Review Article

Knee osteoarthritis prevalence, risk factors, pathogenesis and features: Part I

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Abstract

Osteoarthritis (OA) a common disease of aged population and one of the leading causes of disability. Incidence of knee OA is rising by increasing average age of general population. Age, weight, trauma to joint due to repetiting movements in particular squatting and kneeling are common risk factors of knee OA. Several factors including cytokines, leptin, and mechanical forces are pathogenic factors of knee OA. In patients with knee pain attribution of pain to knee OA should be considered with caution. Since a proportion of knee OA are asymptomatic and in a number of patients identification of knee OA is not possible due to low sensitivity of radiographic examination. In this review data presented in regard to prevalence, pathogenesis, risk factors.

Key words: *Knee, Osteoarthritis, Pathogenesis, Prevalence.*

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Osteoarthritis (OA) is one of the most prevalent condition resulting to disability particularly in elderly population. OA is the most common articular disease of the developed world and a leading cause of chronic disability, mostly as a consequence of the knee OA and/or hip OA (1). The economic costs of OA are high, including those related to treatment, for those individuals and their families who must adapt their lives and homes to the disease, and those due to lost work productivity (2).

Patients with OA are at a higher risk of death compared with the general population by OR of 1.54. History of diabetes, cancer, or cardiovascular disease and the presence of walking disability are major risk factors. Excess mortality is observed for all diseases with specific causes of death but is particularly pronounced for cardiovascular complications. Knee OA is more important not only for its high prevalence rate compared with other types of OA but also for its presentation at earlier age groups particularly in younger age groups of obese women. The incidence of knee OA increases by age and further increase with longer lifetime and higher average weight of the population (3).

Pain and other symptoms of OA may have a profound effect on quality of life affecting both physical function and psychological parameters. Knee OA is not a localized disease of cartilage alone but is considered as a chronic disease of the whole joint, including articular cartilage, meniscus, ligament, and peri-articular muscle that may result from multiple pathophysiological mechanisms. It is painful and disabling disease that affects millions of patients (4).

Despite its severe consequences, however most patients with knee OA can be managed in the community and primary care (5).

Prevalence

About 13% of women and 10% of men aged 60 years and older have symptomatic knee OA. The proportions of people affected with symptomatic knee OA is likely to increase due to the aging of the population and the rate of obesity or overweight in the general population.(6). During a one year period, 25% of people over 55 years may demonstrate persistent episode of knee pain, in whom about one in six have to consult their general practitioner about it in the same time period. About 10% of people aged over 55 years have painful disabling knee OA of whom one quarter are severely disabled (5). Prevalence of knee OA in men is lower compared with women .This was shown in a meta analysis of males and females in which the incidence of knee OA in males aged <55 years was lower than females.

Females, particularly those ≥55 years, tended to have more severe OA in the knee but not in other sites. The results of this study demonstrated sex differences incidence of knee OA particularly after menopausal age (7). In a prospective study in which data were provided by radiographs, physical performance assessment, and interviews in 1996 and again (with the addition of magnetic resonance imaging assessment) in the follow-up visit during the years 2007, 2008. The prevalence of moderate-to-severe knee osteoarthritis changed from 3.7% at the baseline assessment to 26.7% in the follow-up visit eleven years later. Middle-aged women had a high prevalence of moderate-to-severe knee osteoarthritis (8). The prevalence rates of knee OA vary according to study population as well as the methods applied for diagnosis.

The prevalence of radiographic knee OA has been investigated in 2282 elderly Japanese people aged ≥ 60 years (817 men and 1,465 women) living in urban regions. There was a high prevalence of radiographic of Knee OA .The prevalence of pain in the knee was age-dependent in women, but not in men (9). Symptomatic knee OA was common among the general adult population especially in women of older age groups. In a cross-sectional study of 7 communities in Greece, symptomatic knee OA was observed in 6% (95% CI 5.6-6). The prevalence rate was significantly higher among women than in men and increased significantly with age. Symptomatic knee OA was significantly more common in rural compared to urban and suburban populations. Logistic regression analysis showed a significant association of female sex and age ≥50 years with all sites of OA. In addition obesity and low level of education were associated with knee OA (10). Knee symptoms, radiographic knee OA, symptomatic knee OA, and severe radiographic knee OA were calculated in 3018 participants (33%) of African Americans (38% men). Diagnosis of knee OA and severity of disease was made based on Kellgren-Lawrence radiographic grade ≥ 2, severe radiographic knee OA as grades 3 and 4, and symptomatic knee OA as knee symptoms in a knee with radiographic OA. Knee symptoms were present in 43% of patients. Twenty- eight percent of symptomatic patients had radiographic knee OA, 16% had symptomatic knee OA, and 8% had severe radiographic knee OA. Prevalence was higher in older individuals and women. African Americans had slightly higher prevalence of knee symptoms, radiographic knee OA, and symptomatic knee OA, but significantly higher prevalence of severe radiographic knee OA compared to Caucasians (11).

Relationship between knee pain and radiographic changes

Knee pain is an imprecise marker of radiographic knee osteoarthritis which is partly dependent to extent of radiographic involvement. Similarly, radiographic knee OA is an imprecise guide to the likelihood that knee pain or disability will be present. Both associations are affected by the definition of pain used and the nature of the study group. The results of knee X rays should not be used in isolation when assessing individual patients with knee pain (12). Many individuals with radiographic knee OA are asymptomatic and in contrary in many patients with knee pain suggestive of OA radiologic findings are absent. Based on clinical examination and history presence of knee OA can be suggested and demonstration of radiologic manifestations may be predicted. For example, in a study of patients with various skeletal manifestations presence of some clinical and or demographic information such as age, sex, body mass index, absence of whole leg pain, difficulty in descending stairs, palpable effusion, fixed-flexion deformity, restricted-flexion range of motion, and crepitus predicted knee OA at sensitivity of 94% and specificity of 93%. In this study, knee pain was associated with more severe diseases defined as KL> 3 rather than milder OA defined as KL=2, in women than in men (13). Available data suggest that the symptoms of knee OA are rather weakly associated with radiographic findings and vice versa (9, 12). In a systematic literature review, 15-76% of those with knee pain had radiographic

OA and 15-81% of those with radiographic knee OA had pain (12). At present the relation between joints lesions and pain is assessed by conventional radiography which is not sensitive enough and has several limitations. In patients suspected to knee OA presence of osteophytes in all knee views (AP, lateral or skyline) predicts knee pain more accurately than joint space narrowing on all knee radiographic views (14).

In middle-aged women, there were significant associations between pain, radiographic severity of OA of the knee, and seven MR imaging-identified parameters (15). Although the presence of osteophytes had the strongest association with knee pain "ever' with an odds ratio for skyline osteophytes of 7. 56, and anteroposterior osteophytes of 5.There was a trend for an association between the severity of narrowing in the lateral and skyline views and knee pain, but the association between joint space narrowing and knee pain was not statistically significant. In another study, of one-hundred six OA knees in 68 subjects (mean age 71.1 years; 85% women) who were followed up in every 6-month interval over 36 months, the subjects with knees who had joint space narrowing had more severe symptoms, and the symptoms tended to be worse for those with higher rates of narrowing. A significant correlation was not found between the severity of symptoms and the growth of osteophytes The result of this study in contrast to previous studies indicated an association between the symptoms of knee OA and progression of joint space narrowing (16).

The differences in association of joint space narrowing and knee pain may be partly explained by biomechanical component. Biomechanical factor may change an asymptomatic radiographic OA to a symptomatic disease. Among the individuals with mild radiographic knee OA (K/L grade 2), those who are symptomatic have significantly higher medial compartment loads than those who are asymptomatic, whereas, those who are asymptomatic do not differ from normal controls (asymptomatic K/L grade 0 or 1) (17). Among the community men and women presence of osteophyte is the radiographic feature that associates best with knee pain in both women and men. Therefore, radiographic assessment of both tibiofemoral and patelofemoral regions should be included in all community studies. Joint space loss is not a feature of asymptomatic aging, and there is not a biological cut off for joint space width below which the likelihood of knee pain markedly increases (18).

The capability of MRI to visualize structural lesions within the knee joint is greater, and there is a growing body of work using MRI for the diagnosis of knee OA as well as to examine the correlation between structural findings and knee symptoms.

In large cohort studies, synovial hypertrophy, synovial effusions, and abnormalities in the subchondral bone have been associated with knee pain (19). Bone attrition detected on conventional x-rays using a simple cheap technique is strongly associated with the presence of day pain, stiffness and disability in knee OA. Bone pathology was reported in 74% of those with radiographic bone attrition compared with 42% of those without bone attrition (20).

In a systematic review of previous studies in which the types of MRI lesions associated with knee pain has been investigated. The presence of bone marrow lesions was associated with knee OA pain with OR of 2 to 5. The OR of having pain in the presence of effusion/synovitis ranged between 3.and 10.0. These findings may indicate that bone marrow edema. Effusion / synovitis being the origin of pain in knee OA (21). In another study of comparing radiographic and MRI findings of knee OA ,there was a significant association between pain, radiographic severity of knee OA and seven parameters identified by MR imaging.In this study defects of cartilage, osteophytes, sclerosis, meniscal or ligamentous tears, joint effusion, and synovitis were strongly related to increasing Kellgren-Lawrence grade (15). In persons with knee OA, knee pain severity was associated with subarticular bone attrition, bone marrow lesions, synovitis/effusion, and meniscal tears. The contribution of bone marrow lesions to pain severity appeared to require the presence of bone attrition (22).

Etiology and risk factors of knee OA

OA has a multifactorial etiologies, which occurs due to interplay between systemic and local factors. Osteoarthritis affects all ages. The etiology of this debilitating disease in which several responsible genes are linked for its occurance. Sports participation, injury to the joint, obesity, and genetic susceptibility predispose adolescent athletes to the development of premature osteoarthritis. Previous knee trauma increases the risk of knee OA 3.86 times (23). Old age, female gender, overweight and obesity, knee injury, repetitive use of joints, bone density, muscle weakness, and joint laxity all play roles in the development of joint OA

Determination of risk factors particularly in the weight-bearing joints and their modification may reduce the risk of OA and prevent subsequent pain and disability (6, 26). Mechanical forces exerted on the joints are a significant cause of OA and one of the most modifiable risk factors as determined by body BMI. Female sex, lower educational levels, obesity, and poor muscular strength are associated with symptomatic disease and subsequent disability (25).

In a review of literature 14 contributing variables including occupational (extrinsic) and personal (intrinsic) were considered as risk factors. Two factors of kneeling and squatting are considered the main primary risk factors in correlation with knee disorders (26).

Frequent squatting predispose people to development of knee OA. Aapproximately 40% of men and approximately 68% of women reported squatting ≥1 hour per day at age 25.Prolonged squatting is a strong risk factor for tibiofemoral knee OA among elderly (27). Occupation involving squatting or kneeling more than two hours daily were associated with two-fold significantly increased risk of moderate to severe radiographic knee OA. Obesity alone or in patients with metabolic syndrome increases the risk of radiographic knee OA but has a lesser effect progression of knee OA (28, 29). Relationship between BMI and OA of the knee is mainly linear, and duration of increased joint loading or gaining weight is also significant.Twenty seven percent of cases of hip arthroplasty and 69% knee arthroplasty may be attributed to obesity (1). In a systematic literature search obesity was consistently the main factors with knee OA by OR=2.63 (23).

Obesity is also associated with the hip and hand OA.This indicates that excess adipose tissue produces humoral factors, altering articular cartilage metabolism. It has been postulated that the leptin system could be a link between metabolic abnormalities in obesity and increased risk of OA (29). Miniscal surgery increases the risk of future knee OA by 2.6 times (30). Patients undergoing partial meniscectomy and reconstruction surgery are significantly more likely to develop radiographic evidence of osteoarthritis than those with normal menisci (31). Inflammatory process has been shown to be associated with OA. Inflammation may have a contributive role in the development and progression of OA. In one study the median level of high sensitive CRP in progressive knee OA was higher than non-progressive disease (32). The median value of CRP is significantly associated with functional disability, joint tenderness, pain, fatigue, global severity, and depression in OA. Mean CRP level in OA is greater than healthy individuals (33).

In a study of relationship between biochemical markers of arthritis and the radiographic grading of osteoarthritis (OA) in knees, a significant relationship was found between the joint space width and radiographic knee OA. The joint space width decreased with increasing Kellgren-Lawrence grade. Pyridinoline and TIMP-1 exhibited a significant relationship to the Kellgren-Lawrence grade but only urinary pyridinoline had a significant correlation (34).In another study, raised serum CRP at entry was predictor of knee OA progression. Serum CRP at entry was not predictive of progression between entry and five years but serum CRP at -3 years was predictive of progression by OR=1.95 (35). Female sex was a strong risk factor even in the subgroup without radiographic knee OA (KL=0/1) (36) For instance, the greater total body fat of the average adult female may partially account for the gender disparity toward OA, given that females theoretically demonstrate higher levels of adipose derived systemic leptin concentrations than their male counterparts.(36). Female gender increases the risk of knee OA 1.84 times (23). In patients with knee OA particularly at early stage of the levels of serum vitamin D is significantly lower than individuals without knee OA.Vitamin D deficiency increases the risk of knee OA by OR=2.63 (37). Higher than 6 pregnancies increases the rik of knee OA by 1.95 times (38).

Table 1. Risk factors of knee osteoarthritis

Age
Genetic susceptibility
Obesity
Female gender
Trauma
Repetitive knee trauma
Muscle weakness
Joint laxity
Mechanical forces
Kneeling
Squatting
Miniscal injuries

Physiopathology

The development of OA is dependent to interactions between several factors and so this process may be

considered the product of an interplay between systemic and local factors (6). This progressive and disabling disease can be resulted from a combination of risk factors, including advancing age, genetics, trauma, knee malalignment, increased biomechanical loading of joints through obesity, augmented bone density and an imbalance in physiological processes (39). There is now a growing body of evidence that obesity is a complex syndrome in which an abnormal activation of neuroendocrine and pro-inflammatory pathways leads to an altered control of food intake, fat expansion and metabolic changes.Activated white adipose tissue increases the synthesis of pro-inflammatory cytokines, such as IL-6, IL-1, IL-8, TNF alpha, IL-18, but decreases the regulatory cytokines,such as IL-10 (40). This observation supports the link between obesity and OA. The obesity gene and its product leptin may have important implications for the onset and progression of OA.

However, leptin can be also produced by osteoblasts and chondrocytes cells and local production of this substance may be of great importance.Significant levels of leptin were observed in the cartilage and osteophytes of people with OA, whereas few chondrocytes produced leptin in the cartilage of healthy people (36). Leptin was found in synovial fluids of OA joints which was correlated with BMI (41, 42). Cytokines, biomechanical factors, and proteolytic enzymes lead to vaiable degrees of synovial inflamatory process which up-regulate metalloproteinases and blunt chondrocyte compensatory synthesis pathways required to restore the integrity of the degraded matrix (43).

A cascade of changes in joint structure start from subchondral bone expansion, bone marrow lesions, meniscal tears and extrusion, to cartilage defects,which ultimately may lead to cartilage loss and radiographic osteoarthritis at late stage. Considerable evidence indicates that the menisci, ligaments, periarticular muscles and the joint capsule are also involved in the OA process. Even infrapatellar fat pad from patients with knee-OA contains inflammatory cells which can partly lead to pain in the anterior area of the knee OA (44). Extravasation of the immune cells from infrapatellar fat pad inflammatory cells which can lead to vasodilation and extravasation of the immune cells that could in part be responsible for anterior pain in knee-OA (44).

Clinical features

Persist knee pain, limited morning stiffness, and reduced function are the three symptoms that are recommended for the diagnosis of knee OA by the EULAR (45). In addition cripitus, restriction of joint movement and bony enlargement are also very useful for diagnosis of knee OA.

Pain is the most common symptom in knee OA, a leading cause of chronic disability, and a major source of the disability attributable to OA. Pain severity ranging from barely perceptible to immobilizing. Pain, in knee OA typically exacerbates by activity and relieves by rest. In the presence of the above six symptoms and signs the probability of having radiographic knee OA increases to 99% (46).

In advanced cases synovities may appear and leads to pain at rest or night. Short duration of stiffness less than 30 minutes may be seen in OA patients in the morning or following periods of inactivity.

Tenderness to palpation of involved joints may be evident in physical examination. Joint effusions may be present, which typically exhibit a mild pleocytosis, normal viscosity, and modestly elevated protein .Crepitus during joint motion or walking is a common .Limitation of range of motion are all common signs of OA of the knee. In advanced cases (46) malalignment may be apparent (genu varus or genu valgus).

Imaging

Although the diagnosis of knee OA in the most cases can be made by the clinical findings and physical examination ,however identification of joint damages are necessary for both diagmostic confirmation as well as extent of joint involvement. Conventional plain radiographs is the first diagnostic procedure as usually requested to demonstrate the structure-pain relationship in knee OA. Radiographic examination has several limitations wheras MRI has the capability to visualize all the structures within the knee joint. There is a growing body of work using MRI to examine the correlation between structural findings and symptoms (47). Conventional radiography predominantly visualizes bone whereas MRI has the ability to directly visualize all the structures of a joint, including soft tissue and cartilage. subchondral bone marrow lesions (48).

Subchondral bone marrow abnormalities determined by MRI have recently been shown to be predictors of radiographic progression in patients with knee OA (49). Greater levels of structural changes at earlier stage can be revealed by MRI

Plain radiography

Identification of bone changes in early knee OA may not be possible due to low sensitivity of radiogragpy. However when articular changes have been observed by plain radiography further imaging studies are unnecessary. The major radiographic features of OA include: Joint space narrowing, subchondral sclerosis, osteophytes, subchondral cysts (table 2). Chondrocalcinosis may be seen in 4.4% of patients which may increase by aging (50)

Non-weight-bearing and weight-bearing radiographs of the knee in extension were found to be of limited value in assessing disease status, whereas all standing flexed knee positions reliably imaged joint space width and bone changes in the tibiofemoral joint. Skyline rather than lateral views of the patellofemoral joint were better at detecting joint changes in osteoarthritis (51) Non-weight-bearing and weight-bearing radiographs of the knee in extension were found to be of limited value in assessing disease status, whereas all standing flexed knee positions reliably imaged joint space width and bone changes in the tibiofemoral joint (52). The presence of osteophyte at the patellofemoral joint was more sensitive but less specific than at the tibiofemoral joint. Among men and women in the community, osteophyte is the radiographic feature that associates best with knee pain. Radiographic assessment of both regions of tibiofemoral and patellofemoral should be included in all studies.In patients with knee pain proportion of patients with osteophyte at patellofemoral joint is greater than tibiofemoral joint and can induce disability in the absence of tibiofemoral abnormality Joint space loss is not a feature of asymptomatic aging, and there is not a biological cut off for joint space width below which the likelihood of knee pain markedly increases (53).

MR imaging

MRI is not necessary for most patients with suggestive symptoms of OA and/or typical plain radiographic features. However, MRI of the knee has a diagnostic role in patients with joint pain and symptoms such as locking, popping, or instability that suggest meniscal or ligamentous damage. The presence of two MRI findings concomitantly correlates with painful OA of the knee. Several types of lesions may be expected to be observed in knee OA by MRI imaging. These include cartilage abnormalities, osteophytes, bone edema, subarticular cysts, bone attrition, meniscal tears, ligament abnormalities, synovial thickening, joint effusion, intra-articular loose bodies, and periarticular cysts (47-49) table 2.

Table 2- Radiographic and MRI findings in knee osteoarthritis

1- Radiographic findings
Osteophytes
Joint space narrowing
Subchondral sclerosis
Subchonderal cysts
2- MRI findings in knee osteoarthritis
Cartilage abnormalities,
Csteophytes,
Bone edema,
Subarticular cysts,
Bone attrition,
Meniscal tears,
Ligament abnormalities
Synovial thickening,
Joint effusion
Intra-articular loose bodies
Periarticular cysts

Laboratory findings

Although mild synovitis may be seen in patients with knee OA but markers of inflammation such as erythrocyte sedimentation rate (ESR) and C –reactive protein (CRP) levels are usually normal. Synovial fluid in knee OA is of non-inflammatory type. Serum and synovial fluid levels of CRP in OA are markedly lower than inflammatory arthritis. Synovial fluid anti-cyclic citrullinated peptide antibody is negative in both serum and synovial fluid of patients with knee OA. In suspected cases of knee OA synovial fluid level of anti-CCP can be used for differentiation of OA from RA (55). The rest of this Review Article will appear in the next issue.

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