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Original Research Article

Metabolic-Inflammatory burden and functional disability in Knee Osteoarthritis with Type 2 Diabetes Mellitus: A comparative cross-sectional study

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Abstract:

Background: Knee osteoarthritis (KOA) and type 2 diabetes mellitus (T2DM) are highly prevalent chronic diseases that often coexist, leading to worsened clinical outcomes. Both conditions share inflammatory pathways, yet the combined impact of glycemic control and systemic inflammation on functional disability has not been well studied.

Aim: The present study aimed to evaluate the association between glycemic indices, inflammatory markers, and functional disability in patients with T2DM, KOA, and their coexistence.

Methods: A total of 300 participants aged ≥60 years were enrolled and divided into three groups: Group 1 (T2DM + KOA, n = 100), Group 2 (T2DM only, n = 100), and Group 3 (KOA only, n = 100). Glycemic indices (HbA1c, FBS, PPBS), inflammatory markers (IL-6, hs-CRP), and functional disability (WOMAC index) were measured. Statistical analysis was performed using ANOVA and Pearson's correlation, with $p < 0.05$ considered significant.

Results: Group 1 exhibited significantly higher HbA1c (8.95 ± 0.45%), FBS (209.6 ± 15.8 mg/dL), and PPBS (270.5 ± 22.1 mg/dL) compared with Groups 2 and 3 ($p < 0.001$). Inflammatory markers were also highest in Group 1 (IL-6: 16.6 ± 3.6 pg/mL; hs-CRP: 6.63 ± 1.30 mg/L), followed by Group 3, and lowest in Group 2 ($p < 0.001$). Functional disability was most severe in Group 1 (WOMAC total 62.7 ± 5.3), moderate in Group 3 (45.9 ± 4.4), and minimal in Group 2 (12.2 ± 3.7, $p < 0.001$). Correlation analysis showed positive associations between HbA1c, inflammatory markers, and WOMAC scores.

Conclusion: Patients with coexisting T2DM and KOA demonstrated significantly higher glycemic indices, elevated systemic inflammation, and greater functional disability compared with either condition alone. These findings highlight the synergistic impact of metabolic dysfunction and inflammation in exacerbating disability and underscore the importance of integrated management strategies targeting both metabolic and musculoskeletal health.

Keywords: Osteoarthritis; Type 2 diabetes mellitus; HbA1c; IL-6; hsCRP; WOMAC.

Introduction

The dual burden of knee osteoarthritis (KOA) and type 2 diabetes mellitus (T2DM) represents a growing global health challenge. It is estimated that 595 million people were living with OA worldwide in 2020, with knee OA constituting the majority of cases and which will further rise by 2050 [1]. In India, the number of individuals with symptomatic OA increased markedly from approximately 23.46 million in 1990 to 62.35 million in 2019, reflecting a steep national rise

[2] [3]. Parallelly, the International Diabetes Federation (IDF) reported that 537 million adults (20–79 years) were living with diabetes in 2021 and expected to increase to 643 million by 2030 and 783 million by 2045 [4]. The Indian Council of Medical Research (ICMR) recently documented that India alone contributes over 101 million adults with diabetes, highlighting the scale of the challenge nationally [5]. Current research suggests that the relationship between OA and T2DM is complex and involves both metabolic and inflammatory mechanisms [6] [7]. Large cohort studies and systematic reviews have demonstrated that people with T2DM have a significantly higher likelihood of developing OA, while OA patients show an increased prevalence of diabetes as well [8]. Importantly, studies also reveal that patients with

both T2DM and KOA suffer from greater functional impairment than those with OA alone, with evidence pointing to worse physical performance and higher disability indices in comorbid populations [9] [10]. On a mechanistic level, inflammatory biomarkers such as interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) have been consistently associated with OA severity, pain, and functional outcomes measured by WOMAC scores [11]. Poor glycemic control in type 2 diabetes mellitus (T2DM) leads to the accumulation of advanced glycation end-products (AGEs) in cartilage and bone, which not only cause structural damage but also trigger pro-inflammatory pathways, resulting in elevated cytokines such as interleukin-6 (IL-6) and acute-phase proteins like high-sensitivity C-reactive protein [12] [13]. Knee osteoarthritis (KOA) itself is associated with systemic inflammation, and higher IL-6 and hs- CRP levels correlate with greater pain, stiffness, and functional limitation measured by WOMAC scores [14]. Since hyperglycemia fuels inflammation which in turn accelerates joint degeneration, both processes act together to worsen disability in patients who have both conditions. Assessing glycemic indices, inflammatory markers, and functional disability in isolation fails to capture their interrelated effects, whereas evaluating them together in the same patients allows a clearer demonstration of the mechanistic pathway in which poor glycemic control promotes systemic inflammation, which in turn contributes to greater functional disability. Therefore, we aim to compare glycemic control, inflammatory markers, and functional disability across three groups (a) Group 1 is patients with type 2 diabetes mellitus (T2DM), (b) group 2 patients with knee osteoarthritis (KOA) and (c)group 3 patients with both the conditions to analyze the correlations between them. This study may help to identify markers that predict disability in patients with T2DM and KOA. This can guide clinicians to detect high-risk patients earlier, plan integrated treatment strategies and improve quality of life.

Materials and Methods

This comparative cross-sectional study was conducted at Bowring and Lady Curzon Hospital, Sri Atal Bihari Vajpayee Medical College and Research Institute (SABVMCRI), Bangalore, after obtaining approval from the Institutional Ethics Committee (Approval No: SABVMCRI/IEC/UG-RP/05/24-25, dated 25.06.2024). The study was carried out over a period of one year, from July 2024 to July 2025.

The sample size was calculated using the formula $n = 4PQ/d^2$, where P was assumed as 50%, Q = 100 – P = 50%, and d was the allowable error of 10%. This yielded a minimum of 100 participants per group, giving a total sample size of 300. This formula has been recommended for health research when prevalence is unknown [15]. Patients aged 60 years and above with a confirmed diagnosis of type 2 diabetes mellitus (T2DM) based on ADA criteria and/or radiologically confirmed knee osteoarthritis (KOA; Kellgren–Lawrence grade II–IV) were included. Patients with type 1 diabetes, gestational diabetes, pancreatic diabetes, or those younger than 60 years were excluded. In addition, patients with autoimmune arthritis, chronic liver disease, chronic kidney disease, malignancy, or acute infections were not eligible. Participants were divided into three groups: Group 1 included patients with both T2DM and KOA (n = 100), Group 2 included patients with T2DM only (n = 100), and Group 3 included patients with KOA only (n = 100). Sociodemographic and clinical details including age, sex, education, lifestyle habits, body mass index (BMI), blood pressure, and duration of diabetes were recorded using a structured questionnaire.

Venous blood samples were collected under aseptic precautions. Fasting blood sugar (FBS) and postprandial blood sugar (PPBS) were measured by the glucose oxidase-peroxidase method, and glycated hemoglobin (HbA1c) was estimated by high-performance liquid chromatography (HPLC). Inflammatory markers were assessed by measuring serum interleukin-6 (IL-6) using enzyme-linked immunosorbent assay (ELISA) and high-sensitivity C-reactive protein (hs-CRP) using immunoturbidimetric assay. Functional disability was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), which evaluates pain, stiffness, and physical function, with higher scores indicating greater symptom severity and disability.

Data were analyzed using SPSS version 25.0. Continuous variables were expressed as mean ± standard deviation and categorical variables as proportions. Intergroup comparisons were performed using one-way analysis of variance (ANOVA) with post-hoc Bonferroni correction, while categorical data were analyzed using the chi-square test.

Correlations between glycemic indices, inflammatory markers, and WOMAC scores were assessed using Pearson's correlation coefficient. A p-value <0.05 was considered statistically significant.

Results

The baseline characteristics of the study groups are summarized in (Table 1). The mean age in all groups was above 60 years, age did not differ significantly across groups ($p = 0.266$). In contrast, BMI was significantly higher in group 3 compared with the KOA and T2DM groups ($p < 0.001$). Both systolic and diastolic blood pressures were also significantly elevated in the combined group ($p < 0.001$). Duration of diabetes was longer in participants with

T2DM + KOA than in those with T2DM alone ($p < 0.001$). Smoking prevalence was highest in group 3, while alcohol consumption and income distribution showed no significant differences between groups. Educational attainment varied significantly, with more graduates in the T2DM group and a higher proportion of primary educated individuals in the Group 3 ($p < 0.001$). Regional distribution also differed ($p = 0.001$), with the majority of participants across groups residing in Bengaluru Urban, particularly in group 3.

Male predominance in Group 1 (T2DM) reflects global trends where men are diagnosed earlier and at lower BMI, likely due to greater visceral adiposity and hepatic insulin resistance. In our study we have found that knee osteoarthritis is more common in women especially post menopause, driven by estrogen decline, altered biomechanics, and pain sensitivity. Our study is consistent with the Rotterdam cohort showing radiographic KOA prevalence approximately twice as high in females compared to males. A meta-analysis also confirmed that women have higher incidence and prevalence of KOA compared with men. Group 3 shows female predominance because of diabetes related inflammation, advanced glycation end products and clustering of metabolic risk factors disproportionately affect women in the post-menopausal period, amplifying OA risk (Figure 1)

The inflammatory markers, both IL-6 and hsCRP levels were significantly elevated across the three groups, with the highest values consistently observed in group 3, followed by group 2 and group 1 with significant differences ($p < 0.001$) observed across the group (Table 2). Patients with KOA alone showed intermediate IL-6 and hsCRP levels, while those with T2DM alone had comparatively lower inflammatory marker concentrations. Glycemic indices also showed significant group wise variation ($p < 0.001$). Group 3 consistently displayed the poorest glycemic profile, with mean FBS exceeding 209 mg/dL, PPBS averaging 270 mg/dL, and HbA1c approaching 9%, all indicative of severe hyperglycemia and suboptimal glycemic control. Patients with T2DM showed elevated glycemic indices (FBS ~156 mg/dL, PPBS ~212 mg/dL, HbA1c ~7%), while the KOA group-maintained values within or close to the normal range (Figure 2). Notably, patients with T2DM+KOA also exhibited higher systolic and diastolic blood pressures and greater BMI compared to the other two groups, pointing to a clustering of metabolic and cardiovascular risk factors beyond glycemia alone. Therefore, the patients with coexisting T2DM and KOA exhibit a compounded metabolic and inflammatory burden relative to those with either condition alone.

Assessment of functional disability through WOMAC domains highlighted a progressive worsening of pain, stiffness, and physical dysfunction across the three groups (Table 3). Group 1 reported minimal symptoms, while Group 2 showed moderate impairment, and Group 3 consistently exhibited the highest scores, indicating severe functional disability. Total WOMAC scores exceeded 62 in the combined group, compared to 46 in KOA and only 12 in T2DM. These differences were highly significant on ANOVA. Post-hoc Bonferroni comparisons confirmed that each group differed significantly from the others across all WOMAC domains (Table 4). The co-occurrence of T2DM and KOA was associated not only with greater absolute disability but also with disproportionate increases in pain and physical function impairment relative to either condition alone.

In our study we have found that patients with combined T2DM and KOA consistently exhibited the highest levels of inflammatory markers, poorest glycemic control and greatest WOMAC scores, indicating substantial functional disability compared to either condition alone ($p < 0.001$). These findings indicate that hyperglycemia and inflammation act synergistically and their coexistence markedly worsens disability, making the results both statistically significant and clinically meaningful. (Secondary table 5 to table 11)

Table 1: Baseline demographic and socioeconomic characteristics of the study participants

Clinical variables	Group 1 (T2DM) (Mean ± S.D.)	Group 2 (KO) (Mean ± S.D.)	Group 3 (T2DM + KOA) (Mean ± S.D.)	Significance ANOVA (p)
Age (years)	74.700 ± 8.861	72.680 ± 8.452	73.700 ± 8.954	0.266
BMI (kg/m²)	26.467 ± 2.436	23.489 ± 2.178	27.621 ± 3.167	**<.0001**
SBP (mmHg)	124.557 ± 7.773	117.827 ± 5.578	129.481 ± 10.369	**<0.001**
DBP (mmHg)	76.374 ± 6.150	74.943 ± 4.918	78.954 ± 8.227	**<0.001**
Diabetes Duration (years)	12.42 ± 4.13	NA	15.52 ± 4.11	**<0.001**
Current Smoker (%)	4%	6.0%	14.0%	0.022
Drinking (%)	13.0%	12.0%	7.0%	0.338
Income				
Lower class (%)	13.0%	15.0%	20.0%	0.583

Lower middle class (%)	21.0%	27.0%	21.0%	
Upper lower class (%)	62.0%	52.0%	52.0%	
Upper middle class (%)	4%	6%	7%	
Education				
Primary (%)	20.0%	14.0%	30.0%	**<0.001**
Middle school (%)	7.0%	29.0%	22.0%	
Graduate (%)	73.0%	57.0%	48.0%	
Region				
Bengaluru Rural (%)	16.0%	19.0%	3.0%	0.001
Bengaluru Urban (%)	84%	81%	97%	

The table summaries baseline variables of Group 1 (T2DM), Group 2 (KOA), and Group 3 (T2DM + KOA). It is presented as mean ± SD or percentage (%). No significant differences were observed for age, alcohol consumption, or income distribution ($p > 0.05$). BMI, systolic and diastolic blood pressures, diabetes duration, smoking status, education level, and region showed significant group-wise variation ($p < 0.05$). Statistically significant p-values are shown in bold.

Table 2: Biochemical characteristics of the study population

Clinical variables	Group 1 (T2DM) (Mean ± S.D.)	Group 2 (KO) (Mean ± S.D.)	Group 3 (T2DM + KOA) (Mean ± S.D.)	Significance ANOVA (p)
IL-6 (pg/mL)	4.084 ± 2.592	7.741 ± 1.359	16.583 ± 3.616	**<0.001**
hsCRP (mg/L)	2.537 ± 0.816	5.431 ± 1.099	6.632 ± 1.298	**<0.001**
FBS (mg/dL)	155.809 ± 12.788	84.500 ± 8.494	209.633 ± 15.799	**<0.001**
PPBS (mg/dL)	211.894 ± 17.145	120.000 ± 11.726	270.508 ± 22.129	**<0.001**
HbA1c (%)	7.011 ± 0.388	5.485 ± 0.276	8.948 ± 0.454	**<0.001**

Group 1: Patients with Type 2 Diabetes Mellitus (T2DM), Group 2: Patients with Knee Osteoarthritis (KOA), Group 3: Patients with both T2DM and KOA. Data are expressed as mean ± standard deviation. ANOVA test was applied to assess statistical significance across groups. Age did not differ significantly among the groups ($p = 0.266$). However, inflammatory markers (IL-6, hsCRP), glycemic indices (FBS, PPBS, HbA1c), blood pressure (SBP, DBP) and BMI showed highly significant differences ($p < 0.001$). Bold p-values indicate statistically significant differences across groups.

Table 3: Variation in WOMAC domains across groups

WOMAC Domain	Group 1 (T2DM) (Mean ± S.D.)	Group 2 (KO) (Mean ± S.D.)	Group 3 (T2DM + KOA) (Mean ± S.D.)	Significance ANOVA (p)
Pain (0-20)	1.067 ± 0.449	9.164 ± 2.482	12.886 ± 2.177	<.001
Stiffness (0-8)	1.017 ± 0.496	3.859 ± 1.081	5.197 ± 1.077	<.001
Physical Function (0-68)	10.250 ± 3.135	32.906 ± 3.748	44.598 ± 4.108	<.001
Total WOMAC score	12.230 ± 3.744	45.928 ± 4.433	62.681 ± 5.262	<.001

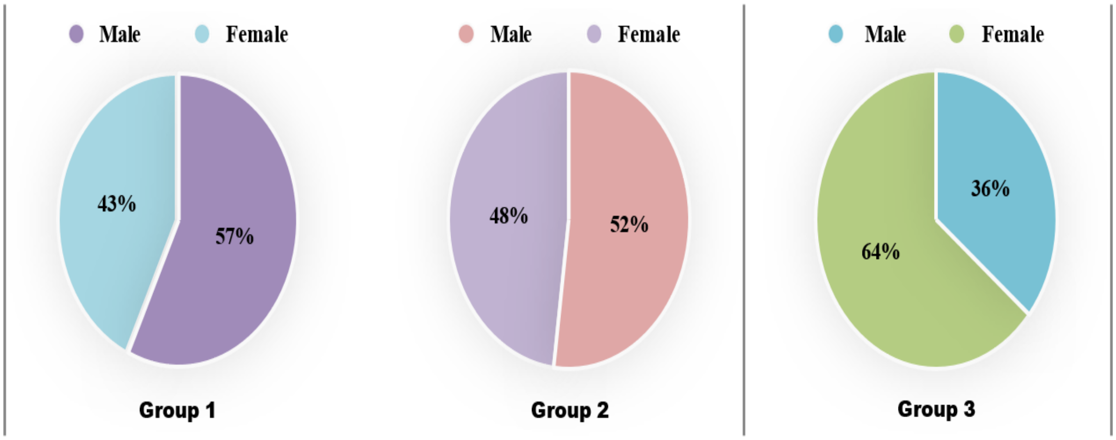
The table presents the mean ± standard deviation (S.D.) of WOMAC domains: pain, stiffness and physical function along with the total WOMAC score in the three study groups. Group 1 showed minimal symptoms, while Group 2 and Group 3 exhibited progressively higher scores, indicating worsening pain, stiffness, and physical disability. The differences among groups were statistically significant (ANOVA $p < 0.001$)

Table 4: Post-hoc analysis (Bonferroni) of WOMAC Scores

Domain	Group Comparison	Mean Difference (95% CI)	p-value
Pain	T2DM vs KOA	-8.10 (–8.75, –7.44)	<0.001
	T2DM vs T2DM+KOA	-11.82 (–12.47, –11.16)	<0.001
	KOA vs T2DM+KOA	-3.72 (–4.38, –3.07)	<0.001
Stiffness	T2DM vs KOA	-2.84 (–3.16, –2.53)	<0.001
	T2DM vs T2DM+KOA	-4.18 (–4.50, –3.86)	<0.001
	KOA vs T2DM+KOA	-1.34 (–1.65, –1.02)	<0.001
Physical Function	T2DM vs KOA	-22.66 (–23.91, –21.40)	<0.001
	T2DM vs T2DM+KOA	-34.35 (–35.60, –33.09)	<0.001
	KOA vs T2DM+KOA	-11.69 (–12.95, –10.44)	<0.001
Total WOMAC Score	T2DM vs KOA	-33.70 (–35.24, –32.16)	<0.001
	T2DM vs T2DM+KOA	-50.45 (–51.99, –48.91)	<0.001
	KOA vs T2DM+KOA	-16.75 (–18.29, –15.21)	<0.001

Pairwise comparisons (Bonferroni-adjusted) demonstrate significant differences in Pain, Stiffness, Physical

Function and Total WOMAC scores between Type 2 Diabetes Mellitus (T2DM), Knee Osteoarthritis (KOA), and combined T2DM+KOA groups. Values are expressed as mean differences with 95% confidence intervals. All comparisons remained statistically significant at $p < 0.001$.



Chi Square Tests	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	9.637a	2	.008
Likelihood Ratio	9.739	2	.008
Linear-by-Linear Association	5.109	1	.024
N of Valid Cases	300		
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 48.33.			

Figure 1: Gender distribution across groups. Male predominance was noted in Group 1 (Type 2 Diabetes Mellitus, T2DM), while females were predominant in Group 2 (Knee Osteoarthritis, KOA) and Group 3 (combined group of T2DM + KOA). Differences in gender distribution across groups were statistically significant (Pearson's $\chi^2 = 9.637$, df = 2, $p = 0.008$; Linear-by-Linear Association, $p = 0.024$).

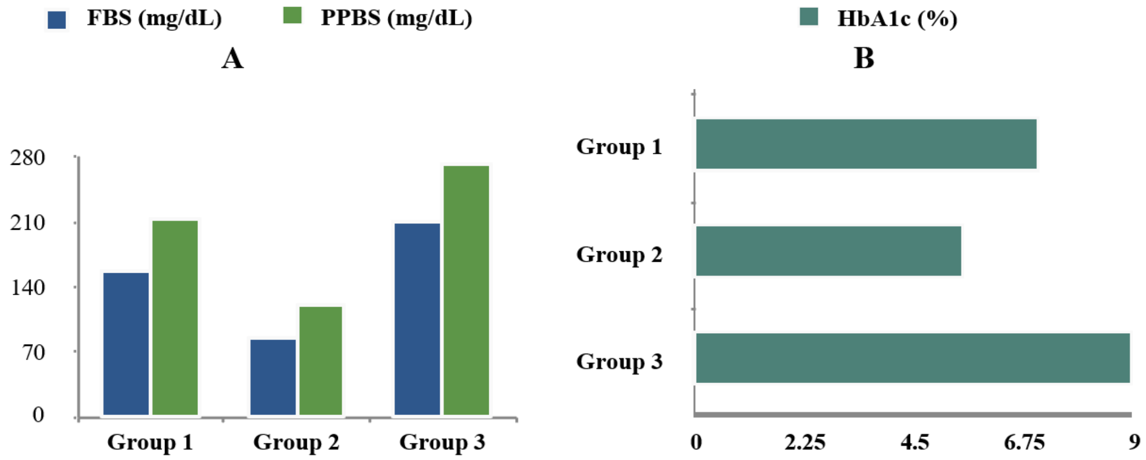


Figure 2: Comparison of glycemic control parameters among study groups. (A) Bar graph showing mean FBS and PPBS levels in Group 1 (T2DM), Group 2 (KOA), and Group 3 (T2DM + KOA). Both FBS and PPBS are significantly higher in diabetic groups, with the highest values seen in Group 3. (B) Horizontal bar graph of mean HbA1c (%) across groups. Group 3 shows markedly elevated HbA1c compared to Group 1, while Group 2 remains within the normal range, indicating good glycemic control.

Discussion

In this study we assessed the relationship between glycemic control, inflammatory markers, and functional disability among patients with type 2 diabetes mellitus, knee osteoarthritis, and the coexistence of both conditions. We observed that patients with combined T2DM and KOA had significantly higher HbA1c, fasting and postprandial glucose values, greater systemic inflammation as reflected by elevated IL-6 and hs-CRP, and markedly worse WOMAC pain, stiffness, and functional scores compared with those who had either condition alone. These findings indicate that hyperglycemia and inflammation act synergistically to exacerbate disability when the two diseases coexist.

Our results are consistent with recent literature. Louati et al.,2015 reported that diabetes is associated with a higher prevalence and severity of OA, and that the coexistence of both conditions contributes to greater functional impairment. Similarly, Alenazi et al.,2023 showed that KOA patients with diabetes experience worse pain and physical performance than KOA patients without diabetes [16]. Inflammatory markers such as IL-6 and hs-CRP have been identified as important mediators linking metabolic and musculoskeletal disorders [17]. It has been demonstrated that interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) show significant correlations with both radiographic severity and functional outcomes in knee osteoarthritis (KOA). Furthermore, elevated IL-6 levels have been found to be strongly associated with greater WOMAC pain and disability scores [18] [19] [20]. Our study supports these findings and extends them by showing that when poor glycemic control is present, inflammatory markers rise further and functional disability becomes significantly more severe.

The biological explanation for this association is well established. Chronic hyperglycemia in T2DM promotes the formation of advanced glycation end-products (AGEs), which accumulate in cartilage and bone, weakening their structural properties and activating inflammatory cascades. This contributes to higher levels of circulating IL-6 and hs- CRP [21] [22]. On the other hand, KOA is already characterized by low-grade systemic inflammation and cartilage degeneration. When diabetes and KOA coexist, these processes reinforce one another, producing higher inflammatory levels and accelerating disability. The higher BMI and blood pressure values observed in the combined disease group in our study also suggest that metabolic syndrome components may further amplify this adverse interaction [23].

We have found that patients with T2DM and KOA represent a particularly high-risk subgroup, with significantly worse metabolic status, systemic inflammation, and functional decline compared with those with either condition alone. Prior studies have highlighted individual associations between glycemia, inflammation and KOA, but our results add strength to the evidence by demonstrating these links simultaneously in the same patient cohort. Therefore, controlling glycemia and systemic inflammation in patients with KOA and diabetes may not only reduce vascular complications but also attenuate pain and disability, ultimately improving quality of life.

However, our study has some limitations that need to be acknowledged. First, being cross-sectional in design, it cannot establish causality between poor glycemic control, inflammation, and functional disability; only associations were demonstrated. Second, as the study was conducted in a single tertiary care hospital, the findings may not be fully generalizable to the wider community, particularly rural or primary care populations. Third, we assessed only two inflammatory markers (IL-6 and hs-CRP), whereas other cytokines such as TNF-α, IL-1β, and adipokines could provide additional mechanistic insights. Fourth, the reliance on clinical and questionnaire-based functional scores without imaging or biomarker validation may have limited the precision of disability assessment. Finally, potential confounding factors such as dietary patterns, physical activity levels, and socioeconomic status were not deeply analyzed, although baseline data were collected.

Future research should focus on longitudinal cohort studies to determine whether improving glycemic control leads to reductions in inflammatory markers and functional disability over time. Interventional trials combining optimized diabetes management, targeted anti-inflammatory therapies, weight reduction, and physiotherapy could evaluate integrated care strategies for patients with coexisting T2DM and KOA. Expanding biomarker profiling to include additional cytokines, oxidative stress markers, and cartilage degradation products would provide a deeper understanding of pathophysiological pathways. Large scale multicenter studies across different populations would also improve generalizability and help establish predictive models for identifying high-risk patients.

Conclusion

In this study we found that patients with coexisting type 2 diabetes mellitus and knee osteoarthritis had significantly poorer glycemic control, higher systemic inflammation, and greater functional disability compared with those with either condition alone. These findings demonstrate that hyperglycemia and inflammation act synergistically to worsen outcomes and highlight the need for integrated management strategies that address both metabolic and musculoskeletal health.

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