THERAPEUTIC ADVANCES in
Musculoskeletal Disease

Review

Regenerative medicine for early osteoarthritis

Ther Adv Musculoskelet Dis

2023, Vol. 15: 1–6

DOI: 10.1177/1759720X231194813

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***Abstract*:** The concept of early osteoarthritis (OA) is based on the expectation that if found and treated in the early stage, the progression of the disease might be arrested before affected joints are irreversibly destroyed. This notion of early OA detection can also bear meaning for regenerative medicine (RM) which is purposed to cure a disease by regenerating the damaged tissue. RM can be a category of disease-modifying osteoarthritis drugs (DMOADs) and provide an attractive treatment for OA, restoring structural damage incurred during the disease by repopulating cells and reconstituting. While cell therapy including the use of stem cells is conflated with RM, it may also comprise gene therapy, exosomes, and other cell or cell-free-derived products. Considering that not all early OA will become advanced OA and that RM has a characteristic of personalized medicine, it would be very important to foretell, even roughly, which patients will progress rapidly and who will favorably respond to regenerative treatment. Subclassification and comprehensive endotyping or phenotyping (E/P) can be very helpful in detecting the population who would benefit from RM as well as rapid progressors who need closer monitoring.

Keywords: early osteoarthritis, regenerative medicine

Received: 29 April 2023; revised manuscript accepted: 28 July 2023.

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The origination of the concept of early osteoarthritis and its implications in regenerative medicine

Osteoarthritis (OA) becomes clinically evident in most cases after the pathophysiologic process has advanced to an irreversible state. Radiological change has been essential in the diagnosis of OA, although magnetic resonance imaging (MRI) is increasingly used to detect earlier changes that are not detectable in plain radiographs. However, even these earliest changes are preceded by biochemical changes occurring in the articular cartilage, synovium, or subchondral bone. Therefore, OA can be viewed as a continuum from no disease, to the first onset of joint tissue metabolic disorders OA without clinical symptoms/signs, to symptomatic OA at an early stage, to fully established OA, and finally to end-stage disease.[1,2]

Early detection of OA or its risk factors is important, to allow the implementation of preventive actions, and thus delay or slow down its progression. The concept of early OA is meaningful on the premise that if found and treated in the early stage, the progression of the disease might be arrested before affected joints are irreversibly destroyed. Therefore, early detection of the disease or its risk factors is a key step to allow the implementation of preventive actions. This concept for the early detection and management of OA was principally influenced by a similar concept that had been developed in rheumatoid arthritis (RA). Early diagnosis and treatment of RA, before its full clinical manifestation appears, have significantly diminished patient morbidity and indirect costs related to the disease in the previous decades. Although the etiology and natural course of OA and RA are quite different, with RA showing much faster progression, early detection, and intervention may be reasonably anticipated to lead to better outcomes by alleviating disability and associated social burden coming from OA.[3]

Early OA is a challenging condition with its definition, diagnosis, and management still controversial. The first clinical definition of early knee OA was announced in 2012, based on the following items: knee pain, Kellgren–Lawrence (K–L) grade

0, 1, 2 (osteophytes only), and structural criteria, including either arthroscopic or MRI findings.[4] In 2014, these criteria were modified, comprising patient-reported outcomes such as pain and function, clinical signs, and K–L grade 0 or 1.[5] Considerations for best practice were published in 2019 containing patient-reported outcomes, clinical features, physical function outcomes, and modifiable lifestyle-related outcomes.[6]

This concept of early OA is useful not only for identifying and treating rapid progressors but also for improving the design of the clinical trials of new treatments.[4] The treatments of OA so far have been largely symptomatic with (1) the association of nonpharmacological modalities (e.g. exercises, weight loss, physical agents including transcutaneous electrical nerve stimulation, and pulsed electromagnetic fields stimulation[7]) and pharmacological treatments such as painkillers, nonsteroidal anti-inflammatory drugs (NSAIDs) or intra-articular treatments (i.e. corticosteroids or viscosupplementation) to alleviate pain and suppress inflammation and (2) joint replacement surgery to eliminate one source of pain and inflammation. Of course, there have been constant efforts to develop disease-modifying osteoarthritis drugs (DMOADs) which are expected to change the course of OA by offering symptom relief and structural improvement. These attempts have not been successful so far for various reasons.[1,2,8] One of the causes of unsuccessful results with DMOADs is that they have been prescribed to patients who already have advanced disease. Given that the OA progresses over a long period, there are chances to detect and cope with OA in the early stage of the disease. The importance of early OA detection lies in finding a window of opportunity to change its natural course before considerable irreparable damage is done to the articular cartilage (AC). This opens up the possibility that a drug that is ineffective in a patient with advanced osteoarthritis may be effective if given earlier before serious structural, metabolic, and mechanical changes occur.

This notion of early OA detection can also bear meaning for regenerative medicine (RM) because these technologies may achieve better results when irreversible joint damage is not pronounced.[9] RM is an interdisciplinary field of research and clinical applications focused on the repair, replacement, or regeneration of cells, tissues or organs to restore impaired function. It uses a combination of several technological approaches that move beyond traditional transplantation and replacement therapies, which may include, but are not limited to the use of soluble molecules, gene therapy, stem cell transplantation, tissue engineering, and the reprogramming of cell and tissue types.[10] RM, which is purposed to cure a disease by regenerating damaged tissue, can be a category of DMOADs. While RM has typically meant the use of stem cells or other cell-based therapy, it can be expanded to involve gene therapy, exosomes, and other cell or cell-free-derived products.

The clinical reality in detecting early OA

As seen in other chronic diseases, the progression of OA takes a continuous course. OA develops over decades, potentially giving a wide window of opportunity to alter its course and final outcome.[1] OA in its early stage is first seen mostly by primary physicians while specialists frequently see the patients in a later period when the disease is already clinically evident beyond doubt.[11,12] Expectably, detecting early OA will be more challenging than the diagnosis of clinically evident OA. Pathognomonic signs and symptoms are not fully expressed in the early period, somewhat appearing partially and incompletely.[13] Also, the typical findings of established OA in the simple radiographs mean that it is not an early OA. Noticeable radiographic changes (KL$>$1) in symptomatic patients should be deemed as an established disease rather than an early disease. MRI can detect a wide range of pathological changes occurring in joint tissues at the onset of OA. Whether MRI should be included in diagnosing early OA is controversial. While MRI provides very valuable information on early structural changes, it is a quite expensive technology, not readily accessible to primary physicians who would see the bulk of new early OA patients. On the other hand, when regenerative therapy is considered in detecting early OA, MRI will probably be an essential tool because expensive therapeutics such as cell therapy need evidence of definite structural changes. In this context, ultrasound could be useful, provided that echogenic signals showing early changes in tendons, menisci, or ligaments are identified and characterized. When associated intraarticular damages necessitating surgical treatment are suspected, arthroscopy can be performed to confirm the changes in cartilage, meniscus, and synovial tissue, and provide possible treatment at the same time.[14] Also, it can be more useful in detecting small cartilage defects even compared to MRI. However, arthroscopy at

this point lacks an objective and standardized method of assessing cartilage softening expected in the early stages. Nonetheless, of course, arthroscopy is not suitable for defining early OA considering its invasiveness.

Exploratory studies have demonstrated that biomarkers can reflect the earliest OA changes before morphological changes occur. Hence, if the knowledge of specific individuals or combinations of effective markers for early OA is well established, they can provide the fastest information on disease progression. Recent advancements in the proteomic analysis will provide information on the combination panel of markers that would better define early OA and predict the progression of the disease.[15,16] Of course, these biomarkers are not yet available for routine use in daily medical practice but are beginning to be used for screening patients with early OA in clinical trials. Either way, these soluble biomarkers are useful tools to understand and define the 'early osteoarthritis' endotype.

So far, very few studies have investigated the role of serum biomarkers in early OA. Low-grade synovitis results in the production of cytokines that may contribute to the pathogenesis of OA.[17] C-reactive protein is modestly but significantly increased in women with early knee OA, with higher levels predicting progression over 4 years. This means that low-grade inflammation plays a significant role in early OA and indicates a chance for therapeutic intervention.[18] Interleukin-6 and tumor necrosis factor alpha have also been proposed as possible markers of radiographic knee OA. In addition, serum concentrations of cartilage oligomeric matrix protein and bone-derived molecular fragments, such as bone sialoprotein, have been proposed as potential markers in the early stages of OA.[17]

MRI may provide a tool to assess the early qualitative change of AC and other joint structures before radiological changes occur. Cartilage homogeneity visualized through the water distribution by MRI has been proposed as a potential marker for early knee OA.[19] Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) technique has shown promising results in pilot clinical studies of early OA.[20] Also, T1rho and T2 techniques which detect changes in proteoglycan and collagen type II, respectively, may be used to identify healthy subjects who have a higher risk for developing cartilage pathology.[21]

Application of RM in the management of early OA

Ideal management of OA should reduce the disease burden by altering its clinical course and thus preventing long-term disability. However, so far, OA treatments have typically focused on patients in the later stages of the disease. Detecting and caring for patients in the early stages of the disease have been outside of routine OA management. Early intervention might offer a better chance of success before joint destruction causes reduced function, disability, and the development of comorbidities in patients.[22–24]

One of the problems in the application of the early OA concept is the lengthy and prolonged course of OA compared to other diseases. Because several years or even decades may be needed to confirm the results of early intervention, many patients will not comply with the treatment if tangible effects are not obtained within a short period. The two components of a positive response are structural improvement and symptomatic relief. If both improvement components are not realized, the patients are likely to quit the treatment program. Therefore, having rapidly appearing efficacy signals to show the patient the benefit of RM in the early phase of the disease will be a challenge, which must be met if the doctor hopes to convince his patients to seek treatment.

RM can be an attractive treatment for OA as it is purposed to restore structural damage incurred during the disease by repopulating cells and reconstituting tissue. Symptomatic improvement only is not sufficient for this expensive form of treatment. RM may work more effectively in early OA where less damage to the AC has occurred. However, the overdiagnosis of early OA and too broad application can lead to the unnecessary wasting of medical and financial resources.

Cell therapy using either unprocessed autologous cells or culture-expanded autologous/allogenic cells isolated from bone marrow or adipose tissue has been applied to clinically evident OA patients with variable success. Symptomatic improvements in pain and function were reported with minor complications in the majority of studies (12 out of 15 random clinical trials), either autologous or allogenic if not accompanied by notable structural improvement.[25–27] Also, an increase in cartilage volume was demonstrated in some studies.[28,29] Dosage was 3.9×10^6 to 150×10^6 cells, with moderate to high doses ($>40 \times 10^6$) tend to

show more effect.[27] Still, currently, there is an absence of large, controlled trials with standardization of cell product manufacturing, and defined target patient populations that are needed to prove the usefulness of cell therapy. In addition, endotypes, combined therapies, and tissue sources can be considered in future studies.

The mode of action seems to be mostly paracrine. Also, exosomes isolated from stem cells which are thought to contain major components of their paracrine action can be applied to patients with early OA.[30]

Gene therapy using various therapeutic genes, either *in vivo* or *ex vivo*, has been investigated from animal models of OA, although there are very few reports on human trials to treat OA.[31–33] Safety issues related to the use of viral vectors have been major concerns for the application of gene therapy for nonlethal diseases like OA. Late recognition of the safety and effectiveness of adeno-associated virus vectors leads to the development of several therapeutics for intractable genetic diseases in the last decade.[34,35] While gene therapy for OA targeted genes that suppress inflammation, one targeting genes promoting tissue regeneration can be included in the category of RM. Although gene therapy has not been considered for early OA, regenerative gene therapy may become a possible therapeutic modality if the correct target gene can be identified in future studies.

The place of RM in early OA

RM is a new therapeutic modality based on biological treatment which has become a hot focus in OA treatment. Although the clinical outcome of regenerative therapy is unpredictable and largely unestablished, it is expected to be greatly influenced by the individual characteristics of patients and the disease status of the whole joint. Considering that not all early OA will become advanced OA and that RM has a characteristic of personalized medicine, it would be very important to foretell, even roughly, which patients will progress rapidly and who will favorably respond to regenerative treatment. There is a possibility to use RM preventively in special cases of OA such as posttraumatic OA. The current high costs of available RM therapies are probably prohibitive for their use as preventive methods, at least in the larger category of patients. Nevertheless, RM may provide a solution as a preventive measure against OA in the particular situation of high-league athletes and competitive professional sports people.

While ideally, the diagnostic criteria for early OA should be highly sensitive and applicable without using biochemical markers or MRI, subclassification and comprehensive endotyping or phenotyping (E/P) using these techniques can be very helpful in detecting the population who would benefit from RM as well as rapid progressors who need closer monitoring. So both biochemical makers and MRI, as well as other clinical evidence, should be utilized for this purpose. As there is no established classification of E/P agreed upon by most OA stakeholders and the biomarker profiles obtained from patients with clinically evident OA will be different from those from an early stage of OA, a prospective collection of data on early OA biomarker profiles in different endotypes and phenotypes will be necessary as well.[36]

Conclusion

The concept of early OA can provide a chance of intervention for RM which can be employed before progressive and irreversible changes occur. Detailed definitions and classifications of early OA validated by a prospective study including biochemical markers and MRI are necessary to detect the pool of patients who would be benefited from the application of RM. Considering that not all early OA will become advanced OA and that RM has a characteristic of personalized medicine, it would be very important to foretell, even roughly, which patients will progress rapidly and who will favorably respond to regenerative treatment. Subclassification and comprehensive E/P can be very helpful in detecting the population who would benefit from RM as well as rapid progressors who need closer monitoring.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Gun-Il Im: Conceptualization; Data curation; Methodology; Project administration; Writing – original draft; Writing – review & editing.

Yves Henrotin: Conceptualization; Methodology; Project administration; Writing – review & editing.

Acknowledgements
None.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was supported by the National Research Foundation of Korea (2020R1A2C2008266) and the Korean Fund for Regenerative Medicine (RS-2022-00070271).

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
Not applicable.

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