Review

Bridging Disciplines as a pathway to Finding New Solutions for Osteoarthritis a collaborative program presented at the 2019 Orthopaedic Research Society and the Osteoarthritis Research Society International

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ARTICLE INFO

Keywords:
Osteoarthritis
Biomechanics
Biomarkers
Imaging

SUMMARY

Objective: To stimulate future research directions that seek solutions for osteoarthritis (OA) at the interface between diverse disciplines and address osteoarthritis (OA) as a serious disease with a complexity that has presented a barrier to finding safe effective solutions.

Methods: Sessions were conducted at the 2019 meetings of the Orthopaedic Research Society (ORS) and Osteoarthritis Research Society International (OARSI) that included presentations and questions/comments submitted from leading OA researchers representing imaging, mechanics, biomarkers, phenotyping, clinical, epidemiology, inflammation and exercise.

Results: Solutions for OA require a paradigm shift in research and clinical methods in which OA is contextualized as a complex whole-body/person disease. New OA definition(s)/phenotype(s) and OA markers/signals are needed to address the interplay between genetic and environmental factors of the disease as well as capture the mechanosensitivity of the disease. The term “Mechanokines” was proposed to highlight the importance of incorporating whole body mechanics as a marker of early OA. New interventions and apparent paradoxical observations/questions (e.g. exercise vs. load modification) were also discussed in the context of considering OA as a complex system.

Conclusion: To advance new OA treatments that are safe and effective, OA should be considered as a “Whole Person” disease. This approach requires a concerted effort to bridge disciplines and include interactions across scales from the molecule to the whole body, including psychosocial aspects.

1. Introduction

There is compelling evidence that the disabling symptoms experienced by patients with osteoarthritis (OA) have substantial societal and financial impact [1,2], yet there remains an unmet need for solutions that address both symptoms as well as the physical changes (mechanical, biological and structural) associated with OA. Diagnosis and treatment of OA is challenging since patient reported symptoms (pain) often do not coincide with detectable physical changes or occur late in the disease when structural disease modification is not possible. As such at present there are no validated solutions that prevent or modify the progression of OA. Further, current pharmacological treatments for symptoms only
provide temporary relief and are often associated with adverse effects. Thus, there is a critical need for disease modifying treatments that considers OA as a complex system that calls for combining diverse treatment modalities (e.g., pharma + mechanical) as a pathway to finding new solutions to address the individual and societal consequences of OA.

There is growing evidence [3–6] that new solutions will require a paradigm shift that addresses OA as a complex and heterogeneous disease involving interactions between multiple organ systems (e.g., muscular system, nervous system, lymphatic system). These interactions suggest OA behaves as a complex system that involves mechanical, biological and structural elements that will require new comprehensive approaches that bridge diverse disciplines. One of the reasons there have been only modest benefits from treatments is because of a “one size fits all” approach to OA where clinically there is tremendous heterogeneity that is not incorporated in research that can lead to new treatments for OA. As such the purpose of this narrative was to raise questions and provide suggestions for new multidisciplinary approaches that consider OA as a disease of the whole body that should include the patient voice (explicitly or implicitly) in finding solutions for OA.

2. Methods

This narrative was based on sessions titled “Bridging Disciplines as a Pathway to Finding New Solutions for Osteoarthritis” held at the 2019 meetings of the Orthopaedic Research Society (ORS) and the Osteoarthritis Research Society International (OARSI). Each session included four presentations (Fig. 1) and discussion based on questions and comments submitted from the OA research community (Fig. 2). The Program covered a broad range of disciplines including imaging, mechanics, biomarkers, phenotyping, inflammation and exercise in the context of promoting multidisciplinary research as a pathway to finding solutions to OA.

The multidisciplinary nature of the Program focused on the impact of interactions across multiple factors of the disease that eventually manifest as degenerative joint tissue (Fig. 3). The Program highlighted unanswered questions (“What do we need to know?”) that extended from “What is Known” to consider new definitions of OA that might inform the development of new biomarkers and treatments (Fig. 4). While each of the presentations and discussions covered different topics, a common theme was the fundamental need for a comprehensive definition and phenotyping of OA that addresses the heterogeneity and complexity of the disease. The following summarizes existing knowledge that motivates questions for future research that addresses fundamental and translational issues related to the definition and treatment of OA.

3. What is Osteoarthritis and Why Haven’t We Found Solutions?

There were several issues raised in the presentations and discussions that pointed to critical gaps in our understanding of OA and present barriers to finding solutions for the disease. A common theme throughout was the need to seek multidisciplinary approaches to understanding the complexity and heterogeneity of OA. More specifically, that understanding will start with developing a comprehensive definition/phenotyping of OA that can be applied to seeking new approaches to biomarkers, prevention strategies and disease-modifying treatments. The following provides the specific areas for research and related unanswered questions covered in the Program.

- OA Definition and Phenotyping: There is a fundamental need for a comprehensive approach to the study of OA [3] that consolidates the broad scope of multidisciplinary issues [5] that result from the interplay between genetic [4] and environmental factors (e.g. activity, age, obesity, trauma, ambulatory mechanics, etc.). Importantly, many of these environmental factors change over time as the result of trauma, development of obesity and aging [5]. Additionally, the potential combination of factors (Fig. 3) that contribute to OA suggest that there can be many OA phenotypes or subtypes [6,7].
  > Is OA one disease/phenotype or many (e.g. cartilage, bone, mechanical, metabolic, inflammatory, genetic, etc.)?

- OA Heterogeneity/Complexity: Phenotyping is complicated by evidence that OA can involve multiple organ systems (e.g. muscular system, nervous system, lymphatic system) that cannot be classified by a single phenotype but rather as a complex system that involves mechanical, biological and structural elements interacting at scales from the whole body (movement) to the molecule [5–7]. There are likely combinations of biomechanical, biological and structural elements that are present irrespective of the phenotype, and perhaps treatment should address the multiple elements of the disease. For example, knee OA associated with a varus knee (mechanical disease) might respond quite differently to being treated with a mechanical treatment (load modification) depending on the absence or presence of elevated proinflammatory cytokines (biological factor).
  > Should OA be defined/treated in terms of the multiple elements (mechanical, biological, structural) that influence the disease status for a specific patient?

Presentations

Integrating MRI UTE-T2* with Mechanics and Biology to Combat Post-Traumatic Osteoarthritis
Constance Chu (Stanford University)

OA as a disease of the whole joint: A Phenotyping Perspective
Rich Loeser (University of North Carolina-Chapel Hill)

The importance of assessing interaction between inflammation and mechanics in OA.
Tim Griffin (Oklahoma Medical Research Foundation)

The role of exercise as a beneficial intervention for OA as supported by MRI. (@ORS)
Leif Dahlberg (Lund University)

The importance of exercise intervention for OA: Consequences on clinical status of OA. (@OARSI)
Ewa Roos (University of Southern Denmark)

Fig. 1. The formal presentations covered a diverse scope of topics ranging from phenotyping to whole body mechanics.
3.1. Can OA markers/signals be improved?

New approaches to the development of markers or signals for OA are needed to indicate early risk for developing the disease [8], predict those who will progress as well as to provide markers for rapid and efficient assessment of new treatment methods. These new approaches for developing markers should be based on the definition/phenotyping of OA (Fig. 4). The general term “marker” is used here to include biomarkers, imaging markers, and mechanical markers. In this context it is useful to consider a broad classification system for OA markers as previously proposed [9] to classify five marker categories represented by the acronym BIPED (Burden of disease, Investigative, Prognostic, Efficacy of intervention, and Diagnostic). Clearly separating prognostic markers (signals) for assessing risk from diagnostic markers for assessing disease status would be important since the timing (Fig. 5) or stage of the disease is critical to the use of markers for OA where prognostic markers might be different than diagnostic markers. Finally, analysis of OA markers/signals should be assessed in terms of both the negative (risk) and positive (compensation) effect for OA since cellular and tissue level degeneration can signal compensatory changes at the whole-body level such as gait adaptations to pain. (Fig. 5). For example, patients that adopt a change in gait mechanics that lowers the load at the knee could be considered a positive signal that is beneficial for patients with knee OA, whereas patients with increased load are more likely to progress more rapidly [10, 11].

- Biomarker Signals: Biological and structural (imaging) markers have been used extensively for investigative studies of OA. However, there remains an unmet critical need for more sensitive prognostic markers for early detection and diagnostic markers for assessment of OA status as well as markers for assessing the efficacy of intervention [9, 12–14]. Commonly, biological or imaging markers are assessed in isolation of other factors that can influence OA (e.g. mechanical); however, they may not be sufficiently sensitive to evaluate early stages of OA by themselves. Thus, it should be considered that all stages of OA can be influenced by the interaction of diverse elements ranging from mechanical to biological. Furthermore, these elements span scales of organization from the whole body to the tissue and cellular level. It has been suggested [15] that new approaches could enhance marker sensitivity by integrating mechanical, structural and biological elements using a stimulus-response model. This approach could account for the interactions between gait mechanics, tissue structural changes and cellular activity to alter biomarker concentration.
Can early OA marker sensitivity be enhanced by utilizing interactions between multiple elements of the disease?

Mechanical Signals - "Mechanokine": The term "Mechanokine" was introduced at the first ORS Research Interest Group on Osteoarthritis in 2018 as part of this Program to highlight the need to consider mechanics on an equal plane with cytokines as a critical signaling mechanism for OA. Considering the mechanosensitivity of the chondrocyte, there is substantial evidence from in vitro experiments that mechanical signals (mechanokines) including stress, strain, fluid flow, osmotic pressure and other mechanical phenomena at the cellular level can influence the biological changes associated with OA [10,16–18]. It is currently not feasible to measure mechanokines at a cellular level in clinical studies due to the invasive nature of acquiring these measures. However, there are mechanokines that have been measured non-invasively in vivo during gait that can utilized [19–21]. For example, specific biomechanical gait metrics (e.g., knee...
Mechanokines differ from cytokines in the sense that they act across scales and are defined as abstractions (moments and forces) where the influence on joint health can only be measured by associations with tissue or biological changes over time. Thus, mechanical metrics obtained during gait can be clinically useful since they provide surrogates for the local mechanical environment of the cell. As such there is growing evidence that biological and imaging markers are influenced by gait mechanics. However, challenges remain in relating specific mechanical signals to anabolic versus catabolic biological and structural responses. Mechanokines can influence biological and structural stress adaptation, stress resistance and stress resilience resulting in a range of possible outcomes that are influenced by multiple environmental factors.

OA Temporal Changes: There is a need for better information of life. As such it has been suggested that pain and function. Also, loss of function due to pain results in diminished quality and positive). For example, the variable outcomes reported with load-modifying interventions for knee OA could be influenced by biological factors such as elevated proinflammatory cytokines that directly influence pain (33). Similarly, the apparent paradox between the clinical benefits of both increased loading with therapeutic exercise and reduced ambulatory loading could be understood by a more comprehensive view of the relationships between the anti-inflammatory benefits of exercise and the interactions between biomechanics and inflammation.

Developing new solutions/interventions follows a fundamental question raised in this Narrative, i.e.:

1) Can disease-modifying osteoarthritis drugs (DMOADs) be enhanced with load modifying interventions (non-surgical or surgical) as well as with the use of screening methods that account for mechanical and structural disturbances to the joint that can influence treatment outcome?
2) Can cartilage regeneration/replacement procedures be improved by including co-interventions that account for the mechanical and biological environment of the joint?
3) Can a better understanding of exercise therapy for OA and other biomechanical interventions be achieved by considering the interaction between biology (e.g., inflammation) and the mechanical effects of increased activity?
4) Can objective methods be developed to identify the timing when increased activity associated with exercise is beneficial vs. when load modifications should be used?
5) Can the apparent paradox between the benefits of load modification vs. exercise therapy be resolved by considering OA as a whole-body disease?
6) Can a better understanding of the complexity the OA phenotype be achieved by applying methods such as stimulus-response models to probe the nature of OA or artificial intelligence models that consolidate a broad scope of information to characterize OA phenotypes.

Conclusions and Future Directions

Future solutions for OA should account for interactions among multiple diverse elements and scales ranging from the whole body to the molecule. There is evidence to support viewing OA as a condition involving the whole body that ultimately appears clinically as symptoms of pain associated with tissue degeneration and adverse psycho-social
Another approach [14] is to consider the OA patient as a complex systematical model to predict OA risk based on a large array of parameters [47] that can introduce new challenges to capture all the known and unknown elements (Fig. 5). A number of these environmental and genetic factors can be modulated by another element (e.g. mechanical) in a manner that can be positive (mitigate) or negative (worsen) for the risk of progression (Fig. 5).

The Program participants noted that mechanical elements are lacking in the traditional approach to OA markers, yet there is evidence that mechanical signals (mechanokines) can introduce relevant information on the status of OA that cannot be derived from biological or imaging markers. Incorporating mechanical signal into a comprehensive definition of OA should inform classification of markers for specific application such as predicting future onset (e.g. Prognostic markers) or markers to classify the state of the disease (e.g. Diagnostic markers) as previously described [9]. There is also a need to understand the context in which a critical tipping point can occur between the benefits of loading in healthy subjects (perhaps pre-OA) and the negative influence of loading after OA symptoms develops [43].

Considering OA as a “Whole Body” or “Whole Person” system introduces new challenges to capture all the known and unknown elements that can influence the prognostic and diagnostic indicators unique to a specific patient. One method is a big data approach that builds a statistical model to predict OA risk based on a large array of parameters [47]. Another approach [14] is to consider the OA patient as a complex system and introduce a stimulus designed to activate a response to detect the nature of the disease that captures the influence of unknown elements that can’t be detected with current methods. It is possible that research addressing these challenges could lead to breakthroughs in seeking solutions for OA. Additional insight may come from related fields, such as dentistry and orthodontics, where patient care includes lifelong multidisciplinary approaches to disease prevention and treatment involving biological, structural, and functional elements [48].

In conclusion, this Narrative addressed topics that highlight the need for a comprehensive approach to defining/phenotyping OA based on incorporating the interaction between the multiple and diverse factors that influence the disease. At present the discussion leaves open the question as to whether OA is a single disease or many. Perhaps that is a moot question when considering the broad scope of factors that can influence OA at the level of the whole body. In considering new OA definitions/phenotypes, the goal should be to inform future research, interventions, prevention strategies and the application of biomarkers. While guidelines for OA research will vary depending on the goals of a specific study, the material presented here suggests future studies should engage a general framework that accounts for diverse core factors that can influence the nature of the disease. Considering the complexity of OA as noted here, “Bridging Disciplines” is critical to finding solutions for OA.

Author contributions

Conception and design: TPA, TMG, RFL, CRC, EMR, GAH, JCEH, AGF. Drafting of the article: TPA.

Critical revision of the article for important intellectual content: TPA, TMG, RFL, CRC, EMR, GAH, JCEH, AGF.

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Declaration of Competing Interest

The authors have nothing to disclose regarding the content of this manuscript.

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