Annals of Physical and Rehabilitation Medicine 59 (2016) 333–339

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Update article

An update on the pathophysiology of osteoarthritis

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ARTICLE INFO

Article history:
Received 28 March 2016
Accepted 21 July 2016

Keywords:
Synovial joint
Articular cartilage
Synovium
Osteoarthritis (OA)
Pathophysiology
Physical Activity
Physical Rehabilitation

ABSTRACT

Introduction: Osteoarthritis (OA) is one of the most common forms of arthritis. There is accumulating evidence to suggest that OA is an inflammatory disease of the entire synovial joint and has multiple phenotypes. This presents the OA research community with new challenges and opportunities. The main challenge is to understand the root cause of the disease and identify differences and similarities between OA phenotypes. The key opportunity is the possibility of developing personalized and individualized prevention and treatment strategies for OA patients with different phenotypes of the disease. Indeed, it has been suggested that this is the era of 'personalized prevention' for OA. The aim of this mini-review paper is to focus on the pathophysiological aspects of OA development and progression, review the current concepts and discuss the future of personalized medicine for OA.
Method: The PubMed/MEDLINE bibliographic database was searched using the keywords 'pathophysiology' and 'osteoarthritis'.
Results: The PubMed/MEDLINE search yielded more than 12,000 relevant papers. A selection of these papers is reviewed here.
Conclusion: There has been slow but steady progress in our understanding of the pathophysiology of OA over the last two decades. However, large gaps remain in our knowledge of OA pathogenesis and this impacts negatively on patients and drug development pipeline. In the absence of new pharmaceutical agents and disease modifying osteoarthritis drugs (DMOADs) it is clear that lifestyle modification and physical activity are important and may delay the need for surgical intervention.

1. Introduction

Osteoarthritis (OA), also known as osteoarthrosis or degenerative joint disease, is a disease of synovial joints [1]. It is characterized by progressive deterioration and loss of articular cartilage with concomitant structural and functional changes in the entire joint, including the synovium, meniscus (in the knee), periarticular ligaments, and subchondral bone [2]. OA is actually one of the most common, costly and disabling forms of joint disease, being far more common than rheumatoid arthritis (RA) and other forms of joint disease [3]. Cohort studies have demonstrated that after age, obesity and metabolic disease are major risk factors for the development of OA [4,5]. OA is now generally accepted to be an inflammatory and biomechanical whole-organ disease that is influenced by a number of factors including joint shape and dysplasia [6], obesity [7], synovitis [8–10], complement proteins [11], systemic inflammatory mediators [1,12], inflammaging [13,14], innate immunity [15], the low-grade inflammation [16] induced by metabolic syndrome [1,17] and diabetes mellitus [18]. However, despite the fact that all joint tissues are implicated in disease initiation and progression in OA, it is the articular cartilage component that has received the most attention in the context of aging, injury and disease [2]. Articular cartilage is a flexible and mechanically compliant connective tissue

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http://dx.doi.org/10.1016/j.rehab.2016.07.004
1877-0657/

found at the end of long bones in articulating joints and in the intervertebral disc [2]. Its main function is to provide a smooth, lubricated surface for articulation and to facilitate the transmission of loads with a low frictional coefficient [19]. Throughout life, cartilage is continually remodeled as chondrocytes replace the degraded matrix macromolecules with newly synthesized components, although it is recognized that this is an exceptionally slow process in adults; proteoglycan turnover can take up to 2 decades whereas the half-life of collagen is estimated to range from several decades to more than 100 years [20–22]. Although articular cartilage can tolerate a tremendous amount of intensive and repetitive physical stress, it manifests a striking inability to heal even a minor injury [2]. This makes joints particularly sensitive to degenerative processes and the development of OA. The root cause of OA is not completely understood. However, the biomechanical forces that place inappropriate levels of stress on the joints (e.g., excessive or abnormal load bearing, postural or orthopedic abnormalities, or traumatic injuries) that destabilize the joint are thought to interact with other environmental, systemic (i.e. biochemical, metabolic) and genetic factors to contribute to the pathogenesis of OA. The disease has traditionally been defined as a prototypical non-inflammatory arthropathy, but today there is compelling evidence to suggest that in addition to being a disease of biomechanics [23], it has inflammatory and metabolic components [1,16,24–27].

The aim of this concise review article is to provide an update on the pathophysiology of OA. We focus on the pathophysiology and pathogenesis of OA, review some of the current concepts in OA research and discuss the future of personalized medicine for OA. In the absence of disease modifying OA drugs (DMOADs) personalized therapy should include lifestyle evaluation, physical therapy and rehabilitation. Even if structure modifying drugs for OA are on the horizon, it will take decades before we have epidemiological data on efficacy. Therefore, as we eagerly anticipate the development of novel DMOADs it would be prudent to focus on OA prevention rather than treatment. We will set the scene by providing an update on the global burden of OA and the spiraling cost of treatment [3] before discussing the pathophysiology of OA and the need for identifying early inflammatory events and targeting these alterations [12] to ameliorate the major symptoms such as inflammation and pain in OA patients [24].

2. The global burden of OA

OA is the leading cause of chronic disability globally in individuals older than 70 years and has been designated a 'priority disease' by the World Health Organization (WHO) (report WHO/EDM/PAR/2004.7[1]). OA is one of the ten most disabling diseases in industrialized countries. In the Global Burden of Disease 2010 study, hip and knee OA was ranked as the 11th highest contributor to global disability [3]. The prevalence of OA is set to increase in parallel with the increase in the number of people aged 60 years and older and the rise in obesity across the world. In the United States alone OA is the highest cause of work loss and affects more than 20 million individuals, costing the US economy greater than US$100 billion annually [28,29]. OA represents one of the top 5 healthcare costs in Europe [3]. In the United Kingdom a third of people aged 45 and over (8.75 million people) have sought treatment for OA, and at least half of these individuals have knee OA (half of all people seeking treatment for OA have knee OA). The number of people in the UK with knee OA is estimated to increase to 6.5 million by 2020 (allowing for the increasing size of the aging population and the rising levels of overweight and obesity). In France, the direct and indirect costs of OA have been estimated by Le pen et al., in the "COART" France study [30]. The authors used a top-down approach with nationwide data from 2001 to 2003 and estimated the direct costs of OA at €1.6 billion, representing approximately 1.7% of the budget of the French health insurance system. The authors reported a 156% increase in direct medical costs compared with 1993, which was related to an increase in the number of OA patients (+54%). In Canada 4.5 million (one in six) Canadians aged 15 years and older report having arthritis and by 2031, approximately seven million Canadians (one in five) are expected to have arthritis. In Australia OA is the leading cause of chronic pain, disability and early retirement due to ill health and AU$2 million people live with OA; the annual cost of OA to health system is AU$2 billion AUD in joint replacements for OA with AU$1.3 billion paid for welfare payments annually. There are no up-to-date estimates of the global economic cost of OA although a 1997 analysis of the economic costs of musculoskeletal disorders in the world's 5 industrialized countries (Australia, Canada, France, United Kingdom, and United States), in which OA was the most common of these disorders, found a rising trend of costs that had, by then, reached between 1% and 2.5% of the gross national product of these countries [31]. Even if an updated report of global economic burden had been published more recently, it would undoubtedly underestimate the true cost burden to the world's health and social care systems.

3. Modifiable and non-modifiable OA risk factors

Certain factors have been shown to be associated with a greater risk of developing OA. According to the US Centers for Disease Control and Prevention[2] and the Mayo Clinic[3] some of these risk factors for OA are modifiable whereas others are not. The most important OA risk factors are age, gender, overweight/obesity, joint trauma/sports injuries (and the consequent joint instability and muscle laxity), certain occupations that place repetitive stress on a particular joint, genetics (well beyond the scope of this review), bone deformities, metabolic disease (i.e. diabetes), endocrine disorders and having previously had other rheumatic diseases such as RA and gout. The risk of developing most types of arthritis increases with age and OA is certainly no exception [32]. Gender is another critical risk factor for OA. Indeed most types of arthritis are more common in women and 60% of all people with arthritis are women so perhaps it is not surprising that the female sex also represents a significant risk factor for OA [33]. It has been hypothesized that leptin may be a systemic or local factor that mediates the metabolic link between obesity and OA [33]. Leptin and other adipocytokines (adipokines) may actually be the missing links accounting for the gender disparity toward the disease [34–36].

Some of the above are non-modifiable risk factors for the development of OA. There is clinical evidence to suggest that the risk for developing OA can be mitigated and reduced by weight management, avoiding obesity/overweight, maintaining high levels of mobility and avoiding sedentary lifestyles. The challenge will be managing comorbidities (i.e. diabetes, cardiovascular diseases) and mitigating the risks of joint injury. Some of the above are likely to influence the course of disease progression. Experimental approaches using animal models and clinical studies are needed to investigate the underlying mechanisms in order to formulate new OA prevention strategies.

[1] http://apps.who.int/iris/bitstream/10665/68769/1/WHO_EDM_PAR_2004.7.pdf.

[2] http://www.cdc.gov/arthritis/basics/risk-factors.htm.

[3] http://www.mayoclinic.org/diseases-conditions/osteoarthritis/basics/risk-factors/con-20014749.

4. Inflammatory aspects of OA

Inflammation is now well accepted as a feature of osteoarthritis but we have known about this for 40 years, we just chose to ignore some of the published literature. In a paper published in 1975 George Ehrlich described a cohort of predominantly menopausal females who presented with a deforming and inflammatory OA, some of whom went on to develop changes characteristic of rheumatoid arthritis (RA) [37]. The pioneering work that Ehrlich did in this area was well recognized by the WHO because of the work that he did for the organization in New York [38] but his work has gained more recognition in recent years and after his death in 2014. Many recent studies have shown the presence of synovitis OA patients and demonstrated a direct association between joint inflammation and disease progression [1,9,39,40].

5. New insights into OA pathophysiology

The key pathophysiological mechanisms involved in OA involve some the usual suspects, namely the pro-inflammatory (interleukins IL-1β, IL-6, IL-8) and tumor necrosis factor α (TNF-α) and pro-catabolic mediators through their signaling pathways and the well-characterized effects of nuclear factor κB (NFκB) and mitogen-activated protein (MAP) kinase signaling responses plus reprogramming are 'switching' pathways in transcriptional networks [12]. The inflammatory mediators, mechanical and oxidative stress conspire to compromise the function and viability of chondrocytes, reprogramming them to undergo hypertrophic differentiation and early "senescence", making them even more sensitive to the effects of pro-inflammatory and pro-catabolic mediators.

6. Cartilage aging and "chondrosenescence"

Aging is a natural and inevitable process that is characterized by nine hallmarks [41]. These include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. Aging and inflammation are major contributing factors to the development and progression of arthritic and musculoskeletal diseases, including OA [42]. "Inflammaging" refers to the low-grade inflammation that occurs during physiological aging. As stated earlier, one of the hallmarks of aging is cellular senescence. A characteristic of OA is deviant behavior of chondrocytes in diseased articular cartilage [43]. OA chondrocytes resemble terminally differentiated chondrocytes in the growth plate [44] and actively produce pro-inflammatory cytokines and matrix degrading enzymes [45] and these catabolic factors result in further cartilage degeneration. Progressive chondrocyte dysfunction is also characterized by expression of senescence-associated markers, erosion of chondrocyte telomere length and mitochondrial dysfunction due to oxidative damage causing the age related loss of chondrocyte function [46]. We have recently combined the words "chondrocyte" and "senescence" to introduce the term "chondrosenescence". In our view "chondrosenescence" defines the age-dependent deterioration of chondrocyte function that leads to cartilage dysfunction in OA. We developed this concept to stimulate more mechanistic research on chondrocyte aging. We propose that a small number of "senescent chondrocytes" may be able to take advantage of the inflammatory tissue microenvironment and the inflammaging and immunosenescence that is concurrently occurring in the arthritic joint, further contributing to the age-related degradation of articular cartilage, subchondral bone, synovium and other tissues [13]. In this framework "chondrosenescence" is intimately linked with obesity, lifestyle choices and inflammaging and at the molecular level with the disturbed interplay between autophagy and inflammasomes, thus contributing to the age-related increase in the prevalence of OA and a decrease in the efficacy of articular cartilage repair [47]. Understanding "chondrosenescence" and the basic mechanisms by which aging affects articular cartilage and other joint tissues should reveal new therapeutic targets for slowing or preventing the development of OA [42] (Fig. 1).

7. Disruption in circadian clocks and rhythms

The circadian rhythm is a 24-hour cycle in the physiological processes of all animals. Circadian rhythm are strictly set, tightly regulated and endogenously generated, although they can be modulated by external cues such as light and dark cycles. The study of circadian clocks and circadian rhythms is starting to make a significant impact on rheumatology, orthopedics and cartilage

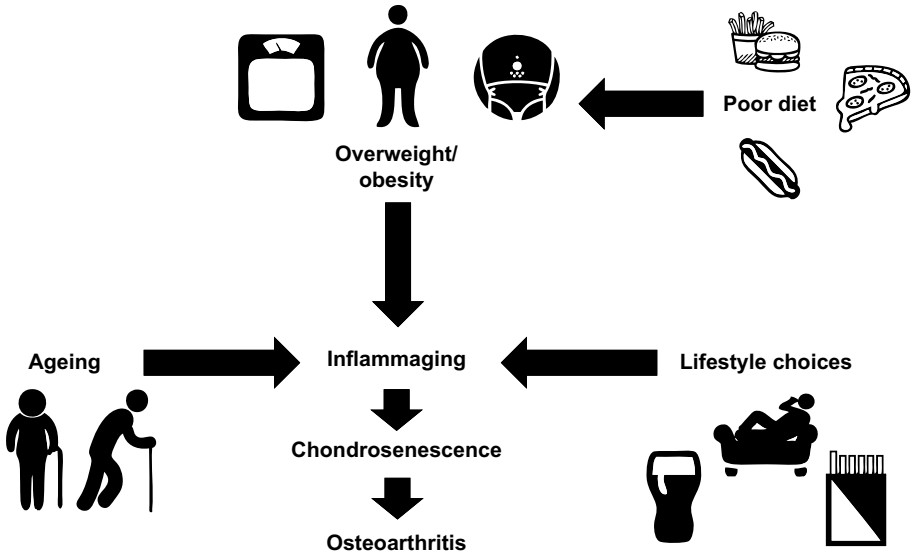

Fig. 1. The convergence of aging, obesity and lifestyle choices in the development of inflammaging and chondrosenescence in OA.

biology [48]. Studies in murine chondrocytes have shown that the circadian clock regulates genes controlling key aspects of cartilage homeostasis [49]. Indeed the catabolic cytokines implicated in the pathophysiology of OA can disrupt the circadian clock and the expression of clock-controlled genes in cartilage via an NFκB-dependent pathway [50]. The chondrocyte core clock gene and transcription factor BMAL1 is one of the key genes that controls cartilage homeostasis and integrity. A new study by Dudek and colleagues shows that BMAL1 is disrupted in human OA cartilage and in aged mouse cartilage. The authors also show that targeted Bmal1 ablation in murine chondrocytes abolishes their circadian rhythm and causes progressive degeneration of articular cartilage. The BMAL1 gene directs the circadian expression of many genes implicated in cartilage homeostasis, including those involved in chondrocyte apoptosis, catabolic and anabolic pathways. Ablation of this gene decreases expression of the major extracellular matrix-related genes Sox9, Acan, and Col2a1. This is the first study that links BMAL1 to the maintenance and repair of articular cartilage. This paper suggests that circadian rhythm disruption is a risk factor for the pathogenesis and progression of degenerative joint diseases such as OA. Clock genes are also believed to regulate reactive oxygen species (ROS) homeostasis and oxidative stress responses suggesting that disruption of circadian rhythms may exacerbate inflammaging and enhance ROS levels and oxidative stress signaling in OA [51].

8. Sleep disturbance and depression in OA

The relationship between OA and sleep might seem obvious if we focus on pain, which clearly is an important part of the equation, but recent research suggests that the connection goes beyond pain and OA symptoms. Indeed, the relationship is far more complex and could indeed be reciprocal. Rather than OA causing insomnia, the two conditions are thought to coexist and may be mechanistically linked. Parmelee et al. have proposed that sleep disturbance in OA is linked with pain, disability, and depressive symptoms [52]. Their work highlights the link between sleep disturbance, pain and disability in OA. Although this is a new and under-researched area, papers are gradually emerging to support the notion that lack of sleep and disease progression are closely linked in humans and animals [53]. The study by Parmelee and colleagues has identified a new and important point of intervention that may provide a new preventive strategy for OA-related functional decline among patients whose sleep is disrupted by OA-related pain [52]. Aside from sleep disturbance another potentially important factor in OA progression is depression. Depression appears to play a strong role in the sleep-pain linkage, particularly when pain is particularly severe. The unique predictive role of sleep in the progression of disability requires further study but may be an important point of intervention to prevent OA-related functional decline among persons whose sleep is disrupted by OA-related pain. It will be very interesting to establish whether drugs that can improve the quality of sleep might slow disease progression in cohorts of OA patients. Future work in this area should provide further insight into the interplay between circadian rhythms and cartilage homeostasis and may reveal new therapeutic targets for the treatment of OA.

On a more practical level, OA patients may wish to explore ways to improve their sleep without using sleep aids and sleep medicines that can have undesired side effects. However, hormones such as melatonin are being used as a pharmacologic aid to sleep, especially in sleep disorders affecting circadian rhythms. Interestingly, melatonin has anti-oxidant properties and is thought to modulate the pathogenesis of inflammatory autoimmune diseases. However, we know nothing about the effects of melatonin on articular cartilage and chondrocytes.

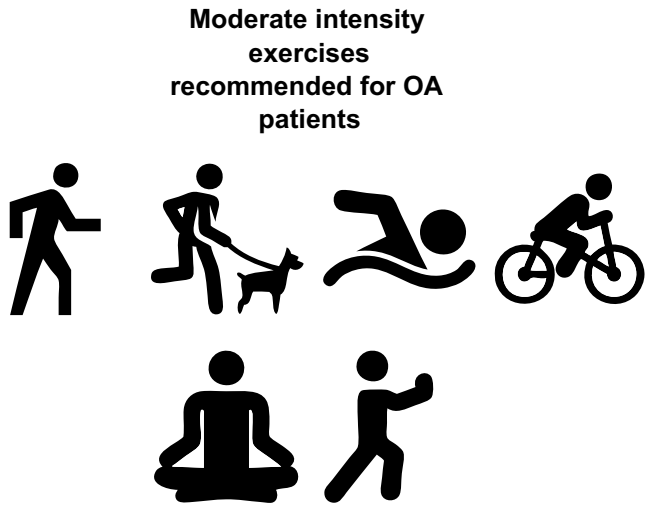

Fig. 2. Moderate intensity exercises that are recommended for OA patients.

These suggestions and sleep strategies may seem trivial but they represent good common sense:

- not eating a heavy meal before bed–eating a heavy meal before bedtime can disrupt sleep rhythms;
- not drinking heavily caffeinated beverages or large quantities of alcohol before bed;
- not watching television and tablets in the bedroom before sleeping;
- keeping the bedroom comfortably cool (65–68 °F, 18–20 °C), quiet and dark (avoiding external light pollution).

9. Exercise and physical activity in the prevention and management of OA

According to reports published by the WHO,[4] we live in a world where the population is becoming increasingly overweight, obese and sedentary. This toxic combination is contributing to an increasing burden of long-term conditions that for most health services in the world is financially unsustainable. Whilst obesity is a well-known risk factor for many chronic diseases through the metabolic syndrome a lack of physical activity is also an independent risk factor, as is the number of hours spent sitting or lying (sedentariness) [54]. Consequently, healthcare systems around the world are developing strategies trying to encourage health and wellness through increased levels of daily physical activity. Physical activity, exercise and sport form a continuum of human exertion. The precise definitions are less important for a public health message, which should encourage more people to be more active more of the time. Nonetheless it is appreciated that some of these activities can potentially result in joint damage, injury and OA. In this section we summarize the existing data and current opinion.

Physical activity is essential for optimal health. It is acknowledged that increasing physical activity and reducing sedentary hours would go a long way to preserving health (physical and mental) and preventing increasing burden of long-term conditions. Moreover, it is recognized that physical activity may be used as treatment for several chronic diseases whose etiology includes poor lifestyle choices. Globally there is an understanding that physical activity and exercise are beneficial with much data to support its prescription, however, the exact prescription program

[4] http://www.who.int/mediacentre/factsheets/fs311/en/.

Fig. 3. Vigorous intensity exercises that are not suitable for patients with established OA.

is yet to be found. This is fundamental as most healthcare systems around the world have shrinking resources and thus it is important to define a commissionable product with known effectiveness. There is increasing appreciation of a dichotomy in the effects of exercise and sport on the health of the musculoskeletal system and particularly joints. Non-elite or recreational activities typically confer health benefits. A number of moderate intensity exercises are actually recommended for OA patients (Fig. 2).

Conversely, participation in elite level activities, particularly contact or collision sports, which are associated with injury, are more associated with post-traumatic OA [55,56]. There is increasingly good evidence that recreational running, as an example of a non-contact/collision activity, is not associated with an increased prevalence or progression of knee OA [57,58]. These studies suggest that long-distance running among healthy older individuals is not associated with accelerated radiographic OA. In fact, long-distance running might even have a protective effect against joint degeneration. However, a number of vigorous intensity exercises may not be suitable for patients with established OA (Fig. 3).

Another important issue that is worthy of discussion is the effect of acute injury on lower limbs and the risk of OA development. The order of prevalence of lower limb OA is typically knee, hip and lastly foot and ankle. However, the association with OA in these joints is almost reverse when one considers injury as a key etiological factor – it is the ankle that ranks first with nearly 80% of ankle OA being post-traumatic in origin. However, unlike the knee there is a significant latency between injury and onset of symptomatic ankle OA [59,60]. Thus for certain joints injury is the primary risk factor for the subsequent development of OA, although the mechanisms have yet to be fully elucidated. It is also appreciated that injury within a given 'node' of the kinetic chain can predispose to injury elsewhere – so that an incompletely rehabilitated ankle sprain may act as a precursor to a subsequent knee injury.

Reviewing the risks and benefits of physical activity and overall musculoskeletal health and OA is beyond the scope of a commissioned article entitled: "Pathophysiology of Osteoarthritis". However, there is an increasing body of evidence to suggest that physical activity is essential for cardiovascular, metabolic, musculoskeletal and mental health. A recent systematic review of exercise for knee OA extracted data from 54 studies to provide high-quality evidence to indicate that land-based therapeutic exercise provides benefits for patients [61]. The study reports that short-term benefits were sustained for at least two to six months after cessation of formal treatment in terms of reduced knee pain. There was moderate-quality evidence shows improvement in physical function among people with knee OA. Interestingly, since the participants in the trials that were included in this systematic review were aware of the nature of their treatment, this may have contributed to their improvement. Another recent systematic review has evaluated the effects of aquatic exercise for people with knee or hip OA. The study provides moderate quality evidence that aquatic exercise may have small, short-term, and clinically relevant effects on patient-reported pain, disability, and quality of life in people with knee and hip OA [62]. Promoting and encouraging physical activity in older adults at risk for developing OA is important and has been shown to be associated with maintained physical function mediated by muscle strength [63]. Positive effects have been reported across a wide range of physical activities, including one of the simplest forms of exercise: walking. A positive effect has also been associated with more daily walking plus intensive diet and exercise among adults with painful knee OA [64,65]. This positive effect may be an important psychological factor to consider for promoting physical activity among people with painful knee OA.

10. Conclusions

It has been over a decade since Wim van den Berg and Johanne Martel-Pelletier published short papers on the "Pathophysiology of osteoarthritis" [66,67]. Knowledge of the pathophysiology of OA is rapidly expanding. Recently published reviews on OA suggest that the disorder is complex and multifactorial, with numerous genetic, biological, and biomechanical components [68]. OA is now viewed as an inflammatory disease with multiple phenotypes [32]. This presents the OA research community with new challenges and opportunities. The key challenge is identifying the differences and similarities between the phenotypes. The main opportunity is the possibility of developing personalized and individualized prevention and treatment strategies for OA patients with different forms of the disease [69,70]. Chronic, low-grade inflammation in OA is now known to contribute to symptoms and disease progression

and multiple mediators are emerging as regulators of this process [12]. However, in the absence of new pharmaceutical agents and disease modifying osteoarthritis drugs (DMOADs) it is clear that lifestyle modification and physical activity are important and may delay the need for surgical intervention. This concept should be especially relevant to the *Annals of Physical and Rehabilitation Medicine* and the readers of this Special Issue on "*Osteoarthritis*".

Funding

The authors' work is supported by the European Commission and Arthritis Research UK. A. Mobasheri is the co-ordinator of the D-BOARD Consortium[5] funded by European Commission Framework 7 programme (EU FP7; HEALTH.2012.2.4.5-2, project number 305815, Novel Diagnostics and Biomarkers for Early Identification of Chronic Inflammatory Joint Diseases). He is also a member of the Applied Public-Private Research enabling OsteoArthritis Clinical Headway (APPROACH) Consortium,[6] a 5-year project funded by the European Commission's Innovative Medicines Initiative (IMI). APPROACH is a public–private partnership directed toward osteoarthritis biomarker development through the establishment of a heavily phenotyped and comprehensively analyzed longitudinal cohort. The research leading to these results has received partial support from the Innovative Medicines Initiative (IMI) Joint Undertaking under Grant Agreement No. 115770, resources of which are composed of financial contribution from the European Union's Seventh Framework programme (FP7/2007–2013) and EFPIA companies' in kind contribution. The author has also received funding from the Deanship of Scientific Research (DSR), King Abdulaziz University (Grant No. 1-141/1434 HiCi). The authors are members of the Arthritis Research UK Centre for Sport, Exercise, and Osteoarthritis, funded by Arthritis Research UK (Grant Reference Number: 20194).

Disclosure of interest

The authors declare that they have no competing interest.

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