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## Determinants of pain in patients with symptomatic knee osteoarthritis

### Abstract

**Background:** Several factors are associated with the development or exacerbation of pain in knee osteoarthritis (KOA). In this study, we reviewed this context based on relevant studies.

**Methods:** Recent published studies which have addressed the relationship between pain and KOA were summarized.

**Results:** Correlates of the clinical, demographic features, laboratory tests and abnormalities on radiographic as well as magnetic resonance imaging (MRI) with the knee pain have been discussed. The results indicated that many factors such as synovitis, synovial effusion, obesity, as well as structural lesions determined by MRI or radiographic examination, serum cytokines, inflammatory markers are determinants of pain in KOA.

**Conclusion:** This context requires further investigations for identification of additional factors which initiate pain in asymptomatic KOA

**Keywords:** Knee osteoarthritis, Pain, Determinants, Synovitis, C-reactive protein, Structural lesions

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**K**nee osteoarthritis (KOA) is characterized by pain and limitation in range of knee joint motion with resultant disability in a substantial proportion of elderly subjects.(1) Pain is the most common clinical presentation of KOA, typically exacerbates by activity and relieves by rest .Persistent pain at rest profoundly affects the quality of life and daily physical activity (1). Pain itself is a risk factor for the development of future functional decline and increasing pain is a predictor of physical functional limitation and disability (2). Nonetheless a proportion of patients with bilateral radiographic KOA present with unilateral knee pain and many asymptomatic subjects have osteoarthritic radiographic changes. On the contrary, a number of patients with knee pain suggestive of clinical KOA, have no radiographic findings (1).

These observations indicate that some risk factors may have a contributive role in the development as well as exacerbation of pain in KOA (1, 3). The association of KOA with several clinical, demographic, structural and laboratory parameters such as age, sex, obesity, physical activity, synovitis / synovial effusion, subchondral bone lesions, muscle weakness, vitamin D deficiency has been shown (1-3). However, the prevalence and contribution of these factors in the development of pain vary according to patient characteristics and disease status. It was shown that increasing pain along with reduced range of motion, decreased muscle strength, higher morbidity count, higher age, longer disease duration are the predictors of future functional impairment and limitation of activity (2, 4).

Treatment of KOA is targeted to suppress pain and improve functional outcome. Therefore, information on risk factors of worsening of pain and decline in functional limitation can be used to construct treatment. This study aimed to present a concise information regarding associated factors of pain in patients with KOA (table 1) provided from recent relevant published studies which have addressed the risk factors of pain in KOA.

**Table 1. Associated factors of pain in patients with knee osteoarthritis**

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Synovitis and synovial effusion
Vitamin D deficiency
Muscle weakness
Obesity
Female gender
Physical activity
Psychological factors
Joint abnormalities
Magnetic resonance imaging findings
Radiographic changes
Cytokines and inflammatory markers

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**Synovitis in KOA:** Recent investigations have found the existence of inflammatory process in several chronic medical conditions as well as osteoarthritis (5-7). Synovial inflammation plays a critical role in the development of symptoms and structural changes in KOA (1, 8-11). In the early stages of KOA synovitis is localized to the regions with chondral defects but at later stages inflammation becomes diffuse and chronic (10, 11).

Arthroscopic examination reveals chondropathy, synovial infiltration of macrophage and proliferation of blood vessels (11). In osteoarthritic patients without radiographic changes in knee joint, synovitis is observed in 55% of cases (12). In the Multicenter Osteoarthritis Study (MOST) 80% of KOA patients with moderate pain had synovitis (13). In a 1-year longitudinal study of patients with tibiofemoral osteoarthritis with mean age of 61 years, synovial abnormalities were observed in 50% (14). Almost all patients with advanced osteoarthritis who were considered for surgical treatment had synovitis (15).

**Diagnosis of synovitis:** Definitive diagnosis of synovitis requires biopsy of the synovium during arthroscopic examination (10, 11). However, all patients do not require arthroscopy and thus in suspected cases noninvasive methods such as clinical examination and imaging techniques like ultrasound particularly magnetic resonance image (MRI) are commonly used to document synovitis. Clinically, the presence of joint pain at rest especially night pain, stiffness, joint effusion indicates synovitis (1, 3). In suspected cases, serum and synovial fluid examination are also helpful to differentiate KOA from other inflammatory arthritis like rheumatoid arthritis (16, 17). In patients with mild or moderate KOA, synovial abnormalities can be detected by using MRI or ultrasound techniques at earlier stages with higher sensitivity than clinical examination even in asymptomatic patients (8, 9, 18-20).

In a study of patients with history of knee pain, a third of cases had synovial thickening or suprapatellar effusion suggestive of synovitis (9). Almost half of patients with KOA show synovial hypertrophy or joint effusion in ultrasonographic examination (21). MRI yields greater sensitivity in detecting joint abnormalities and thus higher proportion of KOA can be recognized by MRI examination. In particular, synovial abnormalities found in MRI show greater correlation with arthroscopic and histologic findings (8, 18, 21). In a study of patients with symptomatic KOA, the types and the frequency of abnormalities seen in MRI examination were synovial thickening, joint effusion, osteophytes and subchondral bone edema which were found in 73%, 60%, 67% and 65% respectively, whereas the respective values in asymptomatic KOA were 0% and 7%, 12% and 7% (8).

**Synovitis and pain:** Like rheumatoid arthritis, osteoarthritis is also associated with inflammation which presents as synovitis. Synovitis in KOA is associated with pain and cartilage loss (13). The association of pain and synovitis in KOA has been shown in several studies (13, 22, 23). The relationship between specific tissue lesions and pain in KOA was shown by Torres et al. In this study, synovitis /synovial effusion as well as MRI abnormalities such as bone marrow lesions, subchondral bone attrition and meniscal tears were associated with severity of pain (22). A similar association of pain and synovitis /joint effusion has been reported in KOA with and without radiographic changes (23). In the Multicenter Osteoarthritis Study, pain in patients with synovitis was 9.2-fold greater than those without synovitis

even in subjects without radiographic evidence of KOA (13). Nonetheless, in a study by Hill et al., synovial effusion was not associated with pain but changes in synovitis was positively correlated with pain (24). In a study of patients with early KOA, patients without synovitis had no pain (12). Even in patients without KOA, the presence of synovitis causes pain. This was shown in patients with meniscal tears undergoing arthroscopic examination. In this study, patients with preoperative pain had synovitis, and the association was independent to age, sex and severity of cartilage injuries (25).

**Vitamin D and Pain:** Vitamin D deficiency is prevalent in general population as well as patients with musculoskeletal diseases presenting to rheumatology clinics (26-30). Vitamin D deficiency is associated with pain in musculoskeletal diseases including osteoarthritis (27, 30-35).

Low levels of serum vitamin D is a risk factor for the development and worsening of knee pain (34) as well as a predictor for incident KOA (27). Vitamin D deficiency contributes to the development of clinical symptoms and severity of pain through sensitization to pain. Obese vitamin D deficient subjects are at greater risk of pain (31, 36, 37). Compared to vitamin D sufficient subjects, those with moderate to severe vitamin D deficiency are at higher risk of postoperative pain (38). There is a dose-response pattern of relationship between vitamin D deficiency and bone pain/bone tenderness (35). There is an independent association between vitamin D deficiency and nonspecific bone pain, low back pain, and unexplained arthralgia (26, 30, 32). Normalization of vitamin D deficiency decreases knee pain in patients with KOA (39).

**Muscle strength and knee pain:** Muscle weakness has a significant contribution in the development and progression of KOA (1, 40-42). In KOA, the quadriceps muscle strength is lower than healthy controls (40).

There is an association between quadriceps muscle weakness and pain as well as disability in KOA independent to radiographic changes (43, 44). In KOA, pain correlates negatively with quadriceps muscle strength and strengthening of quadriceps muscle reduces pain (39, 45). Thus, in these patients muscle strengthening is a target of treatment for relieving pain and improving physical performance (46, 47).

**Obesity, metabolic syndrome and pain:** Obesity and overweight which are prevalent among general population even in young adults and children are strongly associated

with onset and exacerbation of pain as well as development of disability in KOA (48-51) whereas weight loss decreases the pain as well as the risk of symptomatic KOA (52). Furthermore, obesity is a risk factor for the development and progression of KOA (1, 3). In KOA, pain correlates positively with BMI and thus, persons with higher BMI have more severe pain (53). In a cross-sectional study of people with mean age of 58 years, obesity was associated with increased risk of joint pain in hips, knees, ankles and feet (52). In a study by Maddah et al., coexistence of metabolic syndrome with KOA was associated with greater pain and patients with more components of metabolic syndrome had higher Western Ontario and McMaster University Osteoarthritis Index (WOMAC) pain score independent to age and BMI (54). Inasmuch as, abdominal obesity is a major component of metabolic syndrome (55). However, one major component of metabolic syndrome is abdominal obesity (55).

**Female gender and pain:** Several painful musculoskeletal conditions are more frequent in women than men indicating that women are at greater risk of central sensitization than men (56). Proportion of women with symptomatic KOA is significantly higher than men and radiographic features of KOA are more prevalent in women than in men (57). Prior to total knee replacement surgery, women with KOA have more pain and greater functional impairment than men (58). In a study of elderly community residents with radiographic KOA, women had worse mean WOMAC and SF-36 scores than men with similar radiographic changes (56). In patellofemoral osteoarthritis, women report greater knee pain than men irrespective to severity of radiographic findings (59). In participants of the Rotterdam Study, female gender was a risk factor for pain (60). The association between quadriceps weakness and pain in women is stronger than men. This may partly explain higher susceptibility of women to pain (61).

**Physical activity and pain:** Influence of physical activity on KOA is not clear and data regarding the harmful effect of different types and intensity of exercise programs on KOA are insufficient (62). Nonetheless, in advanced KOA physical activity aggravates knee pain (63), whereas regular swimming exercise reduces pain and improves muscle strength and functional capacity (64).

The results of a systematic review showed that physical activity increases osteophytes but decreases cartilage lesions (65). Depending on preexisting anatomical changes and type, or duration of activities, physical activity may affect knee or

hip joints differently (66). Individuals with history of heavy physical activities show greater joint abnormalities versus those with lower physical activities who have less tibiofemoral or patellofemoral OA (67). High moderate to vigorous activity in subjects with mild knee pain but without radiographic features of KOA will increase bone marrow lesions as well as medial meniscal injuries (68). Also KOA prolong duration of moderate to vigorous daily physical activity increases pain and decreases functional capacity (69). In a longitudinal study, high level of leisure time physical activity increased the risk of total knee replacement surgery in women aged <45 years old but not in men (70). However, the results of a systematic review showed that in older adults with knee pain, long-term physical activity over 3-30 months was safe and did not increase pain or total knee replacement surgery, particularly increasing the level of physical activity reduced disease progression, decreased total knee replacement surgery (71). Similarly, regular to moderate physical activities exerts preventive and therapeutic effect (72). Nevertheless, absence of mechanical stimulation as seen in subjects with spinal injuries results in cartilage thinning (69).

#### **Psychological and sociodemographic factors and pain:**

Psychosocial factors contribute to the development and progression of musculoskeletal pain and disability. In patients with KOA, the prevalence of psychiatric morbidities are higher than expected (73), and these patients have higher number of painful sites in other parts of the body (74). Depression is strongly linked to pain specifically in patients with severe osteoarthritis (75). Presence of depression increases the risk of self-reported knee pain irrespective to severity of radiographic changes. Even in patients with minimal or moderate radiographic changes particularly middle-aged women and elderly subjects, the presence of depression increases pain (76). Furthermore, cognitive factors but not behavioral factors have also a role in the development of pain in osteoarthritis (77). In a longitudinal study with 12-months postoperative follow-up period, postsurgical pain both at rest and activity was higher in depressed patients. In addition, knee function was lower prior to and after surgery and the prevalence of dissatisfaction was higher (78). Socioeconomic factors affect osteoarthritis symptoms and treatment results. Subjects of higher socioeconomic levels have less pain and higher functional capacity prior to total knee replacement surgery (79).

**MRI abnormalities and pain:** MRI is a sensitive method for visualization of various joint structures including cartilage, bone marrow, synovium, meniscal and ligament pathology in both tibiofemoral and patellofemoral joints (3, 8, 23, 80), whereas, conventional anteroposterior radiographs have no ability to disclose patellofemoral compartment, ligaments or synovium (80). In a study of patients with definite knee osteophytes in radiograph, all MRI abnormalities such as subarticular bone attrition, bone marrow lesions, synovitis/effusion, and meniscal tears were significantly associated with knee pain (22). However, in another case-control study, only the presence of large bone edema differentiated painful KOA from asymptomatic KOA or healthy controls (81). The results of a systematic review of 22 studies showed a significant association between bone marrow lesions as well as synovitis/effusion with pain. Bone marrow lesion increased the odds of pain 2 to 5-folds and synovitis increased the pain by odds of 3.2 to 10 (82). In a cross-sectional study of 904 randomly selected subjects with the average age of 62.4 years, patellar bone marrow lesions were consistently associated with knee pain particularly going up/down stairs (83). Association between MRI findings and knee pain was also observed in Michigan Study of Women's Health across the Nation (84).

**Radiologic abnormalities and pain:** Knee pain is a vague symptom of KOA and its association with radiographic abnormalities varies according to extent of radiographic changes and radiographic view. The results of studies which have addressed the relation between pain and radiographic changes in KOA are controversial. This may be attributed to types, severity and the prevalence radiographic abnormalities (60, 85). The clinical and radiographic features of KOA are not usually concordant with KOA symptoms.

The results of a systematic review reveals that only 15-76 % of subjects with knee pain had radiographic features of KOA and only 15-81% of subjects with radiographic OA had knee pain (85).

In a study of 2282 elderly Japanese subjects aged > 60 years, the association between radiographic changes and pain varied from none to strong. Nonetheless, the presence of severe radiographic changes were strongly associated with pain (85).

In Baltimore Longitudinal Study of Aging, over a 5-year follow-up period, all measures of radiographic severity were directly correlated with knee pain (86). In a study of the elderly Japanese population-based cohorts, joint space

narrowing was strongly associated with pain especially in men (87). In another population-based study of 250 subjects, osteophytes was strongly associated with knee pain, whereas the presence or absence of joint space narrowing was not associated with pain (88). Radiographic abnormalities can reduce muscle strength and result in pain. (3). An inverse association between quadriceps muscle strength and radiographic progression especially in patients with radiographic grades of 0 and 1 has been reported (89).

**Inflammatory markers and pain:** Chronic systemic inflammation and local synovitis are source of pain in KOA (25). Production of local inflammatory cytokines and nerve growth factor in the synovium promote pain. In the early stage of osteoarthritis, synovium produces cytokines such as interleukin-1, TNF-alpha and IL-6. These cytokines cause increased production of serum CRP and serum amyloid A (8). In addition, serum markers and surrogates of synovial fluid can be used as markers for diagnosis, prognosis, or evaluation of disease, severity or response to treatment (16, 17, 87, 90).

In advanced osteoarthritis, synovitis correlates with both plasma CRP and synovial fluid IL-6 (91). In KOA serum CRP, IL-6, and IL-10 are higher than healthy controls. These markers correlate positively with pain as well as radiographic abnormalities (92-94). Furthermore, serum CRP correlates with synovial fluid CRP as well as severity of osteoarthritis (92). Patients with higher levels of serum CRP have greater postoperative functional impairment (95). Moreover pain in KOA deteriorates by increasing serum levels of both serum CRP, TNF-a and IL-6 (96).

In conclusion, a high proportion of patients with KOA are asymptomatic inspite of radiographic evidence of osteoarthritis. Nonetheless pain occurs in a significant number of these patients which may increase with age. Several factors like synovitis, joint effusion, and structural changes as seen in radiographs or MRI are associated with pain. As a consequence many associated factors of pain such as obesity, muscle weakness, vitamin D deficiency are modifiable. Therefore, in approaching patients with KOA, identification of the associated factors is important for the establishment of treatment and prevention measures.

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