Osteoarthritis and Cartilage 25 (2017) 199–208

Osteoarthritis and Cartilage

Review

Osteoarthritis Year in Review 2016: biomarkers (biochemical markers)

A. Mobasheri † ‡ § * [a], A.-C. Bay-Jensen ||, W.E. van Spil ¶, J. Larkin #, M.C. Levesque ††

† Department of Veterinary Pre-Clinical Sciences, School of Veterinary Medicine, University of Surrey, Guildford, GU2 7AL, United Kingdom
‡ Faculty of Health and Medical Sciences, Duke of Kent Building, University of Surrey, Guildford, Surrey, GU2 7XH, United Kingdom
§ Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis, Queen's Medical Centre, Nottingham, NG7 2UH, United Kingdom
|| Rheumatology, Biomarkers and Research, Nordic Bioscience A/S, Herlev, Denmark
¶ Department of Rheumatology & Clinical Immunology, University Medical Center Utrecht, PO Box 85500, 3508 GA, Utrecht, The Netherlands
# C3 DPU, Immunoinflammation Therapeutic Area, GlaxoSmithKline, King of Prussia, PA, 19406, United States
†† AbbVie Bioresearch Center, 100 Research Drive, Worcester, MA, 01605, United States

ARTICLE INFO

Article history:
Received 1 October 2016
Accepted 14 December 2016

Keywords:
Osteoarthritis
Cartilage
Synovium
Biomarker
Biochemical marker
Assay

SUMMARY

Purpose: The aim of this "Year in Review" article is to summarize and discuss the implications of biochemical marker related articles published between the Osteoarthritis Research Society International (OARSI) 2015 Congress in Seattle and the OARSI 2016 Congress in Amsterdam.
Methods: The PubMed/MEDLINE bibliographic database was searched using the combined keywords: 'biomarker' and 'osteoarthritis'. The PubMed/MEDLINE literature search was conducted using the Advanced Search Builder function (http://www.ncbi.nlm.nih.gov/pubmed/advanced).
Results: Over two hundred new biomarker-related papers were published during the literature search period. Some papers identified new biomarkers whereas others explored the biological properties and clinical utility of existing markers. There were specific references to several adipocytokines including leptin and adiponectin. ADAM Metallopeptidase with Thrombospondin Type 1 motif 4 (ADAMTS-4) and aggrecan ARGS neo-epitope fragment (ARGS) in synovial fluid (SF) and plasma chemokine (CeC motif) ligand 3 (CCL3) were reported as potential new knee biomarkers. New and refined proteomic technologies and novel assays including a fluoro-microbead guiding chip (FMGC) for measuring C-telopeptide of type II collagen (CTX-II) in serum and urine and a novel magnetic nanoparticle-based technology (termed magnetic capture) for collecting and concentrating CTX-II, were described this past year.
Conclusion: There has been steady progress in osteoarthritis (OA) biomarker research in 2016. Several novel biomarkers were identified and new technologies have been developed for measuring existing biomarkers. However, there has been no "quantum leap" this past year and identification of novel early OA biomarkers remains challenging. During the past year, OARSI published a set of recommendations for the use of soluble biomarkers in clinical trials, which is a major step forward in the clinical use of OA biomarkers and bodes well for future OA biomarker development.

Introduction

Osteoarthritis (OA) is a low-grade inflammatory disease of synovial joints and the most common form of arthritis[1]. It is a leading cause of chronic pain and physical disability in older individuals[2]. OA is one of the most costly and disabling forms of joint disease, being far more common than rheumatoid arthritis (RA) and other forms of joint disease[3]. It is characterized by progressive deterioration and loss of articular cartilage[4] with concomitant structural and functional changes in the entire joint, including the synovium, meniscus (in the knee), periarticular ligaments, and subchondral bone[5]. Cohort studies have

* Address correspondence and reprint requests to: A. Mobasheri, Department of Veterinary Pre-Clinical Sciences, School of Veterinary Medicine, University of Surrey, Guildford, GU2 7AL, United Kingdom.
E-mail address: a.mobasheri@surrey.ac.uk (A. Mobasheri).
[a] The corresponding author is a member of the D-BOARD[b] and APPROACH[c] European Commission funded consortia. The other co-authors are members of the APPROACH consortium. A.-C. B.-J. is also a member of the D-BOARD consortium.
[b] http://www.d-board.eu/dboard/index.aspx.
[c] http://www.approachproject.eu.

http://dx.doi.org/10.1016/j.joca.2016.12.016

Abbreviations

ADAMTS-4	ADAM Metallopeptidase with Thrombospondin Type 1 motif 4
ARGS	aggrecan ARGS neo-epitope fragment
AUC	area under the curve
C3M	MMP-degraded type III collagen
CCL3	chemokine (C–C motif) ligand 3
CHECK	Cohort Hip and Cohort Knee
Col2-1 NO2	nitrated type II collagen degradation fragment
COMP	cartilage oligomeric matrix protein
COX-2	cyclooxygenase-2
CRP	C-reactive protein
CRPM	MMP-degraded C-reactive protein
CTX-II	C-telopeptide of type II collagen
DMOADs	disease-modifying osteoarthritis drugs
FMGC	fluoro-microbead guiding chip
FNIH	Foundation for the National Institutes of Health
HA	hyaluronan, hyaluronic acid
hsCRP	high-sensitivity C-reactive protein
IL-1β	interleukin-1β
IL-1Ra	interleukin-1 receptor antagonist
IL-4	interleukin-4
IL-6	interleukin-6
IL-36α	interleukin-36α
JSW	joint space width
LC–MS	liquid chromatography–mass spectrometry
MIA	monoiodoacetate
MMPs	matrix metalloproteinases
MMP-1	matrix metalloproteinase 1
MMP-3	matrix metalloproteinase 3
MPO	myeloperoxidase
MRI	magnetic resonance imaging
MS	mass spectrometry
MSD	musculoskeletal disease
NF-κB	nuclear factor κB
NIH	National Institutes of Health
NOS-2	nitric oxide synthase 2
NTX-I	N-terminal telopeptide of type I collagen
OA	osteoarthritis
OAI	Osteoarthritis Initiative
OARSI	Osteoarthritis Research Society International
PIIANP	N-terminal propeptide of collagen IIA
RA	rheumatoid arthritis
s	serum
S100-A6	S100 Calcium Binding Protein A6
SF	synovial fluid
SME	synovial membrane explant
TNF-α	tumor necrosis factor-α
u	urinary
ucMGP	uncarboxylated matrix Gla-protein
VAS	visual analogue scale
VDAC	voltage-dependent anion-selective channel
WAT	white adipose tissue
WOMAC	Western Ontario and McMaster Universities Arthritis Index

demonstrated that age, obesity and metabolic disease are major risk factors for the development of OA[6,7].

Although OA has been viewed as a "wear and tear" disease for many decades, it is now generally accepted to be an inflammatory and biomechanical whole-organ disease[1,8–10] associated with systemic co-morbidities and death[11]. The pathogenesis and progression of OA is influenced by a number of factors including bone shape and joint dysplasia[12], obesity[13], synovitis[14–16], complement proteins[17], inflammatory mediators[1,18], inflammaging[19,20], innate immunity[21], low-grade inflammation[8] induced by metabolic syndrome[1,22] and diabetes mellitus[23].

The Osteoarthritis Research Society International (OARSI)[d] has recently endorsed a new definition of OA and launched an initiative to critically evaluate and standardize pre-existing definitions of OA. "*Osteoarthritis is a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness*"[24] (Fig. 1). OARSI anticipates that this updated definition of the disease process will be subject to further critique and refinement as new scientific and clinical information emerges and our knowledge of OA pathogenesis and progression expands.

It is clear that OA is a heterogeneous disease with a variety of pathophysiologic drivers leading to multiple phenotypes, many of which may overlap in patients[25] (Fig. 2). Each OA phenotype may potentially be treated and targeted differently, paving the way for the development of stratified medicines for OA[26]. Some of these phenotypes will be amenable to pharmacologic intervention but others are less likely to respond to drugs[27]. The key aim of OARSI and the OA research community is to define and characterize OA phenotypes, develop novel, specific and sensitive disease endpoints, improve the design of OA clinical trials, identify patients that respond to treatment and thus alleviate roadblocks to development and clinical evaluation of disease-modifying osteoarthritis drugs (DMOADs)[28–30].

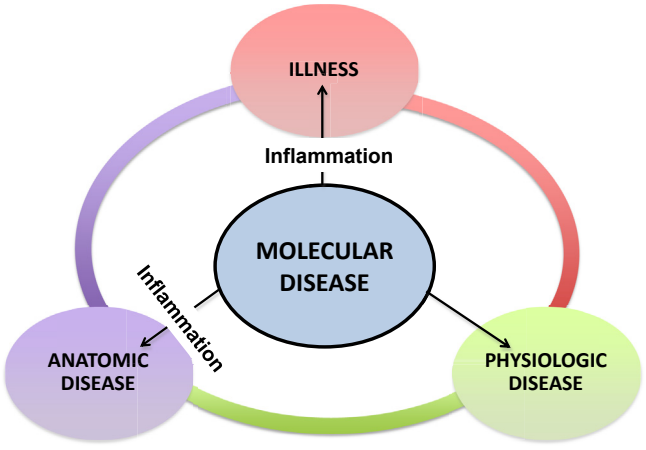

Fig. 1. New definition of OA, as endorsed by OARSI. This figure highlights the relationships between the disease and illness components of OA. The molecular component represents the silent and asymptomatic early stage of OA. Molecular changes precede the anatomic and physiologic aspects by years or even decades. This creates a challenge for detecting the disease early and an opportunity for finding new early marker of disease. Figure adapted from[24] with the kind permission of Dr Virginia Kraus.

[d] https://www.oarsi.org.