Original Article

Osteoarthritis of the knee joint and its association with metabolic syndrome: A case control study

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Abstract

Background: Osteoarthritis of the knee joint (OAK) represents a leading cause of pain, functional limitation, and diminished quality of life, particularly among older adults. The association between metabolic syndrome (MetS) and OAK is of growing interest due to the potential impact of MetS components on joint health. While evidence suggests that MetS and its components may influence the development of osteoarthritis (OA), the specific relationship between MetS and the likelihood of progressing to a stage of OAK that requires Total knee replacement (TKA) remains underexplored. **Aim:** This study aimed to evaluate the association between osteoarthritis of the knee joint (OAK) and metabolic syndrome (MetS) and to know whether the presence of MetS (or its components) increases the risk of OAK requiring Total knee replacement (TKA). **Methodology:** It is a cross-sectional study that includes patients (males and females) above 50. Data collection was done including demographic details, medical history, physical examinations, and laboratory tests. OAK (≥grade 2 Kellgren-Lawrence) and severe OAK (≥grade 3 Kellgren-Lawrence) were evaluated based on radiological findings. **Statistical Analysis:** Mean, standard deviation, frequencies, and percentages were calculated for baseline characteristics. To analyze the association between qualitative factors and MetS, the Chi-Square test was used. For comparing quantitative factors, the unpaired *t*-test was employed. A *P* value of less than 0.05 was considered statistically significant. **Results:** The study involved 107 primary osteoarthritis patients categorized into cases ($N = 57$), requiring TKA, and controls ($N = 50$), not requiring TKA. MetS was significantly more prevalent among cases than controls, with 68.4% of cases and 36% of controls testing positive for MetS ($P = 0.001$). The odds of having MetS were 3.9 times higher in the cases compared to the controls. **Conclusion:** The results of our research could shed light on how MetS affects the onset and course of OAK, guiding primary care and prevention measures. It might also emphasize how critical it is to treat MetS symptoms to lessen the severity of OAK. Understanding whether MetS or its components are linked to an increased risk of TKA could provide crucial insights into preventive and therapeutic strategies for managing severe OAK.

Keywords: Kellgren-Lawrence (KL) grading, knee joint, metabolic syndrome, osteoarthritis, total knee replacement

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Introduction

Globally, osteoarthritis (OA) is the most common chronic joint disease and a leading source of pain and impairment.[1] OA mostly affects the hip, knee, and hand joints, but can also affect other joints. An important public health problem, OA is illustrated by joint stiffness, significant pain, and functional limitations in day-to-day activities.[2] With a prevalence of 22% to 39%, OA is the most frequent joint disease and is the second most common rheumatologic problem in India.[3,4] Osteoarthritis of the knee joint (OAK) accounts for almost 80% of the global OA burden.[5] Though it does not cause mortality, it lowers the quality of life by causing disability. Mechanical stress is thought to be the primary cause of OAK, which is more common in older people and those who are obese. Sex is another risk factor; women have a higher risk than males. The modern world has seen an upsurge in sedentary behaviour and fat intake,[6] both of which directly affect the health parameters like obesity, dyslipidaemia, hypercholesterolemia, hypertension, and diabetes, all these are included under a clinical disease currently referred to as insulin resistance syndrome, or "Metabolic syndrome," (MetS).[7] As per the National Cholesterol Education Program Adult Treatment Panel III (NCEPATP III) guideline presence of any three out of these five parameters is defined as MetS.[8]

The potential link between MetS and OAK has gained attention due to the possibility that the systemic inflammation related to insulin resistance and dyslipidaemia may contribute to the inflammatory milieu in the joint, accelerating cartilage deterioration.[9] Furthermore, current studies have shown that these metabolic changes may potentially play a role in the rise in the incidence and development of OA.[10,11] Possible pathogenic mechanisms which is common between OA and metabolic diseases are low-grade inflammation related to the tissue and oxidative stress.[12] Some studies suggest that these mechanisms might damage cartilage, bone, and synovial tissue, regardless of excess weight.[13,14] Recent research suggests that genetic and neuroendocrine variables may also possibly contribute to the pathophysiology of OAK.[15] Primary care providers are crucial in early detection and intervention. Screening for MetS components (blood pressure, glucose levels, lipid profile, etc.) allows for timely intervention, reducing the risk of cardiovascular disease and diabetes. OA and MetS are both common in primary care settings, particularly among older adults. This paper highlights the association between these two conditions, helping primary care providers recognize that patients with metabolic syndrome may be at increased risk for developing OAK, and vice versa. This understanding can prompt early screening and intervention for patients who may be at risk for both conditions.

Despite these insights, there remains a significant knowledge gap regarding whether MetS or its specific components increase the risk of developing advanced OAK that necessitates TKA. Hence, with this study, our primary objective is to evaluate the association between grading of OAK and MetS and the secondary objective is to know whether the presence of MetS (or its components) increases the risk of OAK requiring Total Knee Replacement (TKA).

Materials and Methods

It is a Case Control study, conducted at two government institutions, All India Institute of Medical Sciences (AIIMS) Bibinagar (Hyderabad) as the primary site and the Nizam's Institute of Medical Sciences (NIMS) Punjagutta (Hyderabad). The Institutional intra-mural funds of AIIMS, Bibinagar supported this study. The research was conducted adhering to the ethical guidelines specified in the 1964 Helsinki Declaration and its recent amendments and got approval by the Institutional Review Committee (IRC) and Institutional Ethics Committee (IEC) of both the institutions [AIIMS/BBN/IEC/DEC/2021/128]. Also, informed and written consent was obtained from all the participants in the study. Measures were implemented to guarantee the confidentiality and security of personal data.

Study population

At an expected proportion of exposed controls of 0.59, assumed odds ratio of 4, a confidence level of 0.95, and desired Power of 0.8 the sample size was calculated to be 43 in each group. The study included a total of 107 patients, 57 patients as cases (N = 57) with primary OA posted for TKA for various grades of OA and 50 patients' controls (N = 50) with clinical features of primary OA reported to the Orthopedics OPD with no indication for TKA. Exclusion criteria included patients with secondary arthritis, neutral, or valgus alignment observed on hip-to-ankle anteroposterior (AP) standing radiographs, traumatic, degenerative diseases of the nervous system, patients who were on medications for metabolic disorders, or who were unfit for surgery from an anaesthesia standpoint and cases with secondary causes of OA, other arthropathies, metabolic bone disease, and neoplasms.

History and clinical assessment

Patients 50 years or above who reported to the Orthopedics OPD with complaints of pain in one or both knee joints were assessed clinically for primary OA by the investigator from the same department. First, a detailed history was taken in the form of a questionnaire on socio-demographic information, anthropometric data, and health conditions. A thorough physical examination of the affected joints was done by the clinicians.

Measurements

Weight in kilograms (kg) and height in centimetres (cm) was measured for each subject to calculate Body Mass Index (BMI) and abdominal (waist) circumference was also recorded (in cm) for each patient.

After calibrating the digital weighing scale, patients were asked to remove shoes; light clothing was preferred. Patients were asked

to stand straight with feet slightly apart, evenly distribute their weight on both feet and gently step on the digital scale. Weight was then recorded to the nearest 0.1 kg.

Height was measured using a measuring tape and a flat ruler. The patient was asked to stand with his/her back against the wall, heels together, and arms by their sides, with eyes looking straight ahead, aligned with the Frankfort horizontal plane. The ruler was then placed on top of their head, ensuring it was parallel to the floor. A small mark on the wall was then made where the bottom edge of the scale touched. Using the measuring tape, we measured the distance from the floor to the mark on the wall and hence recorded the height of the participants. Body Mass Index (BMI) was then calculated, which was considered weight divided by the square of height (kg/m^2).

Waist circumference (WC) was recorded in cm and was considered at the midpoint of the inferior border of the lowest ribs to the anterior superior iliac spine, after the participant had a normal expiration, using an inelastic measuring tape.

Using a sphygmomanometer, blood pressure (BP) was measured. Before taking the blood pressure readings, participants were allowed ten minutes to relax. Then, three separate blood pressure measures from the right arm were recorded at five-minute intervals. The mean of the three values was computed to get the final blood pressure.

Blood investigations

For assessing the factors of MetS, blood specimens were drawn by trained physicians and investigations included triglycerides (TGs), cholesterol, low-density lipoprotein cholesterol (LDLc), high-density lipoprotein cholesterol (HDLc), and fasting blood sugar (FBS), which were all obtained from venous blood samples.

Radiological assessment

Weight-bearing anteroposterior (AP)—and lateral knee radiographs were recorded for both knees for all the patients for the assessment of radiological changes. As per the standard protocol, knee radiographs were taken, with the film cantered 1 cm below the patellar apex for both the AP and lateral views. Using Kellgren Lawrence (KL) staging of the radiographs, two orthopedic surgeons, blinded to the subjects' clinical symptoms, assessed the radiographs independently. Any inconsistencies in viewpoints were resolved through a discussion.[16] Given its validity and reliability, this method was accepted by the World Health Organisation (WHO) and was widely used for studies on OA of knee joints.[17] Radiographs were rated on a scale of 0 to 4, indicating increasing OA severity. A score of 0 meant no OA, while a grade of 4 indicated severe OA [Table 1]. If a participant had at least one knee joint graded K-L 2 or higher, they were diagnosed with radiographic knee OA.

Assessment for Metabolic Syndrome (MetS)

Clinical examination and Investigations for diagnosis of MetS as per the Modified National Cholesterol Education Program (NCEP) criteria III was done.[8] Presence of at least 3 of the 5 factors (or use of medication): abdominal obesity (waist circumference [WC] >90 cm and 80 cm for men and women respectively) (BMI > 30 kg/m^2), hypertriglyceridemia (>150 mg/dL), low levels of HDL cholesterol (<40 mg/dl and 50 mg/dl for men and women respectively), systemic arterial hypertension (>130/85 mmHg), and blood glucose fasting (>110 mg/dL) was considered for presence of MetS[18] The association between the radiological (KL) grading of OA and the presence of MetS was assessed.

Table 1: Kellgren Lawrence (KL) grading of osteoarthritis in the subjects of our study[16]

Grading	Radiological findings	Controls	Cases
0	No radiological findings of OA	0	0
1	Doubtful narrowing of the joint space & possible osteophytic lipping	3	0
2	Definite osteophytes & possible narrowing of joint space	17	0
3	Moderate multiple osteophytes, definite narrowing of joint space, small pseudocystic areas with sclerotic walls and possible deformity of bone contour	18	14
4	Large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone contour	12	43
Total number of subjects		50	57

Statistical analysis

Qualitative parameters such as Gender and Metabolic Syndrome were presented using frequencies and percentages. Quantitative parameters including Age, Height, Weight, BMI, Waist Circumference, BP, Fasting Blood Sugar, TGs, and HDL were reported as means with standard deviations.

To analyze the association between qualitative factors and MetS, we utilized the Chi-Square test. For comparing quantitative factors, the unpaired *t*-test was employed. The likelihood of developing Metabolic Syndrome in the cases group compared to the control group, as explained by the odds ratio. A *P* value of less than 0.05 was considered statistically significant. Data analysis was conducted using SPSS version 28.0.

Results

Demographics and metabolic syndrome prevalence

The study involved 107 primary osteoarthritis patients categorized into cases (N = 57), requiring TKA, and controls (N = 50), not requiring TKA. The gender distribution was similar across the groups with 54.2% females in the cases and 50% in the controls, showing no statistical significance (P = 0.413) [Table 2]. MetS was significantly more prevalent among cases than controls, with 68.4% of cases and 36% of controls testing positive

for MetS (P = 0.001) [Figure 1]. The odds of having MetS were 3.9 times higher in the cases compared to the controls [Table 3]. The mean age of patients with MetS was 58.9 years. Fifty-six percent of female patients with OA had MetS and only 44% of male patients were positive for MetS [Table 4]. This shows that females with MetS have more chances of developing OA of the knee joint.

Radiological findings and MetS association

Radiological findings based on KL grading showed a stark contrast in the severity of OA between the groups. Most notably, cases had significantly higher severe grades (Grade 4) of OA (43 out of 57 cases) compared to controls (12 out of 50 controls), indicating advanced joint damage [Table 1].

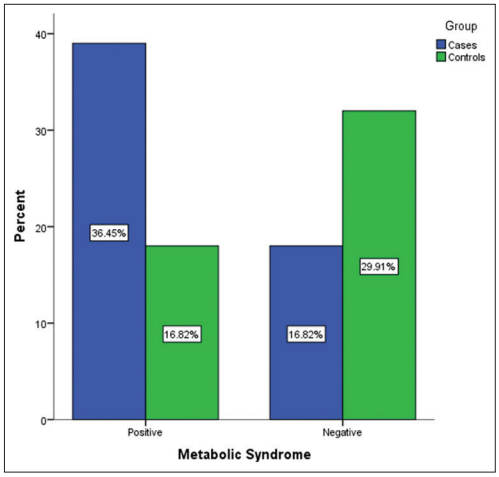

Figure 1: Percentage of patients with (positive) or without (negative) Metabolic syndrome

Table 2: Gender distribution of the patients with primary osteoarthritis as cases (*n*=57) and controls (*n*=50), showing no statistical significance (*P*=0.413)

	Group		Total	*P*
	Controls	Cases		
Gender				
Male	25 (50%)	24 (42%)	49 (45.8%)	0.413
Female	25 (50%)	33 (58%)	58 (54.2%)	
Total	50	57	107	

Table 3: Percentage of patients with (positive) or without (negative) Metabolic Syndrome (MetS). Odds Ratio: 3.9 (*P*=0.001). The odds of having Metabolic Syndrome are 3.9 times higher among those who are in cases

Parameter	Study groups		Total	*P*
	Controls (*n*=50)	Cases (*n*=57)		
MetS				
Positive	18 (36%)	39 (68.4%)	57 (53.3%)	0.001
Negative	32 (64%)	18 (31.6%)	50 (46.7%)	
Total	50	57	107	

Correlation of metabolic syndrome with KL grading of knee osteoarthritis

A detailed analysis revealed a strong correlation between MetS and higher grades of OA with KL grading. Among those with MetS, 34 (59.6%) were at the highest KL grade (Grade 4) compared to 21 (42%) in the non-MetS group. This association suggests that MetS may influence the progression of joint damage in OA patients (P = 0.029) [Table 5].

Independent risk factors and metabolic parameters

Body Mass Index (BMI) and waist circumference (WC) showed significant differences, particularly in cases. Cases had an average BMI of 29.041 kg/m^2 and a WC of 91.32 cm, significantly higher than controls, who had a BMI of 24.908 kg/m^2 and a WC of 82.90 cm (P = 0.021 for BMI and P = 0.001 for WC, respectively) [Table 6].

Blood pressure, fasting blood sugar, and lipid profiles (HDL and TGs) did not show significant differences between cases and controls, suggesting that while these factors contribute to MetS, they do not independently differentiate the severity of OA in this study cohort. Table 6 shows the group statistics of the components of MetS in the cases and controls of our study.

Discussion

The gender distribution was similar across the groups with 54.2% females in the cases and 50% in the controls, showing no statistical significance (P = 0.413) [Table 3]. In contrast, several studies have found that OAK is more common in women than in men.[19]

MetS was significantly more prevalent among cases than controls in our study. Our study found a significant association between

Table 4: Mean age and gender distribution of the patients with (positive) or without (negative) Metabolic Syndrome (MetS)

	Age (Mean)	Gender		
		Male	Female	Total
MetS				
Positive	58.93	25 (44%)	32 (56%)	57
Negative	56.88	24 (48%)	26 (52%)	50

Table 5: Strong correlation between participants with Metabolic Syndrome and higher grades of Osteoarthritis with Kellgren Lawrence (KL) grading (*P*=0.028)

	KL Grading				Total	*P*
	1	2	3	4		
Metabolic syndrome						
Positive	0	5 (8.7%)	18 (31.6%)	34 (59.6%)	57	0.028
Negative	3 (6%)	12 (24%)	14 (28%)	21 (42%)	50	
Total	3	17	32	55	107	

Table 6: Demographics and Group statistics including components of the Metabolic syndrome in the cases and controls of our study

Group	*n*	Mean	Std. Deviation	Std. Error Mean
Weight (Kg)				
Controls	50	65.082	9.3051	1.3159
Cases	57	69.491	12.6845	1.6801
Height (cm)				
Controls	50	165.58	7.426	1.050
Cases	57	159.35	9.039	1.197
BMI (Kg/m^2)				
Controls	50	23.726	2.9268	0.4139
Cases	57	27.514	5.4272	0.7189
Waist circumference (cm)				
Controls	50	82.90	13.609	1.925
Cases	57	91.32	12.624	1.672
Systolic BP (mmHg)				
Controls	50	128.58	16.199	2.291
Cases	57	127.98	18.403	2.438
Diastolic BP (mmHg)				
Controls	50	81.60	10.711	1.515
Cases	57	83.33	9.602	1.272
Blood sugar (Fasting) (mg/dl)				
Controls	50	115.14	57.558	8.140
Cases	57	106.09	25.918	3.433
TGs (mg/dl)				
Controls	50	163.956	81.4566	11.5197
Cases	57	164.649	61.6052	8.1598
HDL Cholesterol (mg/dl)				
Controls	50	56.256	14.4935	2.0497

BP: Blood Pressure, TGs: Triglycerides, HDL: High Density Lipoprotein, Weight (in Kilogram), height, Body Mass Index (BMI in Kg/m^2), and waist circumference (in centimetres)

MetS and the severity of OAK as indicated by the need for TKA and higher Kellgren-Lawrence (KL) grades.[20] This aligns with the hypothesis that systemic metabolic factors contribute to the pathophysiology of OA. Notably, patients with MetS were found to have more severe joint damage, which likely contributed to the higher incidence of TKA in this group. In their meta-analysis, Liu SY *et al*.[21] found that there were bidirectional relationships between MetS and OA in cross-sectional research and that there was a higher prevalence of OA in prospective cohort studies when baseline MetS was present.

Previous research has suggested that components of MetS such as obesity, dyslipidaemia, and insulin resistance may exacerbate the inflammatory milieu within the joint, thereby accelerating cartilage degradation. In 2007, Schett *et al*.,[22] conducted the first significant investigation into this connection of OA and MS. The findings revealed two-fold increases in knee or hip arthroplasty rates due to OA in individuals with type 2 diabetes mellitus (DM), a relationship between the duration of diabetes and the risk of arthroplasty, and increased levels of pain and synovial inflammation in diabetics. These findings supported the theory that metabolic components play a role in the pathophysiology of OA. Dahaghin *et al*.,[23] also discovered that diabetes patients had a twofold greater rate of hand OA than non-diabetic patients, demonstrating that the pathophysiology of OA is unaffected by weight and loading.

Studies by Puenpatom and Victor[24] and Stannus *et al*.,[25] have found associations between MetS components and increased OA prevalence and progression. Our findings extend this by demonstrating not only an increased prevalence of OA but also increased severity with higher grades on the KL scale in patients with MetS. After controlling for confounding variables such as age and sociodemographic characteristics related to exercise, alcohol consumption, and smoking, a study utilizing nationwide data found no correlation between MetS and the onset of OAK.[18]

Body Mass Index (BMI) and waist circumference (WC) showed significant differences, particularly in cases in the present study. A substantial correlation was discovered between OA risk and WC by Maddah *et al*.[26] who assessed the relationship between OA and MetS, with an increase in the severity of symptoms observed by some researchers.[18,27] However, this link has not remained significant in some studies after controlling for confounding factors such as weight and BMI.[27] The disparities in the results may be due to sample variables, such as ethnicity and age, as well as the lack of uniformity of diagnostic criteria for OA and MetS.

In contrast to findings by Lee BJ *et al*.,[19] which indicate that patients with hypertension and abdominal obesity have a significant risk of OAK, while blood pressure, fasting blood sugar, and lipid profiles (TGs and HDLc) did not significantly differ between cases and controls in the current study. In a study, hypertension was linked to a higher incidence of bilateral radiographic knee OA, regardless of BMI, but not to unilateral OA.[28,29] Zhang *et al*.[30] found that the proinflammatory cytokine interleukin-6 or a combination of genes are involved in the connection between knee OA and hypertension. A study found hypertension to be significantly associated with a risk of TKR among participants aged under 50 years, but there was no significant association in older age groups.[31]

Inflammation is a well-known pathological component of both MetS and OA. The pro-inflammatory state induced by MetS, characterized by elevated levels of pro-inflammatory cytokines, may contribute to the progressive nature of OA and may thus be a crucial link in the accelerated progression of OA observed in these patients, leading to increased severity and a higher likelihood of requiring surgical intervention. This is supported by studies such as those by Yusuf *et al*.,[32] and Berenbaum *et al*.,[33] which link systemic inflammatory markers with OA progression. MetS should be given further consideration while diagnosing and treating OA. Interfering with modern technology and lifestyle choices is one practical strategy that could help avoid and mitigate the effects of OA.[21] Our findings suggest that managing MetS may not only address systemic health but could potentially slow the progression of OA.

Strengths and limitations

Our study, while insightful, is not without limitations. The case-control design limits our ability to conclude the causality of MetS in the progression of OA. Additionally, our patient population, derived from a single clinical setting, may not be generalizable to all OA populations. Family physicians frequently manage comorbid conditions in their patients. Since OA and MetS often co-occur and share modifiable risk factors (such as obesity and inflammation), our study is relevant for readers looking to provide holistic, coordinated care.

Future directions

Given the significant impact of MetS on OA severity, future research should focus on longitudinal studies to assess whether early intervention in MetS can alter the progression of OA. Additionally, interventional studies targeting specific components of MetS, such as hyperglycaemia and hyperlipidaemia, and their direct effects on joint health would be valuable. Research into the basic mechanisms that link MetS and OAK might assist in gaining insight into how metabolic imbalances lead to joint degeneration. Investigating biomarkers of inflammation and cartilage degradation in the context of MetS may offer new avenues for therapeutic strategies.

Conclusion

Our study highlights the strong link between MetS and advanced OAK, necessitating TKR. Addressing MetS components such as abdominal obesity and hypertension may be critical in controlling and even avoiding severe OAK. By incorporating metabolic health management into OA care, healthcare providers may enhance patient outcomes and reduce the need for early surgical intervention.

In the future, we plan to expand the project into a larger sample size and investigate the relationship between therapeutic intervention for MetS, clinical results, and cartilage metabolism. Overall, there seems to be a complex interaction between MetS and OA, even though the precise mechanisms relating to both are not entirely understood. Particularly in weight-bearing joints, managing MetS through lifestyle changes (such as weight loss, regular exercise, and a healthy diet) may also help reduce the risk and severity of OA. Similarly, addressing OA through appropriate management strategies may help mitigate the impact of the condition on overall metabolic health.

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Conflicts of interest

There are no conflicts of interest.

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