Clinical Comorbidity Phenotype in Knee Osteoarthritis Is Associated With Higher Intensity Scores

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Abstract- Knee osteoarthritis (OA) is a common osteoarticular disease. Its prevalence increases with age, as well as the coexistence of other chronic diseases. Recent research has revealed an association between OA and cardiovascular diseases. However, the association between knee OA and comorbidities has not been fully studied. Therefore, the purpose of this study was to investigate the association between knee OA and comorbidities. In this cross-sectional study, patients with knee OA were enrolled. Sociodemographic data, as well as comorbidities, were collected. Grading of knee OA was performed using the Kellgren-Lawrence (KL) grading system. The functional impact of knee OA was assessed by KOOS-Physical Function Shortform (KOOS-PS). This study assessed 104 patients with knee OA (10 men and 94 women). The mean age was 65.83±11.08 years. Mean VAS pain was 6.56±1.72. Mean KOOS-PS was 15.58±6.73. Up to 81 patients (77.9%) had severe knee OA, according to the KL grading system. Comorbidity was noted in 92 cases (88%). The most frequent comorbidities were obesity (62.5%), hypertension (61.5%), and dyslipidemia (43.3%). Comorbidities in knee OA were associated with age (*P*=0.04), axial deviation in the sagittal plane (*P*=0.01), neuropathic pain component (*P*=0.02), and VAS pain (*P*=0.04). Our study also showed a significant correlation between comorbidities and structural grading of knee OA (*P*=0.04). However, comorbidities were not correlated with the KOOS-PS score (*P*=0.06). The accumulation of comorbidities is significantly associated with higher intensity scores in knee OA. Physicians should additionally pay close attention to the prevention and treatment of comorbidities in the routine management of OA.

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Introduction

Osteoarthritis (OA) is the most frequent form of arthritis that presents with joint pain and stiffness and reduces the patient's function and quality of life (1). Its natural history is still poorly understood. It is a heterogeneous group of arthritis sharing radiographic features and symptoms with a multifactorial etiology (2,3). OA of the knee is one of the most common sites of OA, with a prevalence of over 250 million people in the world (4). The prevalence of knee OA is expected to rise in the future due to the increasing prevalence of obesity and the growing aging populations (5). Risk factors for knee OA include age, obesity, menopause as well as genetic variations (6,7). However, recent research has suggested that other factors, such as neuroendocrine, cardiovascular, and metabolic factors, may play a role in the pathogenesis of knee OA (8). It has been reported that patients with OA have a number of cardiovascular risks (CVR) factors such as restricted physical activity (9), depressive symptoms (10), metabolic abnormalities such as diabetes (11), hypertension (12), and metabolic

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syndrome (SM) (13,14). Since OA shares several risk factors with cardiovascular diseases (CVDs), people with OA are more likely to develop comorbidities than the general population (15). Some studies linked OA to CVDs and comorbidities on the basis that OA is a metabolic disease as well as a mechanical disease (16,17). In fact, it has been reported that OA may be associated with excessive proinflammatory cytokine production with atherogenic effects. This inflammatory process contributes to vascular inflammation and atherosclerosis, resulting thus in the development of CVDs such as hypertension, myocardial infarction, heart failure, and cerebrovascular disease (18).

Researchers have studied the association between diabetes, obesity and cardiovascular risk with the development of OA. However, most studies only investigated the association between individual metabolic and cardiovascular conditions and OA (5,11,12,19-21). The association between knee OA and comorbidities has not been fully studied. Therefore, the aim of the present study was to investigate the association of comorbidities with the development of knee OA. In addition, the study attempted to evaluate the impact of these comorbidities on the structural severity of knee OA and their functional impact.

Materials and Methods

Study design and patients

Patients underwent their regular consultation in the outpatient clinic of our rheumatology department, those diagnosed with knee OA according to the criteria of the European League Against Rheumatism (EULAR) (22) were included in our cross-sectional study. The inclusion criteria were patients over the age of 18 with knee OA. Exclusion criteria were: history of knee trauma or surgery, knee arthroplasty, pregnancy, chronic inflammatory disease, fibromyalgia, acute/chronic central nervous system disease, rheumatic or metabolic bone disease, active inflammation, patients under treatment due to malignancy, known diabetic neuropathy and cognitive or psychiatric disorders. The study was approved by the Hospital local medical Ethic Committee and all patients gave their written informed consent for the study.

Investigated variables

Sociodemographic data was collected. Data on health-related risk factors (smoking status, physical activity, and alcohol consumption) were collected. Physical activity and alcohol consumption were self-reported as categorical variables 'physical activity ≥30 minutes by day' (yes/no). The following data on comorbidities were documented for each patient: diabetes, hypertension, hypercholesterolemia, hypertriglyceridemia, obesity, CVDs (coronary heart disease, stroke, and obliterating arteriopathy of the lower limbs), gout, depression, Peripheral vessel disease, respiratory pathology, and gastrointestinal comorbidities. Patients were divided into two groups: group 1 (patients without comorbidities) and group 2 (patients with comorbidities).

Axial deviation in the frontal (varum/valgum) and sagittal (flessum/recurvatum) planes were noted. We also noted the site of knee OA (femorotibial/femoro-patellar). Mean disease duration and other OA localizations (spine, hand, hip) were recorded.

Knee OA was assessed using plain anterior-posterior and lateral radiographs of the knees, and the grading of knee OA was performed using the Kellgren-Lawrence (KL) grading system (23). Patients with KL grade 3 or greater were defined as having severe knee OA. The pain was assessed using the Visual Analogue Scale (VAS). The neuropathic pain component was assessed using the Arabic version of the Neuropathic Pain Diagnostic Questionnaire (DN4) (24). A score of 4 or more indicates the presence of neuropathic pain. The functional impact of knee OA was assessed by KOOS-Physical Function Shortform (KOOS-PS) (25).

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences software (SPSS) version 11.5. Data were expressed as a range, mean and standard deviation. For the analytical study, we divided patients into two groups: group 1 (without comorbidities) and group 2 (with comorbidities), and we compared them. The correlation between two quantitative variables was performed using the Pearson test and between two qualitative variables using the Chi2 test. The Student's test was used to study the association between a qualitative and a quantitative variable. In the case of small numbers, the Mann and Whitney test was used. The significance threshold in all the statistical tests was set at 0.05.

Results

There were 104 patients in our study compound of 10 men and 94 women with an average age of 65.83±11.08 years. The mean disease duration was 3.5 years (3months-20 years). Mean body mass index (BMI)

was 31.64±6.27 kg/m^2: 82 cases (78.8%) were overweight (>25 kg/m^2). Eighty-seven patients were physically active (82.7%). Four patients (3.9%) were smokers. Sociodemographic characteristics of patients are presented in (Table 1).

Table 1. Sociodemographic characteristics:

Characteristics		
Age in years (mean±SD)		65.3±11 (37-95)
Female, n (%)		94 (90.4)
Duration of knee OA (mean±SD)		3.4±3 (2 months- 20years)
Socio-economic class: n, (%)	**High**	67(64.4)
	Low	37(35.6)
Number of children (mean±SD)		4.03 ±2.15 (0-10)
Marital status, n (%)	**Married**	57 (54.8)
	Single	1 (1)
	Divorced	10 (9.6)
	Widowed	36 (34.6)
Education status: n, (%)	**Illiterate**	64(61.5)
	Primary school	25(24)
	High school	11(10.6)
	University	4(3.8)
BMI, weight in kg/height in m2 (mean±SD)		31.6±6.2 (19.9-52.3)
Normal, n (%)		20(19.2)
Overweight, n (%)		17(16.3)
Obesity, n (%)		65(62.5)
Health-related risk factors, n (%)	**Physical activity**	87 (82.7)
	Smoking	4 (3.9)

BMI: body mass index; n: number of cases; OA: osteoarthritis; SD: standard deviation;

Comorbidity was noted in 92 cases (88%): 25 patients had one comorbidity (24%), 23 patients had two comorbidities (22.1%), and 44 patients (42%) had at least three comorbidities. The most frequent comorbidities were obesity (65 patients; 62.5%), hypertension (64 patients; 61.5%) and dyslipidemia (45 patients; 43.3%). (Table 2) summarizes the frequency of the different comorbidities in our study.

Table 2. Frequency of the different comorbidities

Comorbidity	Frequency	Percentage %
Types 2 Diabetes	38	36.5
Hypertension	64	61.5
Gout	1	0.9
Hypercholesterolemia	30	28.8
Hypertriglyceridemia	36	34.6
Coronary heart disease	2	1.9
Stroke	1	0.9
Peripheral vessel disease	43	41.3
Respiratory pathology	8	7.6
Gastrointestinal comorbidities	3	2.8
Depression	2	1.9

Axial deviation in the frontal plane was noted in 60 cases (57.7%), varus (26.9%), and valgum (30.8%). Axial deviation in the sagittal plane was noted in 6 cases (5.7%); flessum (4.7%) and recurvatum (1%). Up to 83.7% of cases had femorotibial OA, while 1.9% of cases had femoropatellar OA. Fifteen patients (14.4%) had both femorotibial and femoropatellar OA. Knee OA in our study was bilateral in 95.2% of cases. According to the KL grading system, 81 patients (77.9%) had severe knee OA.

Seventy-one patients (68.3%) had neuropathic pain with a mean DN4 of 4.81±2.45. The mean VAS pain of 6.56±1.72. Mean KOOS-PS was 15.58±6.73.

Correlation between comorbidities and knee OA

Comorbidity was all the more common as age increased in knee OA (*P*=0.04). However, it was not correlated with the increase of BMI (*P*=0.3). There was a significant correlation between comorbidities and DN4 score (*P*=0.02) as well as the pain intensity evaluated by VAS pain (*P*=0.04). (Table 3) summarizes the association between comorbidities studied and clinical findings in knee OA patients.

Table 3. Association between the different comorbidities studied and kneed OA characteristics

Variable		Group 1	Group 2	*P*
Female gender, n		11	83	0.83
BMI>25 kg/m^2		9	73	0.61
Neuropathic pain		11	60	0.64
Duration of pain (years)		4.3	3.3	0.42
	Spine	6	18	
Other sites of OA %	**Hips**	1	2	0,3
	Hands	0	2	
Deviation in the	**Varum**	2	26	0.59
frontal plane, n	**Valgum**	5	27	
Deviation in the	**Flessum**	1	0	0.01
sagittal plane, n	**Recurvatum**	0	5	
	Femorotibial	10	77	
Knee OA site, n	**Femoropatellar**	1	1	0.19
	Both	1	14	
Bilateral knee OA, n		11	88	0.54

BMI: Body Mass Index; n: number; OA: osteoarthritis

Impact of comorbidities on the severity of knee OA and functional disability

There is a significant difference between the two groups in the structural severity of knee OA evaluated by the KL grading system with higher grades in the comorbidity group (*P*=0.04). However, comorbidity was not correlated with functional disability assessed with KOOS-PS score (*P*=0.06).

Discussion

In this study, we demonstrated that comorbidities were significantly correlated with knee OA. Our study also showed a high frequency of comorbidities among knee OA patients (88%). Knee OA phenotypes with comorbidities were associated with higher intensity scores and severe radiographic knee OA. Comorbidities were correlated with age (*P*=0.04), axial deviation in the sagittal plane (*P*=0.01), neuropathic pain component (0.02), and VAS pain (*P*=0.04). There was also a significant correlation between comorbidities, and the structural progression of knee OA assessed using the KL grading system (*P*=0.04). However, comorbidities did not seem to have an impact on functional disability assessed with KOOS-PS score (*P*=0.06).

This study has strengths and weaknesses. The study of this association is interesting given the high prevalence of these conditions in the general population. However, this association remains largely underestimated in the evaluation of patients in current practice. Our patients were recruited from outpatient examinations. Therefore, our sample is representative of patients consulting in general hospitals in our country. However, this study has some limitations: Firstly, comorbidity was assessed on the basis of self-reported diseases and not on clinically ascertained diagnoses. The reliability of the self-reported diagnoses, which was confirmed by the medications used by the patients, can nevertheless be considered high. Secondly, analyses did not consider whether the development of comorbidities may have been driven by other conditions. These findings of the high prevalence of comorbidities and CVDs among OA patients are concerning. In fact, comorbidities may lead to premature mortality, while OA, which remains a burdensome chronic musculoskeletal condition, often results in a functional disability.

Recently, there has been a growing interest in comorbidities in patients with OA. The recent OARSI guidelines for the management of knee OA provide guidance for four subgroups representative of clinically relevant comorbidity heuristics that are common in

people with OA and confound its treatment (gastrointestinal comorbidities, CVDs, frailty, and widespread pain and/or depression); initial assessment should diagnose comorbidities (26). The longer life expectancy in the general population was, the higher prevalence of degenerative diseases and chronic conditions was, increasing thus the impact on the quality of life. In fact, an important proportion of OA patients present with CVDs and co-existing chronic medical conditions. Hall *et al.*, reported in a meta-analysis the presence of 40% of CVDs among OA patients (5).

Calders *et al*., in a systematic review and meta-analysis, reported that the presence of comorbidities was a common situation in patients with knee and hip OA (hypertension and cardiac disease 45%, diabetes 24%, depression 14%) (27). In a study conducted by Kovari, the prevalence of comorbidities in patients with OA was twice that of the general population (28). In another study, conducted by Bin Kim *et al*., on patients with knee OA, the prevalence of comorbidities varied from 6.1% to 65.5%, with hypertension being on the top of the list followed by osteoporosis and diabetes (29).

Some epidemiological studies have evaluated the impact of comorbidities on OA. They suggested that comorbidities exacerbates the severity of OA and affects negatively the deterioration of symptoms (30). In a meta-analysis evaluating the association between comorbidities and severity of pain and physical dysfunction in patients with knee and/or hip OA, Calders *et al*., found that greater comorbidity burden contributes to worse pain, more severe symptoms and deteriorated physical function (27). Our study demonstrated that the association between knee OA and comorbidities increases with age (P=0.04). Our findings were consistent with those of the literature (31). It has been reported that cardiovascular comorbidity, given the influence on aerobic activity, has an impact on physical dysfunction as well as on the severity of joint pain during OA (27,32). Morever, MS has been reported to be associated with OA (13,14,16,18). Some studies also showed an association between MS components and the development of knee OA (14,33). In order to determine the relationship between MS components and severity of knee OA (evaluated by KL grading system), Lee *et al*., analyzed the association between the number of MS components and development of knee OA or severe knee OA. They found that the risk and the severity of knee OA tended to increase with the number of MS components (14). A study conducted by Yoshimura et al showed similar results (34). Our findings were consistent with those of the literature since two thirds of our patients had a MS (hypertension, diabetes, dyslipidemia and/or obesity). Further studies are needed to determine the exact mechanism. In the mentioned studies, the effect size of each component was not considered. This wasn't the case of our study, in which we analyzed the effect of different metabolic factors on knee OA.

Several studies reported that 10 to 14% of OA patients suffered from diabetes (12,35,36). Eitner *et al.*, reported an association between diabetes and severity of pain in OA and suggested that synovitis may be an important mechanism to enhance pain sensations in diabetic knee OA patients (37). Neuropathic pain also contributes to worse pain symptoms (38,39). However, a causal pathway between diabetes and functional disability in OA patients remains unclear (38). In several previous studies, diabetes has been reported to be positively associated with OA and joint replacement (37). Eymard *et al*., studied the impact of diabetes on radiographic progression on knee OA based on an annual accurate joint space narrowing (36). They highlighted the potential effect of diabetes on disease progression. In fact, in response to prolonged hyperglycemia, knee OA chondrocytes increase the production of reactive oxygen species, which induces degradation of cartilage matrix proteins (40). Cartilage was shown to be softer in diabetes which leads to more severe damage (41).

High blood pressure was associated with OA in previous studies (34,42). However, cross-sectional analyses of this association may be challenging since nonsteroidal anti-inflammatory drugs, generally used for treating OA pain, can raise blood pressure (13). It has been reported that proinflammatory cytokine (interleukin-6) plays a role in the association between knee OA and hypertension (43). Although OA is not considered an inflammatory disease, it is usually associated with a low-chronic inflammation grade that could have a role in the development of CVDs and especially hypertension (37).

Howard *et al.*, demonstrated that patients with gout had a higher prevalence of knee OA than the general population (44). They also found that gout was associated with more severe structural progression with higher KL grades and more bilateral knee involvement (44). However, another study suggested that patients with gout were more likely to have widespread OA of a small joint of the hand and foot (45).

A prevalence of high cholesterol levels of 32% was estimated in OA patients, while it is estimated that it reaches 23% in the general population (19). In the

literature, high serum cholesterol levels were associated with knee OA (46,47).

Sedentary and obesity are well-known risk factors for weight-bearing joints OA (20,48). Abdominal obesity may increase the risk of the development of knee OA by the metabolic effects of adipose tissue and mechanical stress of the excess of body weight (14,48). In our study, being overweight was not associated with knee OA (P=0.6). This result seems surprising since weight status is associated with the severity of symptoms in knee OA. Reports had linked overweight to radiographic progression in knee OA (3,49,50). Other reports had linked obesity to axial deviation of the knees and radiographic progression (51,52). Larsen *et al*., implied that KOOS score varies significantly with obesity (53).

High prevalence of CVR factors, vascular disorders and CVDs in patients with OA have been reported in the literature (5,24,54)). In fact, osteoarthritic changes were found to be related to aortic calcification (55).The pathological link between OA and CVDs (myocardial infarction, cerebrovascular disease and arteriopathy of the lower limbs) has been supported by the fact that a transmembrane protein existing in human carotid arterial plaque, was also found in osteoarthritic synovial lining (56). Morever, the association between knee OA and CVDs is higher compared to other OA sites. This can be explained by the fact that the parameniscal capillary plexus in the synovial tissue of the marginal meniscus, formed by the branches of the popliteal artery, supplies blood to 10-30% of the medial meniscus and 10-25% of the lateral meniscus (57). CVDs prevalence in OA patients may have an impact on management strategy of OA since patients with such comorbidities are less suitable for surgical procedures.

This study did not show a significant association between knee OA and depression. This may be explained by the low prevalence of depression in our study population (1.9%). Our results were consistent with those of Calders *et al.*, who found no significant association between depression and severity of OA (27). However, depression and persistent severe OA knee pain generally occur together with reciprocal contribution to higher risk of physical decline and more severe disability (10,58).

Our findings demonstrated that comorbidities increased the structural severity of knee OA (P=0.04). To our knowledge, there are no other studies in the literature that evaluated the influence of comorbidities on the structural progression of knee OA. Some studies evaluated the impact of comorbidities individually on the structural progression of OA (36,41,42). Our study showed that comorbidity was not correlated with functional disability assessed with KOOS-PS score (P=0.06). These results are consistent with those of Zambon *et al*., who demonstrated that comorbidity is neither a confounder nor an effect modifier in the association between OA and physical function and that pain mediates the effect of OA on physical function tests (59). However, Kadam *et al*., demonstrated that comorbidities have a negative impact on physical function in patients with OA (54).

In summary, our study suggested that comorbidity was frequent and had an impact on knee OA. Knee OA phenotypes with comorbidities were associated with higher intensity scores and severe radiographic knee OA. Improving the physical health of OA patients also requires the management of associated comorbidities. However, questions remain unanswered about the most effective care strategy that can manage to reduce and prevent comorbidities in OA patients, especially in a context with limited resources.

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