within the cartilage tissue, DWI techniques can probe tissue microstructure changes.[76]

A variant of DWI is diffusion tensor imaging (DTI), which enables the measurement of diffusion anisotropy. In this technique, diffusion gradients are applied in at least six orientations and the data are fitted to a diffusion tensor model. DTI correlated with the orientation of collagen fibrils, with collagen disruption and cartilage degeneration.

Quantitative MRI techniques can provide indirect information about the structure and composition of cartilage using relaxation time analysis. Based on the subject-specific implementation of joint geometry and cartilage structure and composition using quantitative MR imaging, computer-aided functional modeling of cartilage enables us to visualize the stress and strain patterns in cartilage under different joint loading activities. This may ultimately help us predict the probability of load-related cartilage injuries and subsequent OA development.[77]

Arthroscopy

Arthroscopy remains, in some respects, the gold standard in cartilage characterization; structural damages are defined by arthroscopy as shown, for example, in the ICRS score. However, in this context of pre-OA, the cartilage lesions are still at a cellular level and structural damage has not yet taken place (= ICRS 0). Therefore, adjuvants to arthroscopy are needed such as ultrasound[78] or mechanical probing.[79]

New quantitative *probing techniques* are under active development and may offer ways to detect changes typical to early cartilage degeneration. Ultrasound reflection from the cartilage surface and backscattering from internal tissues provide information about the microstructure, especially collagen architecture of the tissue.[61,80] Better precision in mapping has been suggested using high-frequency ultrasound (>10 MHz).[61,81]

Contrarily, minor PG depletion in matrix is less sensitively revealed by ultrasound. OCT is an intra-articular imaging modality with microscopic resolution to diagnose minute degenerative changes in cartilage, including high-resolution quantitative analysis of surface roughness.[67,68,82] In OCT, limited penetration of light in tissue can prevent detailed imaging of deep layers of thick human cartilage.

Arthroscopically guided indentation[83,84] or streaming potential[85] measurements provide diagnostic information on intrinsic tissue qualities, including cartilage mechanical or electromechanical properties, respectively, at the site of interest. These measurements can help reveal local tissue lesions with normal surface appearance. For diagnostics of pre-OA or early OA, however, normal site-dependent values for the measured parameters of intact cartilage would be desirable. When the arthroscope is equipped with a near-infrared (NIR) spectroscope probe,[86] measurement and analysis of the reflection spectrum of NIR light (about 800 nm to 2500 nm) yields information on cartilage composition, for example, tissue water content.[87,88]

Discussion and Conclusion

We believe that "pre-OA" is indeed an entity that merits scientific distinction; one can deduce that it "must" exist due to the known biologic processes on the cellular level and the timeline that constitute the etiologic origin of the disease. These processes precede clinical manifestations by years/decades. This long-term phase is when the disease is

most receptive to treatments of various kinds. The definition of pre-OA would be the following: A knee exhibiting one or many risk factors without pain, normal standing radiographs, no structural changes on arthroscopy or standard MRI, that is, before early OA can be diagnosed.

Currently no biomarkers are used in clinical decisions regarding disease development but some markers could function as diagnostic marker of OA and correlate with radiographic markers of OA and clinical grading. Among the most promising candidates are urinary C-terminal telopeptide of collagen type II (CTX-II),[89] COMP, and collagen II fragments,[90] as well as aggrecan neoepitopes.[91]

MRI is perhaps the most promising diagnostic tool. This technique is presently the focus of intense research and new developments are to be expected. Presently, the findings of Owman *et al*.[92,93] are exciting. These authors used dGEMRIC to investigate patients with knee pain and normal cartilage at arthroscopy. The dGEMRIC data correlated significantly with the development of OA 5 years later. dGEMRIC, however, is hard to standardize and results are sometimes less consistent.

Arthroscopy at the pre-OA stage should appear normal or show some light degree of pathology (ICRS 1-2). Combination with high-resolution probing or imaging using acoustic, optical, mechanical, or electromechanical additions can generate spatial information on tissue structure, composition, and properties. As the measurements, however, are typically conducted invasively during arthroscopic evaluation of the joint, this can be a significant limitation for diagnostics of the pre-OA or early stages of OA.

At this point in time, a combination of diagnostic tools may pin-point the disease with some degree of precision. In order to detect and find patients that have arrived into the zone of pre-OA, we should look for them among those patients that are at increased risk for OA. A large number of risk factors are known such as age, sex, trauma, overuse, and genetics, joint malalignment, and obesity. They may all contribute to turn the patients into a pre-OA state. By finding a pattern of how the cartilage goes from a pre-disease state into an early disease will give us tools of how to prevent the disease development.

Screening possibilities today could as an example be

1. Persons at risk as discussed above are followed
2. Imaging screening with:
    i. T2 mapping for volume assessment
    ii. Delayed gadolinium enhanced MRI (dGEMRIC) and contrast-enhanced computed tomography to reveal cartilage GAG content

3. Biomarkers in urine, serum, and synovial fluid
    i. s-COMP, adiponectin, MMP-1, MMP-3, IL-6, S-BSP, type II collagen C-telopeptide (UCTX-II), systemic CRP. Increased use of proteomics techniques to examine the synovial fluid. Proteomics allow the simultaneous analysis of multiple markers as those suggested above.

4. Possibly arthroscopy using probing techniques such as ultrasound, NIR, or mechanical probing

In Conclusion

It is emphasized that OA should not be regarded as a disease necessitating TKA but represents a continuum of a long-term biological process where TKA is the end stage. We believe that in asymptomatic patients with risk factors and/or a known point of possible onset of cartilage disease, for example, knee trauma, and with normal standing x-ray, the combination of MRI T2-mapping or dGEMRIC, a cocktail of biomarkers, and arthroscopy using sensitive probing techniques hold a promise at this point to be able to delineate between knees with a good and a less good prognosis regarding the long-term development of OA (**Table 1**). Future research should focus on diagnosing the developing OA at the earliest possible time, before the disease reaches the stage of early OA stage, when it may be too late.

In contemporary medicine an increasing emphasis is placed on preventive measures, that is, to address a condition early, or even before, the condition has manifested itself clinically. For a condition with a prevalence as high as knee OA, such preventive measures would have a considerable pay-off. From such a perspective, screening procedures may hold a promise to address the projected "epidemic" of (knee)-OA. Such screening methods could be MRI or even explorative arthroscopy may become indicated at some certain age, say, 50 years. Naturally, such procedures are only warranted when effective treatment protocols have been identified and this is yet to be accomplished.

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