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Altered gait mechanics and elevated serum pro-inflammatory cytokines in asymptomatic patients with MRI evidence of knee cartilage loss

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SUMMARY

Objective: To test if sagittal plane gait mechanics parameters and serum inflammation levels differ between healthy asymptomatic subjects and asymptomatic subjects with magnetic resonance imaging (MRI) evidence of cartilage loss.

Design: Gait mechanics and resting serum tumor necrosis factor-α (TNFα) concentrations were measured for two groups of asymptomatic subjects recruited for a previous study: Pre-Osteoarthritis (OA) subjects had MRI evidence of partial- or full-thickness knee cartilage loss in at least one compartment ($n = 52$ (30 female), 1.7 ± 0.1 m, 85.3 ± 18.9 kg, 44 ± 11 years); Control subjects had no MRI features of cartilage loss, osteophytes, bone marrow lesions, nor meniscal pathology in either knee ($n = 26$ (13 female), 1.7 ± 0.1 m, 74.6 ± 14.9 kg, 34 ± 10 years). Discrete measures of sagittal plane gait kinematics and kinetics were compared between subject groups and adjusted for age and body mass index (BMI) using analysis of covariance (ANCOVA). Serum TNFα concentrations were compared between groups using bootstrap *t*-test.

Results: The Pre-OA group had less extended knees ($P = 0.021$) and decreased maximum external knee extension moment ($P = 0.0062$) in terminal stance during gait, as well as increased resting serum TNFα concentration ($P = 0.040$) as compared to Control subjects. There were no group differences in heel strike flexion angle ($P = 0.14$), in maximum knee flexion moment ($P = 0.91$), nor in first peak knee adduction moment (KAM) (post-hoc analysis, $P = 0.39$).

Conclusions: The finding that asymptomatic subjects with cartilage loss had gait and inflammatory characteristics similar to those previously reported in symptomatic OA patients supports the idea that there are specific mechanical and biological factors that precede the onset of knee pain in the pathogenesis of OA.

Introduction

Little is known about the very early stages of idiopathic knee osteoarthritis (OA) as the disease is often symptomatically silent until considerable joint damage has developed. In particular, identifying asymptomatic individuals who will go on to develop knee OA is an ongoing challenge that contributes to the current absence of disease modifying interventions[1]. Thus, it is imperative to understand early OA pathogenesis as a basis for developing complementary therapeutic options.

While OA has been described as a disease of mechanics[2], there is increasing awareness that it is ultimately the interplay between mechanical, structural, and biological factors that must be considered in the analysis of OA pathogenesis at the knee[3]. In the context of mechanical loading, loads due to walking are the most frequent

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loading regime experienced at the knee[4]. In healthy knees, the cartilage structure is adapted to withstand this everyday loading[5–7]. For example, tibial cartilage covered by the meniscus is stiffer and has a different biological response to loading than regions not covered by the meniscus, indicating that tissue properties in healthy cartilage vary regionally and develop according to the loads experienced[8–10]. As such, kinematic and kinetic changes during walking that can shift the locations and magnitude of cartilage loading have been implicated in the pathogenesis of OA disease[11]. Furthermore, biological factors such as elevated systemic inflammation have been associated with the development and progression of knee OA[12]. Increased pro-inflammatory cytokines in the joint synovial fluid can have a profound catabolic effect on the cellular response of cartilage due to loading[6], suggesting an interaction between mechanical loading and inflammation leading to cartilage degradation. These local increases in inflammation at the knee can be reflected in increased systemic, serum-derived pro-inflammatory cytokine levels, and vice versa[12–14]. Therefore, both gait mechanics and levels of systemic inflammation should be considered when probing early OA disease pathogenesis.

In evaluating factors associated with early knee OA development, it is useful to consider specific gait and inflammatory differences between OA patients and healthy subjects and factors associated with disease progression. Knee adduction moment (KAM) has long been the gait variable of interest in medial knee OA, as it has been related to greater OA severity[15] and prospective worsening of disease severity in patients with established, symptomatic OA[16,17]. However, recent work has highlighted the importance of sagittal plane kinetics in disease processes, especially the degeneration of cartilage in the early stages of medial compartment OA[17,18]. Specifically, subjects at risk of OA development due to increased age and symptomatic OA patients display a decreased terminal stance peak knee extension moment compared to healthy controls[19–22], which is even further decreased in severe vs mild/moderate OA patients[22,23]. Furthermore, peak knee flexion moment is decreased in OA patients compared to healthy controls[21], and a greater baseline knee flexion moment has been related to greater loss of medial tibial cartilage thickness over 5 years in medial knee OA patients[18]. Sagittal plane kinematics, especially when the knee is near full extension, have been shown to differ with OA status as well. Specifically, at heel strike and in terminal stance, OA patients walk with more flexed knees than control subjects and this difference is greater with more severe OA[20,22,24]. Therefore, sagittal plane knee gait mechanics are of keen interest in analyzing the idiopathic OA disease process.

Inflammation also plays a role in the initiation and progression of knee OA[25] as serum levels of pro-inflammatory cytokines are elevated in OA patients and individuals at high risk for OA, including obese and older individuals[12,26,27]. Specifically, increased levels of the circulating pro-inflammatory cytokine tumor necrosis factor-α (TNFα) have been linked to the presence of radiographic signs of OA, cartilage volume loss over time, increased disease severity, and risk of OA progression[28–30]. Therefore, changes in mechanical loading at the knee, as measured by sagittal plane gait mechanics, and the presence of elevated TNFα, are likely involved in the initiation and progression of idiopathic OA.

While sagittal plane gait mechanics and inflammation levels have been related to the presence and severity of symptomatic OA, these studies compared symptomatic OA patients with asymptomatic, healthy subjects. However, given that cartilage loss typically precedes the onset of symptoms, there is an important "pre-symptomatic OA" phase of disease development in which patients are asymptomatic but have cartilage degradation[31–33]. Current literature is devoid of data during this pre-symptomatic OA phase due to the difficulty in identifying qualified subjects. Nonetheless, examining alterations during this pre-symptomatic OA phase is critical to understanding the temporal sequence of structural, mechanical, and biological changes and the onset of clinical symptoms, and can help guide future disease interventions.

In a previous research study of asymptomatic community dwellers[34,35], approximately 60% of the participants had magnetic resonance imaging (MRI) evidence of cartilage loss. These individuals are therefore pre-symptomatic and at high risk of developing symptomatic OA[33]. Analysis of this subgroup provides a unique opportunity to test for gait and inflammatory differences in the pre-symptomatic stage of OA disease development. Therefore, the first aim of this study was to test if gait alterations previously identified in OA patients are present in asymptomatic subjects with MRI evidence of cartilage loss (Pre-OA group) as compared to a healthy control population. Similarly, the second aim of this study was to test if systemic inflammation is elevated in the Pre-OA group as compared to the control subjects. Accordingly, the following

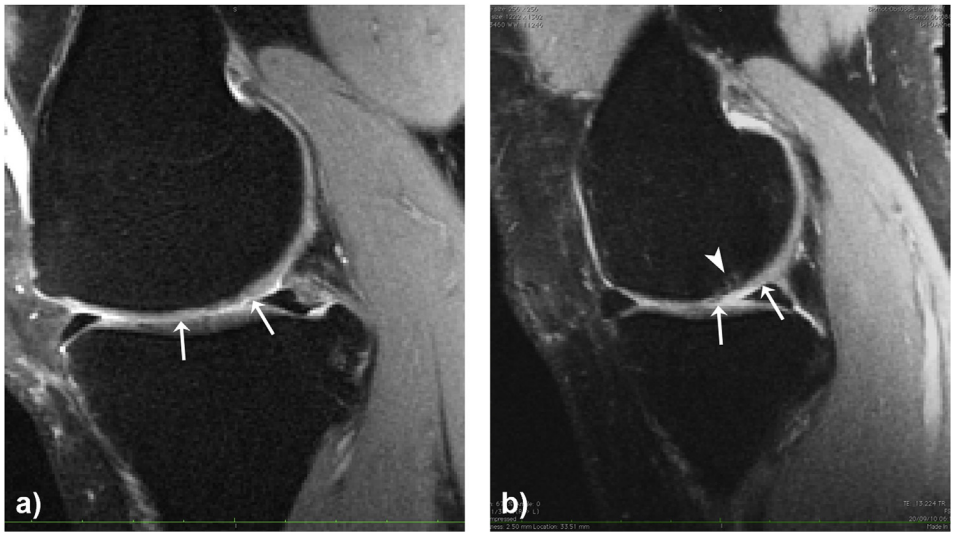

Fig. 1. Examples of MRI evidence of (a) partial-thickness cartilage loss (between arrows) and (b) full-thickness cartilage loss (between arrows) and bone marrow edema (arrowhead).