What steps are needed to achieve perfect diagnostic and monitoring tests for osteoarthritis?

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**Keywords:** biomarkers • joint • osteoarthritis • proteomics

Osteoarthritis (OA) is the most common form of arthritis. It is characterized by joint degradation and is related with aging, so its prevalence is increasing in recent decades. Hip and knee OA was recently ranked as the 11th highest contributor to global disability [1], and estimates are that 9.6% of men and 18.0% of women over 60 have symptomatic OA. The cost of this disease in Europe is valued at 0.5% of gross national product.

**Clinical unmet needs in OA**

OA is a complex disease of multifactorial etiology, primarily characterized by articular cartilage degradation, whose pathogenesis is not fully understood to date [2]. The limited knowledge about OA etiopathogenesis and the absence of specific and sensitive biomarkers impedes its early diagnosis, the performance of prognosis studies and also the development of new efficient disease-modifying osteoarthritis drugs. Emerging data suggest that OA is a heterogeneous disease with a variety of pathophysiologic drivers, and there is still a limited understanding of the diverse OA phenotypes allowing targeted interventions [3]. Although the increase of catabolic processes in cartilage is known to be caused by a complex network of biochemical factors whose upregulation is driven by proinflammatory cytokines such as IL-1β or TNF-α [4], mitochondrial dysfunction and metabolic alterations have been also linked with OA pathogenesis [5,6] and their contribution to disease development and progression remains to be clearly defined. To shed light on these questions, the European League Against Rheumatism released last year some recommendations to reorient research into this disease, including focusing attention on noncartilagenous tissues and their interaction within the joint, the pathogenesis of osteoarthritic pain, new treatment strategies and the description of ‘early’ disease [7].

Currently, diagnosis of OA is based on radiographic criteria (such as joint space width) and clinical symptoms, which are insensitive to detect small changes and do not allow the visualization of the tissue most associated with the disease (articular cartilage). The deficiency of alternative tools for a more precise monitoring of OA hinders the evaluation of efficacy and safety of newly proposed disease-modifying osteoarthritis drugs [8]. Despite the large and growing disease burden, many pharmaceutical organizations have played down or abandoned OA drug development due to observed difficulties. Worryingly, current treatments are predominantly restricted to symptomatic relief or costly and invasive surgical intervention at advanced stages of the disease.
Necessity of useful biomarkers for OA

Given the unmet medical needs mentioned above, there is a clear requirement of specific and sensitive biomarkers of OA to enable diagnosis at early stages, and its further accurate monitoring. Biomarkers are measurable indicators of a biological state or condition, either normal or pathogenic. Biomarker features (‘dry biomarkers’) in OA include questionnaires and imaging parameters (such as radiographs, MRI, ultrasound or visual analog scales) [9]. In this area, the use of quantitative MRI to assess small changes in cartilage shows an interesting potential, although the widespread use of MRI is to date highly limited by cost. On the other hand, the biomarker substances (‘Wet biomarkers’) correspond to genetic and biochemical molecules ideally derived from body fluids that are easily available to researchers (blood, serum, urine or synovial fluid). Disappointingly, after intense efforts carried out in the last decade, none of the biochemical markers that have been described to date is sufficiently well validated, qualified and accepted for systematic use in diagnostic or monitoring tests for OA [10].

Challenges in developing novel OA biomarkers

Considering the above, robust biomarkers are required for improving clinical trial outcomes, defining phenotypes and stratifying interventions for OA management. In order to validate and define their performance, there are two major challenges that remain to be faced: technological issues and the design of clinical trials.

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First, a number of biochemical markers for OA have been evaluated in the last decades, essentially by performing ELISA on blood-derived samples, urine or synovial fluid. The limited multiplex capacity of this strategy has increased costs and hampered the simultaneous evaluation of biomarker panels in large cohorts. This appears to be very advantageous in the study of such a complex disease as OA, for which no single molecule has emerged to date as the gold standard. To solve this problem, there is an essential need of novel technological tools for easing the existing bottleneck in moving novel marker candidates from discovery phases into clinical applications. In this field and after two decades of basic research, proteomics technologies enabling the multiplexed analysis of several molecules in a high throughput fashion have matured to the point that their use in clinic appears practical and helpful [11]. Targeted proteomics strategies either based on MS – such as selected/multiple reaction monitoring assays [12] – or antibodies – such as multiplex bead array assays [13] – are increasingly being applied for biomarker verification. Nevertheless, still standardization and quality control of these procedures need to be established to ensure that proteomics assays are validated for their intended use as in vitro diagnostic tests, so that the analytical validity of the test procedure and outcome are assured.

On the other hand, special attention must be given to the design of clinical trials for the development of diagnostic and monitoring tests. This is extraordinary relevant in the field of OA, where design deficiencies might have been the underlying cause of the number of clinical trial failures and the frustrating lack of progress in the development of treatments suffered in the last years. Given the heterogeneity of this disease, its variable course, the lack of knowledge to prospectively identify patients at risk of progression and the very large number of affected individuals, tools are needed for the characterization of OA phenotypes and patient subtypes [14] to allow their independent evaluation in clinical trials. Just in the last two years, several advances have been made in characterizing OA phenotypes both from a transcriptomic or epigenomic point of view [15,16], and also by the description of pain [17] or clinical characteristics [18]. A better understanding of these different phenotypes is essential to identify specific OA patient subpopulations, which will help to improve the design and data interpretation of clinical trials.

Conclusion

Important efforts still need to be performed to achieve sensitive and specific tests for the early diagnosis and precise monitoring of OA. Although several advances have been made in the last years, even now there is much to be done. For this aim, improvements in imaging technologies and analytical validation of multiplex analyses by targeted proteomics will be highly useful to facilitate the identification and qualification of sensitive and specific imaging or biochemical markers [19]. Furthermore, knowledge being currently acquired on the diverse OA phenotypes must be employed in clinical development plans in order to adopt a personalized medicine mindset, trying to pair patient subpopulations with the right therapeutic modes of action [20]. It is anticipated that this will undoubtedly aid the development of novel therapeutic strategies for OA management.

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References