

Towards the identification of early stage osteoarthritis

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Summary

A variety of genetic and environmental factors contribute to the progressive development of OA. It is necessary to identify people who are developing initial changes in cartilage and/or subchondral bone before onset of classical radiological features in order to detect early phase of OA. Recent quantitative MRI techniques can evaluate the structural, mechanical and biochemical characteristics of cartilage. T2 mapping is able to assess cartilage volume and defects measurement, delayed gadolinium enhanced MRI (dGEMRIC) and Contrast Enhanced Computed Tomography (CECT) can reveal Cartilage GAG content. Accurate and reliable serum, urine and synovial fluid biomarkers are also requested. Several biomarkers have been studied and proposed, but there are many critical issues to consider for inferring useful data from studies on biomarkers in early OA such as phase of disease, specific joint sites, systemic concentrations, circadian rhythm, their clearance from the joint, etc. Recently proteomics has produced great expectations to improve the early diagnosis of OA. These discoveries may open opportunities for the identification of early stage of OA leading to manage the symptoms and ultimately slow the progression of OA.

KEY WORDS: early osteoarthritis; imaging; biomarker.

Osteoarthritis (OA) is a long standing disease characterized by several steps such as a progressive loss of articular cartilage accompanied by new bone formation and synovial proliferation that may culminate in pain, loss of joint function, and lastly disability. A variety of genetic and environmental risk factors and pathophysiologic processes contribute to the progressive advance of the disease over a period of years resulting in the typical features of OA: degradation of articular cartilage, osteophyte formation, subchon-

dral sclerosis, meniscal degeneration, bone marrow lesions, and synovial proliferation.

In order to detect early phase of OA we need to identify people who are developing initial steps of cartilage and/or subchondral bone changes or damage before onset of symptoms and classical radiological patterns. To this purpose we can employ both imaging and soluble new biomarkers in selected high risk subjects.

The potential value of MRI as a 'biomarker' has progressively been evidenced by recent and huge literature. Among recent imaging techniques able to reveal the initial changes or damages in cartilage we consider quantitative MRI techniques that can evaluate the structural, mechanical and biochemical characteristics of normal and damaged cartilage. Techniques for the quantitative and functional assessment of cartilage, synovium, and bone by MRI are advancing, making it probable that MRI will eventually be an essential and sensitive tool to predict and assess disease progression. For instance 3D MRI is able to assess cartilage volume and defects measurement, delayed gadolinium enhanced MRI (dGEMRIC) and Contrast Enhanced Computed Tomography (CECT) can reveal Cartilage GAG content.

The spectrum of cartilage and bone damage can be divided into pre-clinical damage, pre-radiographic damage and radiographic damage, defined by the techniques that are capable of distinguishing damaged from normal, healthy tissue. Radiographic damage and healthy tissue may be delineated using X-ray radiography only in a late phase of the disease. In clinical practice pre-clinical damage cannot be currently recognized using available techniques such as arthroscopy, microscopy and histology. Moreover arthroscopy cannot be easily performed in other joints rather than knee. Most qMRI (1) techniques are reliable for differentiating radiographic damage from healthy cartilage, but reports vary as to their sensitivity in distinguishing the various degrees of pre-radiographic damage from normal when using thickness and volume changes in response to an applied load, T2 mapping, dGEMRIC or T1ρ mapping. Unlike arthroscopy and radiography, the set of qMRI techniques are more recent in their development. Researchers can enhance the diagnostic utility of these techniques by developing criteria to delineate damaged or diseased from normal, healthy cartilage in individual patients, rather than in patient populations. However some studies seem to suggest that dGEMRIC index may have a predictive value for future OA in a pre-radiographic Osteoarthritis in the Knee and Hip. A low dGEMRIC index at baseline is associated with a high risk of developing radiographic OA six years later. In patients with unicompartmental OA, the dGEMRIC index was higher in the spared versus the diseased compartment. Moreover in hip dysplasia the dGEMRIC index was significantly lower than in asymptomatic subjects, regardless of the absence of radiographic OA modifications. In addition surgical treatment of dysplasia (periacetabular osteotomy) is associated with a poor outcome if the patient had a low pre-operative dGEM-

RIC index. MRI techniques are also relevant to detect changes in the subchondral bone. It is well known that alterations in the subchondral bone have direct impact on the mechanical properties of the articular cartilage. An increase in the density of the subchondral bone plate as a result of its thickening is accompanied by a locally reduced elastic modulus of the bone as a consequence of enlarged vascularization and bone remodelling below the articular cartilage. Reliable data show that in early stages of OA, the subchondral bone displays osteoporotic modifications as also seen in some animal models. Therefore, primary osteoporotic changes in the subchondral bone are suggested to precede in early OA subchondral bone sclerosis, latter being considered a secondary event in established OA.

To identify early OA we also need accurate and reliable serum, urine and synovial fluid biomarkers. It is expected that biochemical markers may be used in conjunction or not with imaging to properly assess phase of disease, measure disease activity and predict progression in OA. The Osteoarthritis Biomarkers Network, a consortium of five National Institutes of Health-designated sites, has recently classified five categories of biomarkers (captured in the acronym BIPED) (2) to support the study of OA, from basic science to clinical world: Burden of disease, Investigative, Prognostic, Efficacy of intervention, and Diagnostic. Several biomarkers have been studied and proposed such as U-CTX II, C2C, coll2-1, coll2-1NO2, CP II, PIINP, COMP, 846 epitope, HA, Fib3-1, Fib 3-2, MPO, IL-11, LIF, OP-1, us CRP.

There are many critical needs to consider when we try to infer useful data from studies on biomarkers especially in early OA. It is requested: to develop better structural endpoints for biomarker qualification; to develop biomarkers related to each specific joint sites; to elucidate the specific joint site contributions to the systemic concentrations of biomarkers; to determine the clearance of biomarkers from the joint, and from the body fluids (i.e. blood, urine); to assess if there is a circadian rhythm in the level of a biomarker; to evaluate if some covariates (age, gender, BMI, concomitant diseases, drugs) may affect the concentration of a biomarker; to establish minimal clinically important differences; to develop multiplex assays incorporating existing promising biomarkers to provide efficient, cost-effective assays informing on multiple domains of joint biology.

Proteomics has produced great expectations to improve the diagnosis and management of OA (3). The use of synovial fluid (SF) rather than serum for proteomic techniques is advantageous because it avoids its dilution in other biological fluids. SF is a logical potential compartment for OA biomarkers because it is derived directly from the diseased site and functions in the exchange of proteins between articular cartilage and the systemic circulation. Consequently, many proteomic strategies in OA are designed to identify putative biomarkers in SF before their validation in serum.

A genetic disposition to OA has been clear since Twin pair and family risk studies have indicated that there is a significantly higher concordance for OA between monozygotic twins than between dizygotic twins, and that the heritable component of OA may be in the order of 50 to 65%. In addition, it is clear that multiple genetic factors can contribute to both incidence and severity of OA; moreover these may differ according to specific joint (hand, hip, knee, or spine), sex, and race. Genetic linkage, common polymorphisms and genome-wide association studies (GWAS), have identified several genes affecting the prevalence of knee OA. At

least three loci harbouring alleles with compelling association with OA have been reported: the 7q22 locus, GDF5 (encoding the cartilage-derived morphogenetic protein 1 which belongs to TGF- β superfamily); DIO2 (encoding protein belongs to the iodothyronine deiodinase family). Genes regulating cyclooxygenase, interleukin 1 (IL-1), IL-6, and IL-10 may be also linked to susceptibility to OA due to the involvement of inflammation in the OA process. Potential role of genes involved in pain perception such as catechol-O-methyltransferase, have recently been object of much interest in OA. Since OA is a highly polygenic diseases the genetic risk may be the sum of a small contribution of different several loci. There is also evidence, given the variety of candidate genes predisposing to OA, that there may be an additive effect of individual genes in the development of disease. Moreover there are clear differences between subpopulations of OA and different OA phenotypes, such as distinct genetic traits are linked to OA of the knee, hands or hip. Approximately half of gene pathways seems to be associated with both hip and knee OA, but they are differentially expressed indicating that, although the gene lists are largely different between joints, many of the same pathways are involved in OA.

Both genomics and proteomics may aid physicians in making an early diagnosis. The understanding of these markers will become part of daily rheumatology practice in the near future. Interestingly, although proteomic and epigenetic biomarkers have been and are the last to appear, they can offer useful and basic information about what is happening to patients in the earliest stages of OA and these tests will be utilized before radiographic imaging in the OA diagnosis process. So we will move from managing radiological images from OA to molecular pictures, obtained either from genomics or proteomics.

At this point another relevant issue needs to be considered: to whom administer such tests? In order to detect patients at an asymptomatic early OA and pre-radiographic stage we need to identify them among subjects who are at increased risk for OA. A multiplicity of etiologic risk factors are known such as age, sex, trauma, overuse and genetics, joint malalignment and obesity can contribute to the process of injury in different compartments of the joint. Better knowledge to quantify risk factors in the incidence and progression of OA is requested through larger epidemiological studies on occupational and professional activities, joint mala-alignment, exercise, injury, body mass index, diet and surgery. This is necessary also from an economical point of view since we must reduce costs performing expensive imaging and biohumoral tests (i.e. MRI) only in subjects with a high probability to be affected by early OA, after identifying very high risk subjects.

Conclusions

In summary we are beginning to understand better the mechanisms by which environmental genetic, mechanical, and metabolic factors initiate and perpetuate the biochemical changes that lead to progressive failure of the OA joint. These discoveries may open opportunities for the identification of early stage of OA leading to effective therapies that reduce the symptoms and ultimately slow the progression of OA.

References

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