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Structural correlates of pain in joints with osteoarthritis

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SUMMARY

Objective: To describe the insights on the epidemiology of pain-structure association and the ramifications of these studies for clinical trials.
Design: Narrative review summarizing the pertinent literature in this area, summarizing some of the methodologic challenges inherent and proposing some research initiatives to further understanding of this complex science.
Results: The predominant symptom in most patients presenting with osteoarthritis (OA) is pain. Over recent years a number of imaging based studies have narrowed the discord between structural findings on imaging and symptoms. The interpretation of pain in OA is still enigmatic and difficult to deal with both for clinicians and scientists.
Conclusions: We would envisage that over the next few years many of the pressing questions pertaining to research into the structure pain relationship will continue to be addressed. With this, we can expect clinically appropriate therapeutic advance.

Introduction

Osteoarthritis (OA) is a highly prevalent and disabling disease that consequently has a formidable individual and societal impact. Approximately 10–12% of the adult population have symptomatic OA[1,2]. The risk of mobility disability (defined as needing help walking or climbing stairs) attributable to knee OA alone is greater than that due to any other medical condition in people aged 65 and over[3,4]. Recent estimates suggest that 250 million people worldwide are burdened by the presence of knee OA[5].

This prevalent and disabling disease is heterogeneous and characterized by failure of the synovial joint organ[6]. The disease occurs when the dynamic equilibrium between the breakdown and repair of joint tissues becomes unbalanced, often in a situation where the mechanical loads applied exceed those that can be tolerated by the joint tissues[7]. OA is a heterogeneous disease that is characterized by progressive cartilage loss, subchondral bone remodelling, osteophyte formation, and synovial inflammation, with resultant joint pain and increasing disability. Whilst the progressive joint failure may cause pain and disability[4] approximately 50% of persons with structural changes consistent with OA are asymptomatic[8].

In epidemiological investigation, OA is typically defined using conventional radiographs, and less frequently self-report[9]. The reported prevalence of OA varies according to the method used to define the disease. The characteristic radiographic features used to define and classify OA severity are osteophytes (osteocartilaginous growths), subchondral sclerosis and joint space narrowing. Symptomatic OA in contrast requires the concomitant presence of pain (usually defined as pain on most days of the last month) and radiographic features. It is the presence of symptomatic OA that is important clinically, not simply the radiographic identification of an osteophyte or self-reported OA (where misclassification is even more problematic than the commonly used radiographic OA definition).

The predominant symptom in most patients presenting with OA is pain. Over recent years a number of imaging based studies have narrowed the discord between structural findings on imaging and symptoms[10,11]. This narrative review will summarize these findings and provide insights to the epidemiology of the pain-structure association and the ramifications of these studies for clinical trials especially pertaining to structure modification. We present here a narrative review, supported by a literature search up to January

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2013 using Medline as a search engine. This is not a formal systematic review and prior reviews were referenced for their content.

The determinants of pain

The determinants of pain in OA are not well understood, but are believed to involve multiple interactive pathways that are best framed in a biopsychosocial framework (posits that biological, psychological and social factors all play a significant role in pain in OA)[12,13] (Fig. 1). Psychosocial factors that can predispose to symptoms include self-efficacy and pain catastrophizing, and the social context of arthritis (social support, pain communication) are all important considerations in understanding the pain experience.

From a biological perspective, neuronal activity in nociceptive pathways is responsible for the generation of signals that ultimately are interpreted as joint pain. During inflammation or tissue (joint) injury, mediators are released into the joint that sensitize primary afferent nerves such that normally innocuous joint movements (such as increased physical activity, walking on high heeled shoes) may elicit a painful response. This is the neurophysiological basis of allodynia, i.e., the sensation of pain in response to a normally non-painful stimulus such as walking[14]. Over time, this increased neuronal activity from the periphery (peripheral sensitization) can contribute to plasticity changes in the central nervous system (central sensitization)[15]. In this instance, second order neurons in the spinal cord become more responsive to peripheral input, such as responding to lower-threshold stimuli that would not normally cause the neurons to fire, or an expansion of the receptive field of the dorsal horn neurons such that the transmission of nociceptive information to the somatosensory cortex is enhanced. Central sensitization can intensify the sensation of pain and even lead to pain responses from regions of the body remote from the inflamed joint, i.e., referred pain[14].

Another important component of the biological contribution to pain comes from the multitude of tissues within the joint that contain nociceptive fibres and these are the likely sources of pain in OA. The subchondral bone, periosteum, peri-articular ligaments, periarticular muscle and joint capsule including its inner synovial lining are all richly innervated and are the likely source of nociception in OA. However, subjects with the same degree of structural damage experience widely different levels of pain, a phenomenon that is poorly understood[13].

Research into pain is challenging as a result of the multiple risk factors responsible for pain occurrence and pain severity as well as pain being a subjective phenomenon. In population studies there is a significant discordance between radiographically diagnosed OA and knee pain[8]. Whilst radiographic evidence of joint damage predisposes to joint pain, the underlying pathologies leading to pain cannot be readily discerned from radiography alone and may require consideration of other factors including function and load[16]. Novel study designs are one approach to deal with the so-called structure-symptom discordance. For example, when inter-individual differences influencing the pain experience (e.g., genetics, psychosocial factors, etc.) are adequately accounted for, a strong relationship between radiographic OA and knee pain has been noted[17]. In addition, it is important to consider that structural pathology is associated with somatosensory deficits in OA, since the extent of sensory loss directly correlated with the radiographic severity of knee OA, although causality has not been discerned[18]. One study applying direct unanesthetized examination of articular tissues in the human knee joint has provided some insight into particular structures that do and do not elicit pain when probed[19]. In

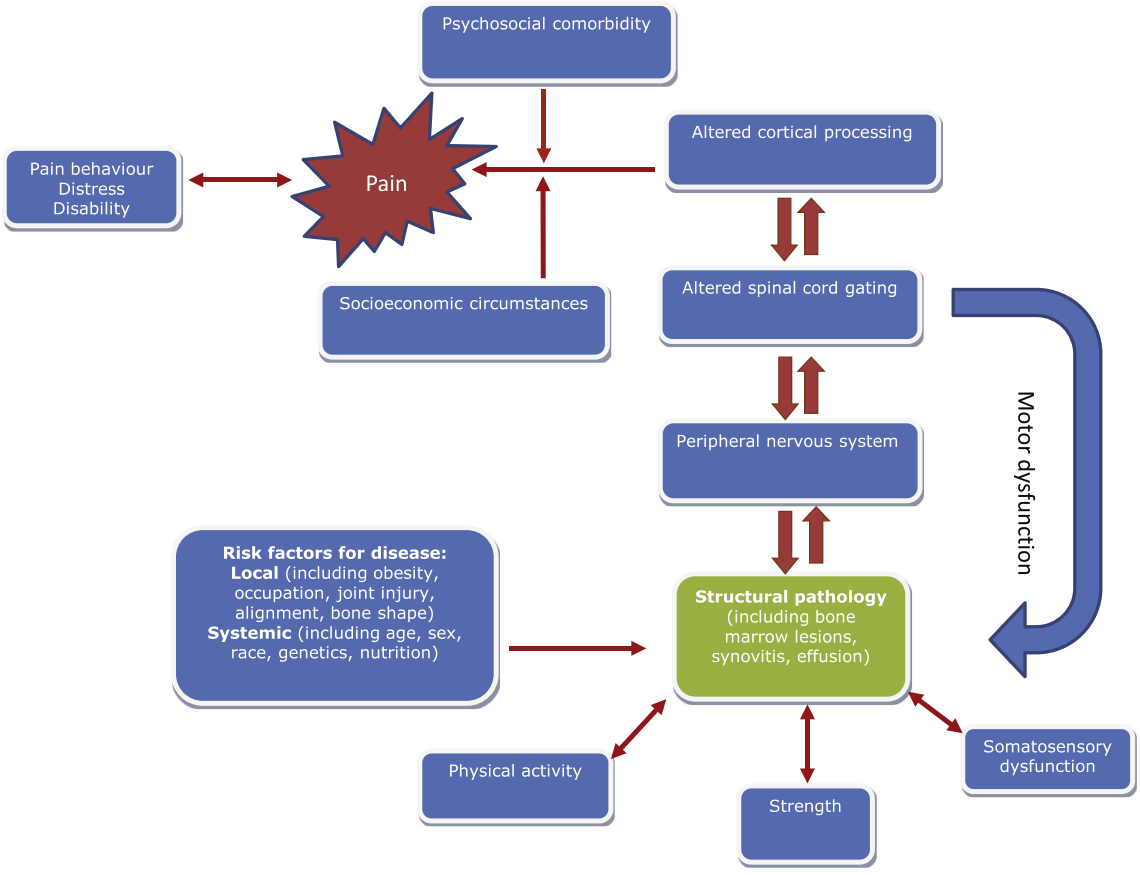

Fig. 1. Biospsychosocial model depicting the relation of structural pathology to the experience of pain.