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Review Article

Biomarkers for Diagnosis of Osteoarthritis

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Abstract

Introduction: Osteoarthritis (OA) is the most prevalent of all the rheumatic diseases and currently only conventional imaging methods are utilised for diagnosis of OA which only detect the disease at an advance stage where there is already irreparable damage to the joint. Therefore the priority in the field is towards identifying reliable biochemical measures for early diagnosis and prediction of at risk patients for progression of the disease. Early diagnosis would enable to improve personalised treatment options and lead to better management of patients with OA.

Methods: We conducted a search for articles on potential diagnostic OA-biomarkers, combining the words “osteoarthritis”, “biomarkers” and “diagnosis” using PubMed/MEDLINE bibliography. We also searched for references containing key words such as “aggrecan fragments”, “CTX-II”, “COMP”, “fibronectin”, “haptoglobin”, and “mass-spectrometry”, “PIIANP”, “PIIINP”, “S100A12”, “YKL-40” and “OA patient outcome”. The search was limited to English language articles on human studies only.

Discussion: This review highlights the potential diagnostic value of established OA-biomarkers as well as new candidate biomarkers identified over the last decade. The heterogeneity of OA-phenotype and the cohort of patients used in different studies often led to conflicting biomarker data. Although currently available biomarkers have some clear relationship to OA progression in general, singly they appear to be of limited value in identifying individual patients in early disease stages and at high risk of progression. However, the renewed interest in the field is leading to discovery and validation of new candidate biomarkers that holds the promise of identifying better biomarkers for diagnosis of OA.

INTRODUCTION

Osteoarthritis (OA) is one of the most common chronic joint disease causing substantial pain and disability and it is becoming increasingly more prevalent as the population ages. A recent estimation by Arthritis Research UK suggests that as many as 1 in 3 individuals aged 45 years and over have sought treatment for OA affecting a total of 8.75 million in the UK and over 500 million worldwide. The burden of OA on individual and on the society is increasing dramatically due to an ageing population and general changes in lifestyle, and it is estimated that by 2020, OA will be the fourth leading cause of disability in the world [1].

The most common joint sites affected by OA are hip and knee. The risk factors for developing OA at different joint site are very different but the process of joint damage following the initial trigger is similar at all joint sites. Current management of symptomatic hip or knee OA includes different options that range from lifestyle measures (loss of weight) and supportive therapies (such as physiotherapy) to oral medication, arthroscopic surgery and hip and knee replacements [2]. The outcome of these treatments are usually rated by self-reported questionnaires

and by the physician-based clinical measures[3]. Recently, the International Consortium for Health Outcomes Measurement (ICHOM) gathered a working group in an effort to standardise these measures and published a new definition of outcomes measures to be implemented globally for a better evaluation and comparison of the clinical care of patients with OA across countries [4]. These set of measures outcomes are essentially patient oriented and assess: joint pain, physical functioning, health-related quality of life, work status, mortality, reoperations, readmissions, and overall satisfaction with treatment result [4]. However, although having a patient-reported outcome measures approach is important, there is an urgent need for more objective outcome measures for better management of OA.

OA PATHOLOGY AND CURRENT DIAGNOSIS

In the past, OA was thought to be the disease of the elderly and defined as a simple process of “wear and tear” but during the last few decades many studies have shown that OA is a more complex disease of unknown aetiology. Moreover, OA does not only affect older people as many younger individuals have been reported to develop OA due to genetic predisposition or joint trauma [5]. The

OA pathology is characterised by the degradation of the articular cartilage, osteophyte formation, presence of cysts, sub-chondral bone thickening, degeneration of periarticular ligaments and meniscus and variable inflammation of the synovium, making OA a disease of the joint organ [6-8]. By nature, OA is a heterogeneous disease that develops over many years and can be asymptomatic and active at sub-clinical level long before a diagnosis can be made [9].

Currently, the diagnosis of OA depends on patient reporting symptoms such as pain, joint swelling or disabilities; and the definitive diagnosis is usually made using x-rays. Radiography is currently the 'gold' standard for diagnosis and monitoring OA, but plain x-ray is rather insensitive as it provides little or no information on soft tissues although it does provide an indirect measure of cartilage loss via measurement of the loss of joint space width [10]. Therefore, x-rays can only diagnose OA at relatively advanced stages of the disease when there is already irreparable damage to the joint(s). To improve detection, Magnetic Resonance Imaging (MRI) can be used early on and can be predictive of radiographic change, but may not be cost-effective [10]. Other imaging techniques are available for diagnosis and assessment of OA such as ultra sonography, dual-energy X-ray absorptiometry and scintigraphy but these are largely being used for research purposes, and may not be suitable for routine diagnostic as each of them still present significant practical problems [11-14]. Consequently, new more sensitive and less invasive tools are required for both early diagnosis and monitoring disease progression. Therefore OA-specific biomarkers are urgently needed for early diagnosis and monitoring of patients with OA. OA-specific biomarkers would provide an improved OA outcome measure in clinical trials and provide a direct measure of drug effect and mechanism of action to help better tailor personalised medicines for OA.

POTENTIAL DIAGNOSTIC BIOMARKERS OF OA

Over the last 3 decades identification of OA-specific biomarker(s) has been the goal of many OA research programmes and despite the active research in this field, none of the current biomarkers has proven to be sufficiently OA-specific for development as diagnostic biomarker test for OA [15,16]. However, the reporting of data on OA biomarkers has been significantly improved by the implementation of the "BIPED" (Burden of disease, Investigative, Prognostic, and Efficacy of intervention and Diagnostic) system, which provides a uniform framework for the dissemination of OA biomarker studies [17]. Many studies are making good use of the BIPED classification and numerous potential diagnostic biomarkers showing differential expression between OA and control subject have been described (Table 1).

As indicated above OA is a complex disease affecting all major tissues (bone, cartilage and synovium) within the joint and therefore structural molecules (or fragments), cytokines, growth factors and other signalling molecules derived from these tissues and their interactions are potential candidate biomarkers of OA. Currently, the most investigated and validated biomarkers for OA are related to changes in cartilage extracellular matrix (ECM), bone or synovium that may reflect tissue degradation or tissue synthesis in OA joint. A cross sectional study from Garnerio et al,

Table 1: List of biomarkers with potential diagnostic value for OA (in alphabetical order).

Biomarkers	Description	Reference
ARGS	Aggrecan ARGS neo-epitope fragment	[17, 18]
BDNF	Brain-derived neurotrophic factor	[19]
C3f	C3 complement fragment	[20]
COMP	Cartilage oligomeric matrix protein	[21-25]
CTX-II	C-telopeptide of type II collagen	[26-29]
Fibronectin		[30, 31]
Fib3-1 and Fib3-2	Fibulin 3 peptides	[32]
FSTL1	Follistatin-like protein 1	[33]
Glc-Gal-Pyd		[26]
Haptoglobin		[34, 35]
PIIANP	Type IIA collagen N-propeptide	[29, 36, 37]
PIIINP	Type III collagen N-propeptide	[26]
S100A12	Calcium binding protein A12	[38, 39]
V65	Vitronectin subunit	[20]
YKL-40	Secreted glycoprotein	[40, 41]

measured 10 of the most established biomarkers in serum and urine of 67 healthy subjects and 67 patients with knee OA and showed that 8 of these biomarkers were significantly increased in OA patients. Amongst these, C-telopeptide of type II collagen (CTX-II), Glc-Gal-Pyd and type III collagen N-propeptide (PIIINP) were also correlated with joint surface area [27] suggesting a potential diagnostic value and disease severity in patients with knee OA. The prognostic value of CTX-II is already well established by many studies [28,29] including one by Sharif et al., that reported elevated concentration of serum type IIA collagen N-propeptide (PIIANP) and urinary CTX-II which were associated with radiologic progression of patients with OA in a 5yr longitudinal study [30]. Measurement of elevated concentration of aggrecan fragments (ARGS) in plasma, urine and synovial fluid have also been correlated with presence of OA [18,19] highlighting the value of aggrecan fragments as potential diagnostic biomarkers. Indeed, aggrecan constitute the majority of the ECM and its proteolysis has been described as characteristic feature of OA [42,43].

The search for good diagnostic biomarkers is sometime hampered by the data discrepancies reported by different studies on the same biomarkers which may be explained by the patients cohort used, or the type of OA studied. Such differences have been observed for cartilage oligomeric matrix protein (COMP), another extensively investigated biomarker which is believed to measure cartilage degradation [15,44]. A study conducted with 100 OA patients and 50 control subjects reported a significant higher concentration in OA patient compared to control but no significant correlations were observed between COMP concentration and Kellgren and Lawrence score [22]. Also, in a cross-sectional study of 663 OA patients, elevated concentration of serum COMP was shown to be correlated with hand OA symptoms and increased Australian Canadian Hand Osteoarthritis Index (AUSCAN) scores, but not with radiographic hand OA [23]. However, in another set of studies, in middle-aged women it was reported

that a high baseline serum COMP concentration was significantly associated with the risk of developing radiographic knee OA at 10 years follow-up [24-26]. Similarly, the reported decrease in the concentration of cartilage synthesis product PIIANP in patients with OA knee and hand compared with healthy subjects [37,38] conflict with the 5-y longitudinal study described by Sharif et al., showing a high concentration of serum PIIANP in knee OA progressors compared with non-progressors [30].

The recent advances in the “omics” technologies are providing a new opportunity for discovery of biomarkers to be investigated in a broad range of biological sample, including articular cartilage from femoral heads and knee, synovial fluid, serum and urine. Some of the recent biomarkers identified by proteomic include our collaborative work with de Seny et al., which reported the discovery of two novel biomarkers C3f- a complement fragment released during the catabolic degradation of C3b after C3 complement activation, and V65- a subunit of vitronectin a cell adhesion and spreading factor [21]. These two biomarkers showed good discrimination between OA and non-OA subjects, could be detected in non-radiographic stage of OA (Kellgren & Lawrence grade 0) and increased as the radiographic disease severity of OA increased [21]. Unlike the currently available biomarkers, these markers may reflect cellular metabolism processes rather than tissue destruction products and therefore represent a new generation of more promising biomarkers.

Using quantitative proteomic to profile synovial fluid obtained from OA and RA patients, two groups independently reported that fibronectin and calcium binding protein A12 (S100A12) were differentially expressed between OA and RA patients [32,39]. These data are consistent with previous findings showing association of these two biomarkers with presence of OA [31,40]. Similarly, fibulin 3 peptides (Fib3-1 and Fib3-2) have been shown to be elevated in OA patients compared to healthy subjects [33] and may also represent potential new diagnostic biomarkers for OA. However, a major limitation of this study is that it was performed using samples from patients with end-stage disease, who are not representative of the general OA population and therefore the value of these markers in investigation of early OA remains to be seen.

Liao et al., looked at the proteomic profiles of synovial fluid from patients with OA knee and compared it with non OA patients; and showed that up regulation of haptoglobin positively correlated with the severity of OA [35]. These data corroborate with previous work that also demonstrated up regulation of haptoglobin in serum of OA patients compared to control [36] but further studies are required to demonstrate the value of haptoglobin as a diagnostic marker for OA.

Other possible candidate biomarkers that could be further investigated to assess their diagnostic value include the glycoprotein YKL-40 and Follistatin-like protein 1 (FSTL1) which have been shown to be associated with the presence of OA as well as disease severity [34,41,42,45]. Also, a recent study of two calcium binding proteins (alarmins S100A8 and S100A9) suggest that these are crucial molecules involved in the regulation of cartilage damage and synovial inflammation during OA [46]. Elevated baseline plasma concentrations of both S100A8 and S100A9 predict osteophytes progression over 2 and 5 years in

patients with early symptomatic hip and knee OA [47]. These four biomarkers appear to be associated with synovial inflammation and therefore may be useful either singly or in combination for identifying presence of OA subsets. Finally, brain-derived neurotrophic factor (BDNF) protein, was found to be elevated in plasma (and not in synovial fluid) from patients with knee OA compared to healthy controls and BDNF was positively associated with joint pain measured by WOMAC score [20]. This observation is very interesting as the data implies that pain in OA is centrally regulated and offers a potential new target for future drug development for management of pain in OA.

CONCLUSION

OA is the most common joint disease of unknown aetiology with poorly defined clinical outcome. OA-specific biomarkers would provide an improved OA outcome measure and help with early diagnosis and better management of the disease. The biomarkers discussed above appear to have some diagnostic value but are not sufficiently OA-specific for diagnosis and monitoring individual patient with OA. The slow progress in the field to identify good biomarkers for OA is due to the complex heterogeneous nature of the disease, the lack of a standardised approach for sample (synovial fluid, blood, urine etc.) collection, processing, biomarker validation and qualification.

The ideal diagnostic OA-biomarker should be easily measurable in small amount of patient's body fluids (e.g., blood and urine). These tests should be non-invasive and both affordable and robust to be surrogate for x-ray and/or MRI in the diagnosis of OA. An OA specific biomarker will not only help with early diagnosis but will also offer a reliable outcome measure for clinical trials, provide rapid indication of therapeutic response, improve safety of phase II trials and reduce costs. The discovery and validation of such a biomarker may involve a long and challenging process but considering its benefit, the search for better OA biomarkers should remain a priority in the field.

AUTHORS CONTRIBUTION

KO and MS collected data and prepared the manuscript. Dr. Ourradi is funded by a Arthritis Research UK project grant (20406).

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