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Update article

An update on the pathophysiology of osteoarthritis

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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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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.