Osteoarthritis research priorities: a report from a EULAR ad hoc expert committee

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ABSTRACT

Osteoarthritis (OA) currently affects over 40 million Europeans, with its associated personal suffering and significant economic burden for health systems set to dramatically escalate in a rapidly ageing Europe. Given the very limited effective therapeutic options for OA, the European League Against Rheumatism (EULAR) created an ad hoc committee of OA researchers, clinicians and patients to consider a research agenda focussed on the areas of epidemiology, pathogenesis, imaging and biomarkers, and therapies. The committee deliberated and listed research needs in these areas and also established some cross-area priority themes: predictors of OA progression, especially where this might enable stratified interventions; understanding mechanisms of OA pain; improved understanding of tissue communication in a process where multiple tissue pathologies are common; developing concepts of, and consequently interventions for, early OA where both pain and structural processes may be more effectively targeted than in typical clinical presentations; and the need for new treatment strategies, with examples discussed on pathology-targeted therapies and optimal combinations of therapies. This research agenda should provide useful guidance for all researchers in this field and hopefully lead to improved OA care.

THE GROWING BURDEN OF OSTEOARTHRITIS

Musculoskeletal diseases are now the second greatest cause of disability in all regions of the world, with osteoarthritis (OA) showing the greatest increase in the last 20 years.[1 2] OA currently affects at least 40 million people in Europe[3–10] and accounts for more than a third of chronic moderate to severe pain.[11] It is strongly age-related, prompting further concerns as population projections suggest that by 2025 there will be over 210 million people over 65 in Europe.[12–14] Quality-of-life studies suggest that the impact of OA is comparable to that of cardiac, neurological and pulmonary diseases in terms of effect on daily functioning and health-related quality of life.[8]

The cost of OA in Europe is currently estimated at 0.5% of gross national product, reflecting the cumulative cost of absence from work, medical costs and community and social services.[15–20] In a 2003 French macroeconomic study, which included an estimated 3–4.6 million people with OA, the direct costs of OA exceeded €1.6 billion, similar to that spent on coronary heart disease. Compared with a similar study conducted 10 years earlier, the population of patients with OA in France had increased by 54%. Physician visits increased by a similar proportion, with 13 million visits attributed to OA in a 3-year period, resulting in 18 million prescriptions at a cost of €570 million, a 400% increase compared with 1993.[20] Indirect costs related to OA are also high, with an estimated £3.2 billion in lost production in the UK attributed to OA in 1999–2000,[19] while in France 5 million sick-leave days are prescribed for OA each year, costing €180 million in sick-leave benefits.[20] In a prospective Swedish study, musculoskeletal disease (most notably OA) was the most expensive disease category, representing 22.6% of the total cost of illness; the greatest costs were indirect costs related to morbidity and disability.[16]

For severe symptoms, joint replacement may be the only option, and this is also rapidly increasing.[20–22] In 2011, 165 000 total hip and knee replacements were performed in the UK, 93% of which were for OA.[21] Similar figures were observed in France, where 118 000 primary joint arthroplasties were performed,[20] and Sweden, where hip arthroplasty is reported to occur at a frequency of 332 in every 100 000 people aged over 40, an increase of 41% in 10 years.[22] Demand is predicted to soon exceed orthopaedic capacity.

In light of the above, the European League Against Rheumatism (EULAR) Executive created an ad hoc expert panel comprising a range of basic, translational and clinical researchers and patient involvement. This committee was charged with setting priorities for OA research, in particular by focusing on the following four areas: epidemiology, pathogenesis, imaging and biomarkers, and therapy.

UNMET NEEDS IN OA RESEARCH

The committee had a 1-day meeting and initially discussed the perceived barriers to the lack of success in improving therapies, both symptom and structure-modifying. Some of the areas highlighted were: the historic focus on inflammatory arthritis by the relevant musculoskeletal research community; a cartilage-centric approach to a process that involves multiple tissue pathologies; lack of engagement of primary care and little cross-specialty communication; waning industry investment; and a lack of focus on pain—the most important issue for people with OA.

It was felt that some of these areas had started being addressed to some extent in the last few years, identifiable in both EULAR initiatives in collaboration with orthopaedics and primary care and in recent trends in OA science and treatments.[23] However, considerable unmet needs remained, including a limited understanding of phenotypes allowing targeted interventions and a lack of conceptual definitions and concepts of what might

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constitute 'early' OA. The group felt that there was an important role for EULAR to continue promoting European collaboration (between both researchers and industry and across primary care and specialties). It was felt we should also learn from successful approaches in other chronic diseases.

With the unmet needs in mind, important research topics according to the four areas within the remit of this committee were then discussed and prioritised in break-out groups.

RESEARCH PRIORITY AREAS

Epidemiology

The natural history of OA is still largely unknown. Two topics especially warrant attention.

- The progressive OA disease course in some patients

The disease course of OA is heterogeneous, with some experiencing rapidly increasing pain, disability or structural damage in a relatively short timeframe, while others have stable disease over many years.[24] The underlying mechanisms and risk factors for progression are still largely unknown. However, the prediction of progression is of interest, from both the patient (prognosis) and research perspective. Identification of progressors will enable phenotyping of OA and preferential inclusion of these progressor phenotypes in clinical trials, which may help to prevent too many negative clinical trials, as have been observed previously. In addition, this may enable the development of a clinical decision tool to predict progression, such as the FRAX, which is used in osteoporosis.

- The early phases in OA development

It could be argued that patients with radiological damage are already in an end stage of the disease. From a patient and research perspective, treatment at an earlier stage, when prevention of radiological damage is still achievable, is much more attractive. To enable the development of treatments and the performance of clinical trials in the early phases of OA, criteria that define early or pre-OA are essential.[25]

Additional topics on the research agenda include the following.

- Criteria to diagnose and classify generalised or multisite OA

The definition of generalised or total body OA could facilitate research in biomarkers and stratification of patients in clinical trials.[26]

- The multidimensionality of OA outcomes

Pain is central in the disease process; however, it is important to also study the relevance of other domains, including function, participation and performance, and to incorporate these domains into outcome assessment in OA.

- Foot OA

This is a common presentation of OA that is seldom studied, but with a potentially high clinical burden.[27] Studies should be performed to elucidate its prevalence and clinical impact, including its role in functional impairment.

Pathogenesis

The pathophysiology of OA is not fully understood and has been dominated by research on the mechanisms of cartilage breakdown and chondrocyte biology. There is a need to develop the concept of OA as a disease of an entire organ, suggesting that it may not be sufficient to understand OA by focusing only on intrinsic changes in the cartilage metabolism. Novel aspects of the pathophysiology of OA have attracted attention, and these frontiers to explore include the following.

- Better understanding of tissue communication in OA

The interactions between cartilage and the adjacent bone, as well as between the synovium and adipose tissue, have not been well explored. Studying this relationship offers opportunities for novel interventions.[28]

- Better understanding of non-cartilage articular pathology

Research would include characterising inflammation of the synovial membrane and the nature of subchondral bone pathology, both abnormalities that are often observed in OA.[29]

- Defining the mechanisms by which comorbidities influence the OA process

There have been limited studies on how common comorbid conditions such as obesity and diabetes affect OA, especially how fat and glucose metabolism may contribute to the initiation and progression of the disease.[30]

- Understanding joint trauma and subsequent repair

Such research would include studying the induction of developmental processes such as chondrocyte hypertrophy in OA.[31] The molecular mechanisms of mechanical joint injury and their translation to inflammation and repair are still poorly defined, but of seminal importance.

- Understanding the pathology of the earliest stages of OA

This area might be addressed by studying the molecular changes following mechanical injury to the joint.[32] Notably, it is still unclear what we consider as 'early OA' and which mechanisms determine whether patients either progress to the full clinical manifestation of OA or have episodic arthralgia.

- Understanding the relationship between pain and structure

Of particular issue is how pain modifies the disease course of OA and how it relates to disease-specific mechanisms.[33]

Imaging and biomarkers

Robust biomarkers are required for both improving clinical trial outcomes and stratifying interventions. Areas requiring particular focus are as follows.

- Defining the performance metrics of imaging and other biomarkers

Imaging has traditionally focused on radiographic outcomes for knee OA. Less is known about the performance metrics of radiographs at other anatomical sites, or for the newer imaging modalities such as MRI and ultrasound, although the information accumulated from MRI studies in the last decade has dramatically improved our understanding of the complexity of OA pathology.[34] The field of OA molecular biomarkers is extensive, and challenges have included establishing the technical validity of candidate biomarkers, having feasible collection of biosamples in trials, and understanding the relationship of such biomarkers to single-joint pathology when multiple joints may be affected in an individual.[35] For both imaging and molecular biomarkers, the technical aspects, validity (including predictive validity), reliability and responsiveness require detailed attention.

- The relevance of biomarkers to a broad range of domains

When examining the importance of biomarkers, not only symptoms and structure should be considered but also other domains including broader constructs such as quality of life.

- Defining predictors of progression, especially those that aid targeted intervention

Little has been done on combining modern imaging with biomechanical variables or non-imaging biomarkers. Consideration should be given to using combinations of structural and molecular biomarkers,[35] especially in stratification for intervention.

Therapy

Existing symptomatic treatment of OA often has poor analgesic effect size and is unsatisfactory for many people with OA.[23] Current pharmacological therapies also have significant toxicities that limit their widespread usage. Recent EULAR guidelines

have emphasised the importance, efficacy and safety of non-pharmacological interventions and also provided specific research recommendations.[36] Structure modification has remained difficult to achieve. Areas requiring further research are as follows.

- Mechanisms of OA pain

Pain mechanisms are not well understood; pain treatment needs to be more targeted to these mechanisms, therefore investigation of the origin of pain in OA and its interrelation with other aspects of the disease is required.[33] A potential benefit gained from studies in this area should be the identification of novel targets for pain management.

- Individualised or pathology-targeted therapies

Knowledge of phenotypes of OA can be used to target specific OA therapies—for example, if increased bone turnover was driving disease progression in a subset of patients, treatment aimed at this increased bone turnover (eg, bisphosphonates) should be evaluated, whereas, in other patients in whom disease progression is driven by synovial inflammation, treatment aimed at this inflammation (eg, methotrexate) should be evaluated.[23] Studies must be performed that consider specific characteristics of patients; such knowledge of phenotypes would be useful for non-pharmacological as well as pharmacological therapies. Possible efficacious interventions may have been discarded because they were not effective in large unselected groups of patients. Therapies may also consider targeting specific related comorbidities such as obesity.

- Optimal combination therapy strategies

Most OA therapeutic studies have focused on assessing individual therapies. Identification of optimal strategies that employ combinations of available therapies would be valuable to see if greater analgesic benefit could be obtained. Such studies might include complex intervention designs and compare different therapeutic options, such as monotherapy versus combination therapy, or investigate combinations of therapies (eg, combination pharmacological or combination non-pharmacological or all combined).

SUMMARY OF PRIORITIES

Finally, after the formulation of research priorities within the above four areas, a series of consensus rounds were conducted with the entire committee. From this process the following broad priority themes were established:

- Predictors of progression of OA
- Mechanisms of pain in OA
- Treatment strategies in OA
- Early OA
- Tissue communication in OA

CONCLUSIONS

This process of bringing together European OA researchers for strategic prioritisation represents an important step for the field of OA. It is hoped this document provides useful guidance for OA researchers and at least a discussion point for national societies with interests in the field of OA. It is of course important that such strategy setting should never exclude novel thoughts or ideas that may move our understanding or treatment of OA forward.

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