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VIEWPOINT

Translation of clinical problems in osteoarthritis into pathophysiological research goals

Peter M van der Kraan,[1] Francis Berenbaum,[2] Francisco J Blanco,[3] de Bari Cosimo,[4] Floris Lafeber,[5] Ellen Hauge,[6] Adele Higginbottom,[7] Andreea Ioan-Facsinay,[8] John Loughlin,[9] Ingrid Meulenbelt,[10] Eeva Moilanen,[11] Irene Pitsillidou,[12] Aspasia Tsezou,[13] Joyce van Meurs,[14] Tonia Vincent,[15] Ruth Wittoek,[16] Rik Lories,[17] On behalf of the EULAR Study group in OA (http://www.eular.org/investigative_rheumatology_study_groups.cfm)

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For numbered affiliations see end of article.

Correspondence to
Dr Peter M van der Kraan; peter.vanderkraan@radboudumc.nl

ABSTRACT

Osteoarthritis (OA) accounts for more disability among the elderly than any other disease and is associated with an increased mortality rate. The prevalence in Europe will rise in the future since this continent has a strongly ageing population and an obesity epidemic; obesity and age both being major risk factors for OA. No adequate therapeutic options, besides joint replacement, are available, although they are greatly needed and should be acquired by adequate research investments. However, the perspective on OA from a researcher's point of view is not always aligned with the perspective of a patient with OA. Researchers base their views on OA mainly on abnormalities in structure and function while patients consider OA as a collection of symptoms. In this viewpoint paper, we discuss the possibility of translating the most important clinical problems into pathophysiological research goals to facilitate the translation from bench to bedside and vice versa. This viewpoint is the outcome of a dialogue within the 'European League Against Rheumatism study group on OA' and People with Arthritis/Rheumatism across Europe (PARE) representatives.

OSTEOARTHRITIS (OA) IS A HUGE AND EVER INCREASING PROBLEM

OA is the most prevalent joint disease and accounts for more disability among the elderly than any other disease. It is estimated that OA affects about 40 million people in Europe.[1 2] OA can affect each and every joint but is most common in the knee, hip, spine and hand. Clinically, it is characterised by joint pain, limitation of movement, tenderness, stiffness, crepitus and various degrees of inflammation. OA is considered a disease of the whole joint organ; structural changes include cartilage fibrillation, fissures, full thickness loss of articular cartilage, osteophyte formation, changes in the subchondral bone plate, synovitis and fibrosis in synovium or capsule.

To provide exact numbers on the incidence and prevalence of disease is a difficult task. A major cause of this is the fact that radiographic changes are not always associated with joint pain and vice versa. Moreover, OA is generally a slow progressive disease. Epidemiological studies are difficult to compare due to differences in study population and disease criteria. OA is relatively infrequent in people under the age of 40 years but definitely increases with age. Under the age of 45 years, women are less affected than males, but this gender difference reverses above 45 years. Europe has an increasingly ageing population as well as an obesity epidemic; old age and obesity are both major risk factors for OA. Since currently no therapeutic options other than pain control and joint replacement are available, the burden of OA will continue to rise in the coming decades.

ABSENCE OF EFFECTIVE PHARMACOLOGICAL TREATMENT

Analgaesics, ranging from paracetamol and opiates to non-steroidal anti-inflammatory drugs (NSAIDs), and intra-articular hyaluronan, are prescribed for treating pain but their effect is often small (mean effect-size from 0.15 to 0.30) and in many patients not sufficient. Osteoarthritic joints that show signs of inflammation are often treated with intra-articular corticosteroid. Another very important opportunity in OA management is

change in lifestyle, mainly by increasing physical activity and improving physical condition, for example, by weight loss. Trials are ongoing with newer treatments for joint pain that are promising but sometimes with limitations due to unexpected drawbacks, for instance, unexpected rapid disease progression in some patients treated with an anti nerve growth factor strategy.[3]

Treatment of structural disease progression in OA joints is still a big challenge. Nutraceuticals, symptomatic slow acting drugs for OA (SYSADOAs) and viscosupplementation are prescribed with this aim in mind, although there is little evidence to fully support this claim. Studies with strontium ranelate show effects on joint space width, but the clinical relevance of the reported small difference and the potential cardiovascular side effects have justified halting its further development for patients with OA.[4] Ultimately, joint replacement is the option for patients with severe symptoms and end-stage OA. Joint replacement is a rapidly increasing procedure and over 90% of joints are replaced due to OA. However, this is a costly procedure and is, especially in relatively young people, not a permanent solution. Moreover, around 20% of the patients continue to experience some form of joint pain even after the procedure has been successfully performed. Thus, the unmet needs in patients with OA are high and the development of OA treatments that can both prevent or treat structural break down and improve symptoms is increasingly needed. Personalised treatment, with a patient-specific strategy, requires biomarkers that stratify patients based on OA subtype and specific pathophysiological processes involved, also taking into account that these processes evolve in a personal manner during the progression of disease.

PATIENT AND RESEARCHER PERSPECTIVE ON OA

As is adequately exemplified by the paper of Kraus *et al*, the perspective on OA from a researcher's point of view is quite different from the perspective of a patient with OA.[5] While the main focus of the researcher is on genes, proteins and cells, signalling, and metabolic pathways and structural aspects, the focus of the patient is on pain, functional limitations, aesthetic damage due to bony proliferations and loss of daily and social activities. A researcher views OA as a 'disease' based on its abnormalities in structure and function originating from biological or (bio)chemical evidence while a patient considers OA as an illness, 'the human response to disease'.[6]

Starting from basic pathophysiological research questions, researchers have taken major steps in understanding OA. We have come from the opinion on OA as a simple wear and tear process of articular cartilage to a concept of OA as an organ disease in complex interaction with the human body as a whole. Our understanding is increasing enormously and only some general insights can be mentioned here. Genetic studies have shown that specific gene variants (Smad3, Dio2 and GDF5, etc) are associated with OA prevalence and or severity.[7 8] The role of ageing and cell senescence has been implicated in OA.[9] Furthermore, it has been shown that changes in chondrocyte behaviour, such as increased production of proteolytic enzymes, and even most likely changes in chondrocyte differentiation, play a crucial role in degradation of the articular cartilage matrix.[10 11] These changes in chondrocyte behaviour are governed by changes in activated signalling pathways and changed responses of aged and senescent chondrocytes to these stimuli.[12 13] Changes in the subchondral bone can predict subsequent symptoms or structural progression, and, recently, it has been shown that not only local joint inflammation but also low-grade systemic inflammation could contribute to the OA disease process.[14–16]

To gain a further and more robust understanding of processes that occur in OA, it is important to take into account interactions between gene expression, epigenetic regulation and environment in clinically well-defined patients.

RECOGNITION OF DIFFERENT OA PHENOTYPES

OA has been historically classified based on joint location but not on the underlying pathophysiological process.[17] It becomes more and more clear that OA, even in a specific joint, is better classified according to specific features that are presumably a result of specific underlying disease processes.[18] End-stage OA in a particular joint in different patients can be viewed as the final common outcome of a variety of pathophysiological processes that differ, or have differed, between these patients. Classification, not based on location but on the underlying disease process, will be a valuable instrument not only to further elucidate OA pathophysiology and also to optimise clinical trials, in particular patient selection.

Not only might better classification of patients by OA phenotype be a major advance, but improved methods for early detection of OA are of crucial importance as well. As early OA has an extended subclinical disease phase early changes in an OA-affected joint remain under the radar. As a consequence, intervention is invariably delayed until severe, and maybe even irreversible, structural damage has occurred. To improve disease-modifying interventions, methods and strategies have to be developed that can detect early, meaningful and predictive OA-associated changes in the joint and that can track the result of an eventual intervention.

THE OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL DEFINITION OF OA

OA is a heterogeneous disease and in this viewpoint and preceding discussions within the European League Against Rheumatism (EULAR) study group, we use the draft definition of the Osteoarthritis Research Society

International[5] as a working definition. The authors of this definition and the OA study group are fully aware that this definition will be modified according to the further elucidation of OA process(es) and disease phenotypes.

> Osteoarthritis is a disorder involving movable joints characterised 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 (characterised by cartilage degradation, bone remodelling, osteophyte formation, joint inflammation and loss of normal joint function) that can culminate in illness.[5]

TRANSLATION OF CLINICAL PROBLEMS INTO PATHOPHYSIOLOGICAL RESEARCH GOALS

A recent EULAR initiative identified four research priority areas: epidemiology, imaging and biomarkers, pathogenesis and therapy,[2] which served as the basis for the first call for projects issued by Foundation for research in rheumatology. In this viewpoint paper, classification of relevant pathophysiological research goals is based on these priority areas (box 1). The research goals that were identified within the study group are not prioritised, as in our opinion the research goals have to be reached in parallel. For example, identification and validation of targets for therapy are not achievable without better insight into the OA pathogenesis and improvement of early detection and disease stratification. Moreover, early detection and disease stratification cannot be accomplished without trustworthy imaging and functional biomarkers.

Box 1 Major pathophysiological research goals

Epidemiology (genetic epidemiology)
- To identify and elucidate the role of genetic variants in Osteoarthritis (OA) phenotypes;
- To identify and elucidate the role of epigenetics in OA phenotypes;
- To identify and elucidate the role of mitochondrial genetic variants in OA phenotypes.

Imaging and biomarkers
- Identify markers for early OA;
- Identify markers for OA phenotypes;
- Identify markers for disease activity;
- Identify markers for disease progression;
- Identify predictive markers of therapeutic response;
- Identify markers to evaluate the therapeutic response.

Pathogenesis
- To understand tissue communication in OA (between cartilage, subchondral bone, synovium, vessels, adipose tissue);
- To understand non-cartilage pathology in OA;
- To understand the role of chondrocyte differentiation in OA;
- To understand the role of joint trauma and repair in OA;
- To understand the mechanism of mechanical joint injury and the translation to inflammation and repair;
- To understand the relationship between synovitis and radiographic progression;
- To understand the earliest stages of OA;
- To understand the difference between OA phenotypes;
- To understand the origins of pain;
- To understand the relationship between pain and structure;
- To understand the relationship between synovitis and pain;
- To understand the relationship between ageing and OA;
- To understand the relationship between gender and OA;
- To understand the role of systemic factors in OA;
- To define the mechanisms by which comorbidities influence the OA process (fat and glucose metabolism).

Therapy
- To identify and validate targets for therapy (symptoms and structure).

EPIDEMIOLOGY

Epidemiology is, in a strict sense, not the major methodology of pathophysiological research. However, due to the integration of epidemiology and genetics (genetic epidemiology) and the recognition of different OA phenotypes, research in this area is of high value in bringing together clinical problems, and pathophysiological research goals and understanding. Identification of genetic variants in patients with OA, both genomic and mitochondrial, will identify phenotype-specific pathogenic pathways that will be fundament for phenotype-specific OA therapies. Moreover, elucidation of the role of epigenetic changes in specific OA phenotypes has the potential to provide a roadmap to targeted and patient group-specific therapy.

IMAGING AND BIOMARKERS

Identification and validation of imaging technologies and biomarkers is of utmost importance for early disease detection, for classification of OA phenotypes, disease activity and prognosis and for evaluation of therapy response. Imaging and biomarkers should both form a reliable reflection of underlying disease processes. Ideally, a biomarker itself should be an integral part of the actual disease process in OA and a sign of a specific OA phenotype. Identification of OA phenotypes and the response to stratified interventions will most likely depend on the combination of joint imaging and biomarker quantification.

PATHOGENESIS

The pathogenesis of OA is far from understood and will be different in the various OA phenotypes. It has become more and more clear that the whole joint is affected in OA and that the different tissues of the joint communicate and influence each other's reactions. To really comprehend the OA disease process, the communication between the various joint tissues should be understood in a phenotype-specific context and be studied in the very early stages of OA development.

In many patient groups, a causal relationship between mechanical changes in the joint and OA is probable.

However, the exact role of mechanical (over) load in normal joint physiology and OA is not yet known. Moreover, the role of intrinsic joint repair or failing intrinsic joint repair in OA is still obscure. The relationship between structural joint changes and symptoms, among others, pain, is still an enigma. It is not clear which tissues are the major source of joint pain, perhaps bone or synovium or whether there is a role for products released by damaged cartilage in joint pain.

The relationship between unavoidable factors, such as ageing and gender, and OA phenotype-specific pathophysiology has still to be elucidated. Furthermore, how systemic factors and comorbidities, such as obesity and diabetes, affect the development and progression of OA, needs further insight.

THERAPY

The major goal of pathophysiological research in OA is the identification and validation of targets for therapy. These targets can either be structural targets or symptomatic targets, mainly pain. Ideally, these targets should be combined as a single agent, albeit without ignoring the fact that different OA phenotypes may require different targeted therapies.

This viewpoint article attempts to bridge the gap between major clinical problems of OA with pathophysiological research goals of the OA research community, to facilitate the translation from bed to bench and vice versa. It is anticipated that this article can be a guide for OA researchers, international organisations and funding agencies to facilitate their discussions on directions of research and funding.

Author affiliations
[1]Department of Experimental Rheumatology, Radboud University Medical Center, Nijmegen, The Netherlands
[2]Faculty of Medicine Pierre and Marie Curie Paris VI, INSERM UMR-S938, Saint-Antoine Hospital, Paris, France
[3]Rheumatology Division, Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas, Universidade da Coruña (UDC), A Coruña, España
[4]Musculoskeletal Research Programme, Institute of Medical Sciences, Foresterhill, Aberdeen, UK
[5]Department of Rheumatology and Clinical Immunology, University Medical Centre Utrecht, Utrecht, The Netherlands
[6]Department of Clinical Medicine, The Section for Rheumatology, Aarhus, Denmark
[7]EULAR PARE Patient Research Partner and Keele University, Newcastle-under-Lyme, UK
[8]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[9]Musculoskeletal Research Group, Newcastle University, Institute of Cellular Medicine, The Medical School, Newcastle upon Tyne, UK
[10]Department of Molecular Epidemiology, LUMC, Leiden, The Netherlands
[11]The Immunopharmacology Research Group, University of Tampere School of Medicine and Tampere University Hospital, Tampere, Finland
[12]EULAR PARE Patient Research Partner, Nicosia, Cyprus
[13]Department of Biology, University of Thessaly, School of Medicine, Larissa, Greece
[14]Genetic Laboratory, Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands
[15]ARUK Centre for OA Pathogenesis, University of Oxford, Oxford, UK
[16]Department of Rheumatology, University Hospital Ghent, Ghent, Belgium
[17]Laboratory of Tissue Homeostasis and Disease, Department of Development and Regeneration, KU Leuven and Division of Rheumatology, Skeletal Biology and Engineering Research Center, University Hospitals Leuven, Leuven, Belgium

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Notes