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Can pain intensity in osteoarthritis joint be indicator of the impairment of endothelial function?

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ABSTRACT

We propose that pathological remodeling in joint tissues of osteoarthritis (OA) patients persistently stimulates local secretion of pro-inflammatory mediators, which overflow into the blood, activating leukocytes that impair endothelial function and accelerate the atherosclerotic process. During periods of pain, endothelial dysfunction progresses more aggressively due to elevated secretion of these pro-inflammatory mediators, which are involved in both atherosclerosis and the sensation of pain. Concentrations of pro-inflammatory cytokines and their antagonists, activating and decoy receptors of the broad interleukin (IL)-1 and IL-17 families, IL-15, and monocyte chemotactic protein-1 should be measured in peripheral blood samples of OA patients and compared with (I) OA clinical severity; (II) subclinical parameters of atherosclerosis; (III) ischemic heart disease risk factors; (IV) soluble factors indicating endothelial dysfunction; (V) degree of bone destruction; and (VI) results of a six-minute walk test. Arthroscopy and joint replacement surgery provide an opportunity to estimate mRNA and protein expression of inflammatory mediators in specimens of synovial fluid, synovial membrane, cartilage, and/or subarticular bone. A range of methods, including questionnaires, X-ray, computed tomography, ultrasound, enzyme-linked immunosorbent assay, immunohistology, immunofluorescence, and reverse transcription and *in situ* polymerase chain reaction are available. Understanding the inflammatory and immune mechanisms underlying OA may allow the early identification of patients at high risk of cardiovascular disease, independently of classical coronary risk factors. Pain may constitute an extrinsic indicator of currently worsening endothelial function.

Introduction

Osteoarthritis (OA), the most common chronic disease affecting all joint tissues, comprises gradual progressive degradation of cartilage by chondrocyte action, secondary synovial membrane inflammation, and subchondral bone changes [1]. Pain is the leading symptom of OA and is produced by repeated or spatially clustered irritation of unmyelinated and small myelinated fibers in the joint capsule, ligaments, synovium, bone, and outer edges of the knee menisci [2]. In addition to pain, stiffness and reduced range of motion result, with ultimate loss of joint function [3]. In OA patients, there is a positive correlation between pain intensity and functional limitations [4]. Moreover, pain can be positively associated with cartilage and bone destruction, as recognized by radiographic changes in joints [5]. However, in some individuals, this close connection between joint damage and pain is not observed, suggesting that other factors participate in determining OA clinical manifestations [6].

Primary OA is a disease of unknown pathogenesis, while secondary OA usually occurs following intraarticular fracture, soft tissue weakness, or congenital or developmental anomalies, where joint impairment is chiefly determined by mechanical causes rather than inflammation [3]. Neuropathic diseases, non-infectious inflammatory rheumatic diseases, joint infection, and

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epiphysitis induce secondary OA with a greater degree of inflammation. Biochemical, metabolic, and endocrine imbalances [3], together with immutable factors such as age, sex, and family history [7,8], encourage the progression of primary and secondary OA by systemic [3] and local pro-inflammatory pathways [9]. Studies in various experimental models and human tissues have illustrated the potential importance of cytokine balance in local tissue changes during the development of OA [1,10,11]. Lately, the nature of systemic inflammation of varying degrees of severity has also been acknowledged in OA patients [3,8], and many similarities have been found in the immune cell profiles of patients with OA and those suffering rheumatoid arthritis (RA), representing typical inflammatory rheumatic disease [11,12]. According to serum and/or local joint cytokine and chemokine profiles, interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor alpha (TNF-α), IL-12, IL-15, IL-17, IL-18, and monocyte chemotactic protein-1 (MCP-1) have been recognized as mediating both RA [11,13] and OA [1,14–16].

Members of the large IL-1 family, including IL-1β and IL-18, play pivotal roles in the initiation of inflammation and immunity by regulating innate immune cell functions and affecting the differentiation and activity of IL-1β-polarized T lymphocytes [17]. In OA-affected joints, increased numbers of IL-1β- and IL-18-expressing cells are found, including synoviocytes, chondrocytes, and osteocytes [1,15]. Both of these cytokines suppress aggrecan synthesis and collagen type II-deposition by inhibition of both mitogen-activated protein (MAP) kinase and caspase-3 activation in chondrocytes [18]. In addition, they are capable of stimulating production of matrix metalloproteinases (MMP)-1, -3, and -13 by activation of the transcription factor nuclear factor kappa B (NFκB) [1], inducing catabolic reactions in cartilage. Importantly, IL-1β also stimulates secretion of pro-inflammatory factors in joint tissue, including the cytokines TNF-α, IL-6, and IL-8, and chemokine (C-C motif) ligand 5, while inhibiting the anti-inflammatory transforming growth factor beta (TGF-β) signaling pathway [1]. Elevated IL-6 levels are associated with pain, fatigue, and depression [7,16,19], while IL-8 is involved in the amplification of pain [20]. TNF-α increases the likelihood of damage to joint cells and structure [1] by cell-mediated cytotoxicity [21], and its elevated levels in serum due to pain [1] may cause major depressive disorder [19] in OA patients. IL-18 also promotes the secretion of harmful TNF-α, and the production of cyclooxygenase-2 and prostaglandin E_2 in synoviocytes and chondrocytes [22]. Changes mediated by the action of IL-1β, IL-18, and TNF-α induce rapid aging and apoptosis of chondrocytes, accompanied by pain [18].

The local inflammatory conditions in OA joints also encourage secretion of the chemokine MCP-1 in chondrocytes and synovial fibroblasts in an autocrine manner [23]. MCP-1 is highly chemotactic for inflammatory CC chemokine receptor type 2-positive immune effectors, principally monocytes, but also $CD4^+$ and $CD8^+$ T, natural killer (NK), and dendritic cells [24], probably participating in their recruitment to the synovia, sustaining inflammation and pain in the affected joint [20]. Indeed, a chronic progressive immune response in OA patients has been confirmed by the presence of infiltrating immune cells in the synovial membrane [25]. T cells and their Th1-oriented $CD4^+$ subset are less numerous in joints of OA patients than in those affected by RA, but show similar activation marker expression [11].

Pro-inflammatory IL-15 is elevated in synovial fluid and synovial membranes in early knee OA [14], suggesting that this cytokine could be responsible for the observed local neovascularization, and chemotaxis, specific *in situ* activation of T and NK cells. Indeed, this has been demonstrated during the mild pro-inflammatory response in early-pregnancy decidua [26], and in viable cardiomyocytes surrounding a necrotic infarction zone [27]. IL-15 increases mRNA and protein expression of perforin, Fas ligand [28], and granulysin, even in early-pregnancy tolerogenic uterine NK cells, and increases their cytotoxicity [29]. This suggests that tissue-infiltrating NK cells might harm chondrocytes and other joint tissue cells in OA patients, causing pain.

The IL-17 family, which includes proteins with inflammatory properties, has also been found to participate in joint destruction in OA patients [13]. IL-17 stimulates the expression of many inflammatory biomarkers, such as IL-1, IL-6, TNF-α, chemokine (C-X-C motif) ligand 1, MCP-1, IL-8, MMP-1, MMP-3, MMP-9, and C-reactive protein, promoting recruitment of neutrophils, T cells, and monocytes to sites of local inflammation in proportion to pain intensity [30]. However, clinical analysis of ongoing immune processes in OA joints is problematic, due to the lack of their specific and sensitive biomarker and the largely unknown immune pathogenesis of this disease.

Hypothesis

We propose that persistent pathological remodeling and destruction of joint tissues (synovial membrane, cartilage, and bones) in OA patients stimulates local production and secretion of pro-inflammatory mediators, such as cytokines, chemokines, and/or growth factors, which overflow into the blood in proportion to pain severity, and accordingly engender a systemic inflammatory milieu. In such circumstances, specific peripheral blood lymphocyte subsets become activated, and may impair endothelial function independently or in concert with classical metabolic risk factors to accelerate the atherosclerotic process underlying cardiovascular diseases. During periods of pain, endothelial dysfunction may progress faster and more aggressively due to a greater abundance of pro-inflammatory mediators, which play roles in both atherosclerosis and sensation of pain in the affected joint. Hence, the pain experienced by OA patients may constitute a key indicator for currently worsening endothelial function due to the following considerations: (I) prolonged duration and/or intensity of pain correlates with pro-inflammatory IL-1β and IL-6 levels in acute myocardial infarction [31]; (II) disuse of joints due to pain increases levels of pro-inflammatory cytokines [9]; (III) pain leads to a tendency for abdominal obesity owing to reduction of daily activity, fostering a strong pro-inflammatory microenvironment mediated by IL-1, IL-6, IL-8, and TNF-α, and added mechanical stress [32]; (IV) the increase in primary OA incidence with age is associated with elevated production of pro-inflammatory cytokines [9]; and (V) heightened pain intensity is connected to greater anxiety and depressive episodes, which have been found to be mediated by the inflammatory cytokines IL-1, TNF-α, IL-6, and IL-18, and soluble IL-2 receptor in individuals not exhibiting overt inflammation [19,33]. Endothelial dysfunction and OA may be two sides of the same coin, consisting of the dominance of pro- over anti-inflammatory cytokines.

Evaluation of hypothesis

The most suitable subjects for examination would be patients with knee OA. OA of the knee joint, a common site of this condition, causes severe pain and demonstrates the most adverse effects on functional status [34] in accordance with its location and the natural course of the disease. Approximately 80% of patients with knee OA exhibit limitations in movement, 25% cannot participate in daily activities, and 11% need help in personal care [35]. Pain in this joint should be assessed in OA patients using (I) a visual analog scale of pain and the Western Ontario and McMaster Universities Arthritis Index questionnaire, designed to assess clinical severity of the disease based on assessment of pain, stiffness, and function in everyday life [36]; and (II) the Short Form-36 Health Survey, a