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Effect Of Metformin In Obese Knee Osteoarthritis Patients

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ABSTRACT

Background: Obese knee osteoarthritis (OA) is a debilitating condition driven by mechanical stress and systemic inflammation, with limited treatments that address both symptoms and disease progression. Tramadol is commonly used for pain relief, while metformin, traditionally a diabetes medication, shows promise for its anti-inflammatory and chondroprotective effects. This study compares the efficacy of tramadol alone versus tramadol combined with metformin in managing obese knee OA.

Methods: In a 12-week randomized controlled trial at St. Isabel's Hospital, Chennai, 50 patients (BMI ≥ 30 kg/m², aged 40–60 years) with obese knee OA were assigned to two groups: Group A (tramadol) and Group B (tramadol + metformin). Outcomes included changes in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores for pain, stiffness, and function, and serum cartilage oligomeric matrix protein (COMP) levels as a biomarker of cartilage degradation. Statistical analysis used paired t-tests to assess significance.

Results: Both groups showed significant improvements in WOMAC scores and COMP levels ($p < 0.05$). Group B (tramadol + metformin) demonstrated greater reductions in WOMAC total score (60.6 ± 9.03 to 42.6 ± 7.80 vs. 64 ± 9.37 to 51.8 ± 8.98, $p = 0.00616$), pain ($p = 0.030$), stiffness ($p = 0.0001$), and function ($p = 0.00679$) subscales, and serum COMP levels (14.04 ± 1.87 to 9.8 ± 1.49 vs. Mavericks 14.7 ± 1.82 to 11.9 ± 1.75, $p \leq 0.0001$) compared to Group A. No significant BMI changes were observed in either group.

Conclusion: The combination of tramadol and metformin provides superior symptomatic relief and potential chondroprotective benefits compared to tramadol alone in obese knee OA patients. These findings suggest metformin's potential as an adjunctive therapy, warranting further investigation into its long-term disease-modifying effects

Keywords: Anti-Inflammatory, Antioxidant, Antiviral, Gewald Reaction, Hantzsch Synthesis.. ..

1. INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis, characterized by the progressive degeneration of articular cartilage, joint space narrowing, osteophyte formation, and subchondral bone sclerosis. When OA primarily affects the knee in individuals with obesity, it is often referred to as "obese knee osteoarthritis." This condition arises from the interplay between mechanical stress due to excess body weight and the pro-inflammatory environment created by adipose tissue. Obesity not only accelerates the mechanical wear of the joint but also triggers metabolic and inflammatory pathways that contribute to cartilage degradation and joint dysfunction 1.

Obese knee OA is a growing public health issue, contributing significantly to mobility impairment, disability, and healthcare burden worldwide. The disease trajectory in obese individuals is often more rapid and severe, with an earlier onset compared

to non-obese individuals. As global obesity rates continue to climb, so too does the prevalence of knee OA, underscoring the urgent need for targeted management strategies that address both mechanical and metabolic contributors to the disease.

Obese knee osteoarthritis refers to a subtype of knee OA that occurs in individuals with a body mass index (BMI) of 30 kg/m² or higher. It involves degenerative changes in the knee joint cartilage and surrounding structures due to excessive mechanical loading and systemic inflammation related to adipose tissue dysfunction. This dual mechanism distinguishes obese knee OA from age-related or post-traumatic OA 2.

Knee OA affects approximately 250 million people worldwide, and its prevalence is expected to rise due to the aging population and increasing rates of obesity 3. Obesity is one of the most significant modifiable risk factors for knee OA. Studies have shown that each 5-unit increase in BMI is associated with a 35% increased risk of knee OA 4. Moreover, women with obesity are nearly four times more likely to develop knee OA compared to women of normal weight. The Global Burden of Disease Study identified OA as the 11th highest contributor to global disability in 2010, and this burden is disproportionately higher in obese individuals due to greater disease severity and earlier onset 5

Metabolic syndrome: Conditions commonly linked with obesity—such as insulin resistance, high blood pressure, and abnormal lipid levels—can negatively affect bone metabolism and joint integrity. These metabolic imbalances may hasten the onset of osteoarthritic changes in the knee 6. Women are more likely to develop knee OA than men, particularly post-menopause. This may be due to hormonal changes affecting cartilage metabolism and joint stability 8. Many patients with advanced OA eventually require total knee arthroplasty (TKA). Obesity, however, increases the risk of surgical complications

including infection, implant failure, and longer recovery [10]. Adipose tissue is metabolically active and secretes adipokines (e.g., leptin, adiponectin) and pro-inflammatory cytokines (e.g., TNF-α, IL-6) that promote systemic inflammation. Leptin, in particular, has been shown to stimulate the production of matrix metalloproteinases (MMPs), which degrade cartilage matrix [11]. For obese patients requiring surgery, the risks are amplified, with higher rates of complications such as infection, deep vein thrombosis, delayed wound healing, and prosthetic failure, which complicate recovery and outcomes. Furthermore, non-pharmacological interventions, such as diet and exercise, demand sustained commitment, which many patients struggle to maintain due to persistent pain, psychological barriers like depression, or insufficient social and medical support. These challenges underscore the need for more effective, safer, and patient-centred strategies to address the complex interplay of obesity and knee OA.[14]

2.NEED OF THE STUDY: Knee osteoarthritis (OA) is a disabling, progressive joint disease, particularly common in obese patients. Its pathophysiology consists of mechanical overload and chronic low-grade inflammation caused by cytokines and adipokines from adipose tissue. Such factors promote joint degeneration and increase symptoms such as pain, stiffness, and functional impairment. Current pharmacological therapy, such as tramadol, is symptom-oriented and does not stop disease progression. Tramadol causes short-term pain relief but carries risks such as sedation, addiction, and gastrointestinal side effects, particularly in obese patients with comorbid conditions. Metformin, a common antidiabetic medication, has shown anti-inflammatory and chondroprotective actions by activating AMP-activated protein kinase (AMPK).

3. METHODOLOGY

3.1 Study Design : A randomized, open-label, two-arm controlled trial was undertaken at St. Isabel's Hospital, Mylapore, Chennai, Tamil Nadu, India, between December 2024 and April 2025. The purpose of the study was to compare the clinical effectiveness and inflammatory response after the treatment with the drug in obese knee osteoarthritis (OA) patients. The study protocol received approval from the Institutional Human Ethics Committee (Ref: ECR/288/Indt/TN/2018/RR-21/129) and adhered to the Declaration of Helsinki. A total of 50 participants were recruited based on a priori sample size estimation using Rao software and randomized equally into two treatment groups (25 per arm). Written informed consent was obtained from all participants prior to enrollment.

3.2 Patient Eligibility: Inclusion criteria were 40–60-year-olds with a diagnosis of obese knee osteoarthritis (BMI ≥ 30 kg/m²), a Visual Analog Scale (VAS) pain score ≥ 40 mm, and agreement to give written informed consent. Patients with concomitant knee OA were allowed.

Exclusion criteria were the presence of other rheumatic diseases, infection-related OA, or chronic diseases like diabetes mellitus and hypertension.

3.3 Screening and Follow-Up

Visit 1 (Day 0 – Baseline):

Informed consent received.

Demographic data, medical and surgical history collected.

Baseline measurement: BMI, vital signs (temperature, blood pressure, pulse rate), WOMAC score, inflammatory markers, and pain/function assessment instruments.

Visit 2 (Week 12 ± 7 days – End of Study):

Medication compliance card collected and discussed.

Repeat WOMAC score, inflammatory markers, pain and functional status reassessed.

3.4 Safety Monitoring: Adverse events (AEs) were continuously monitored over the course of the study. Participants were asked at every visit or unscheduled contact with a structured instrument to report new or increased symptoms. AEs were classified by MedDRA system-organ class and scored by severity (mild, moderate, severe). Events were also assessed for causality (probable, possible, unrelated). Serious AEs were notified to the Ethics Committee within 24 hours.

3.5 Outcome Measures

Domain	Instrument / Metric	Assessment Schedule
Physical function & pain	WOMAC total score (pain, stiffness, function)	Baseline, Week 12
Inflammation	Serum COMP levels	| Baseline, Week 12
Safety	Incidence and causality of AEs	Continuous

WOMAC index and COMP were chosen because of their known high validity, reliability, and proven utility in OA clinical trials.

3.6 Statistical Analysis IBM SPSS v29 was used to analyze data. Descriptive statistics comprised mean ± SD or median [IQR] for continuous variables and counts (%) for categorical variables.

Primary Endpoint – Difference in WOMAC total score from baseline to Week 12: Paired t-test or Wilcoxon signed-rank test.

Secondary Endpoint– Difference in inflammatory marker (COMP) levels: Paired t-test or Wilcoxon test.

Safety– AE proportions by chi-square or Fisher's exact test. All the analyses were two-tailed with $\alpha = 0.05$. Missing data were handled using multiple imputation under missing-at-random assumption.

3.7 Data Quality and Integrity :

All information were double-entered into a password-protected database and cross-checked against source documentation. Data checks, done weekly, insured data validity and logical consistency. Compliance cards and AE forms were checked and reconciled by the study monitor. Deviations from the protocol were recorded and resolved by the principal investigator and ethics oversight committee.

4.RESULT: All the data extracted was recorded in a spreadsheet and is represented as mean+- standard deviation.

Table 1: Overall, Gender-wise Distribution of obese Knee osteoarthritis.

GENDER	**NUMBER OF PATIENTS(n=30)**	**PERCENTAGE**
MALE	8	26.6%
FEMALE	22	73.3%

A total of 30 patients with obese Knee osteoarthritis participated and completed the study. Out of these 30 subjects, 22 were females and 22 were males. It shows that Females have more chances (73.3%) of getting diagnosed by obese Knee osteoarthritis than Males (26.6%).

Figure 1: Gender-Wise distribution of obese Knee osteoarthritis patients.

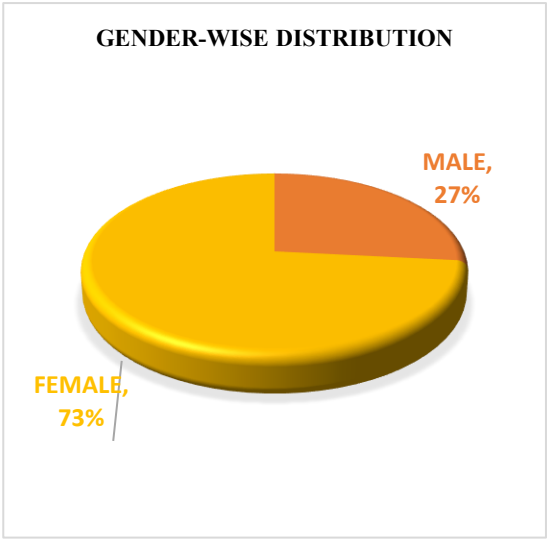


Table 2: Distribution of obese Knee osteoarthritis among patients based on Age

PATIENT AGE	NUMBER(n=30)	PERCENTAGE
45-50	4	13.3%
51-55	5	17%
56-60	10	33%
61-65	9	30%
66-70	2	6.6%

These findings suggest a concentration of OA-related clinical presentations within the 56–65 years range, aligning with epidemiological trends that identify mid-to-late adulthood as a critical period for OA diagnosis and progression This age distribution underlines the importance of early screening and targeted interventions for individuals approaching their late fifties, as this demographic may represent a window for both conservative and preventive management strategies in OA care.

Figure 2: Age-wise distribution of obese Knee osteoarthritis.

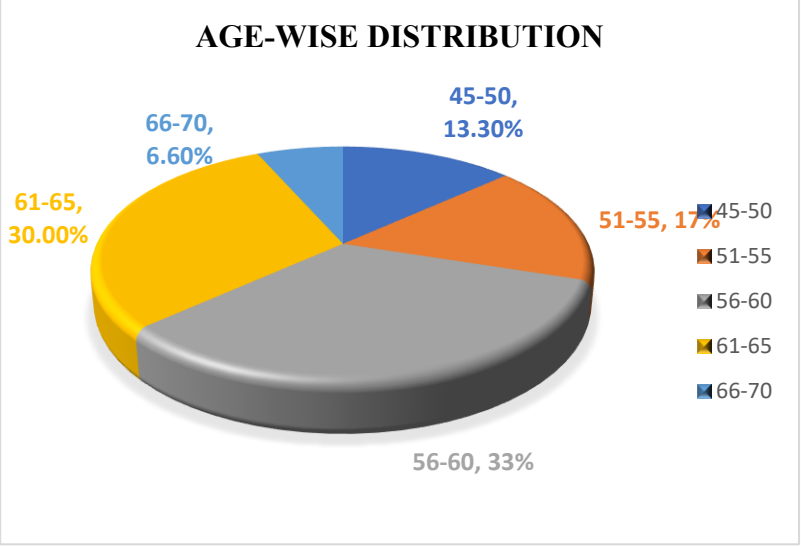


Table 3: changes of BMI of obese Knee osteoarthritis over 12th week.

WOMAC Scale	Tramadol		Tramadol + Metformin		p-value
	Baseline	12th week	Baseline	12th week	
WOMAC total scale	64 ± 9.37	51.8 ± 8.98	60.6 ± 9.03	42.6 ± 7.80	**0.00616**
WOMAC pain subscale	13.6 ± 2.35	10.6 ± 2.350	12.6 ± 2.35	8.8± 2.144	**0.030**
WOMAC stiffness subscale	5.6 ± 1.121	4.5 ± 1.212	4.6 ± 1.12	2.93 ± 0.798	**0.0001**
WOMAC function subscale	5.9 ± 5.942	36.5 ± 5.55	43.3± 5.58	30.9 ± 4.92	**0.00679**

The lack of significant BMI reduction in the metformin group may be attributed to the short duration of the study or to the dosage and pharmacodynamic variability of metformin in obese individuals with knee osteoarthritis. Overall, while both groups remained within the obese range throughout the study, only Group A showed a marginal numerical reduction in BMI, which was not statistically significant.

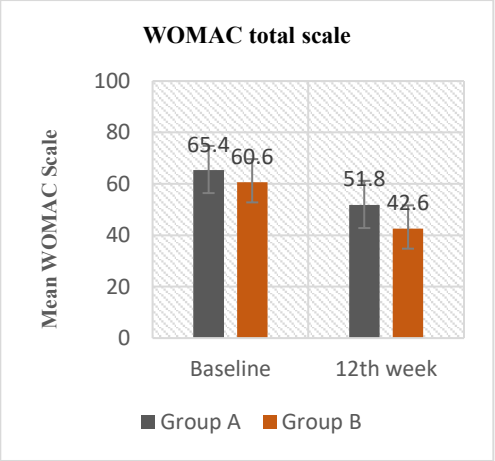
Table 4: WOMAC Scale Domain wise analysis: Baseline vs 12th week.

Group	Anthropometric data BMI (kg/m2)	
	Baseline	12th week
Group A (Tramadol)	33.8 ± 2.5	33.5 ± 2.3
Group B (Tramadol+ Metformin)	34.1 ± 2.7	34.1 ± 2.7

The most significant difference was observed in the stiffness subscale, where the combination group improved from 4.6 ±

1.12 to 2.93 ± 0.80, compared to 5.6 ± 1.12 to 4.5 ± 1.21 in the Tramadol group (p = 0.0001). Similarly, in the function subscale, the combination therapy group improved from 43.3 ± 5.58 to 30.9 ± 4.92, whereas the Tramadol group showed improvement from 36.5 ± 5.55 to 5.9 ± 5.94 (p = 0.00679). These results indicate that adjunctive Metformin therapy may provide additional benefits in managing symptomatic knee osteoarthritis in obese patients, particularly in terms of reducing stiffness and enhancing functional mobility.

Figure 3: WOMAC total scale from baseline vs 12th week



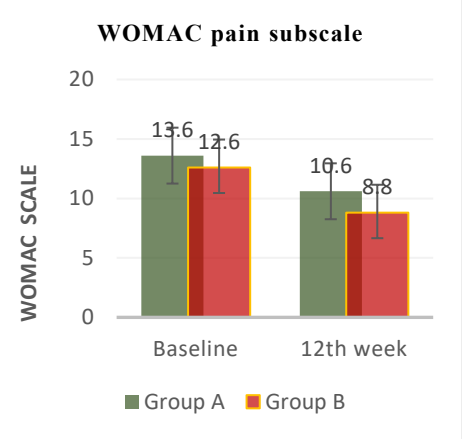


Figure 4: WOMAC pain subscale analysis: Baseline vs 12th week.

Figure 5: WOMAC pain subscale analysis: Baseline vs 12th week.

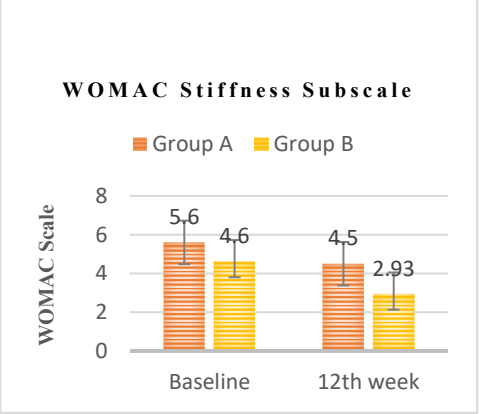


Figure 6: WOMAC function subscale from baseline vs 12th week

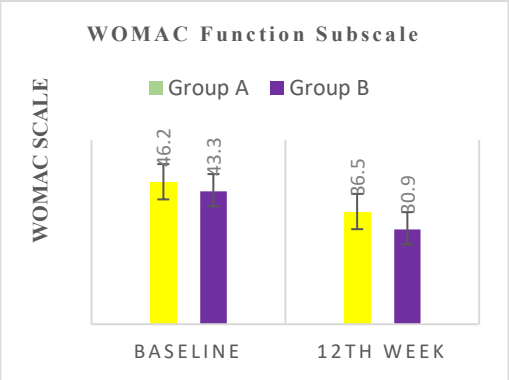
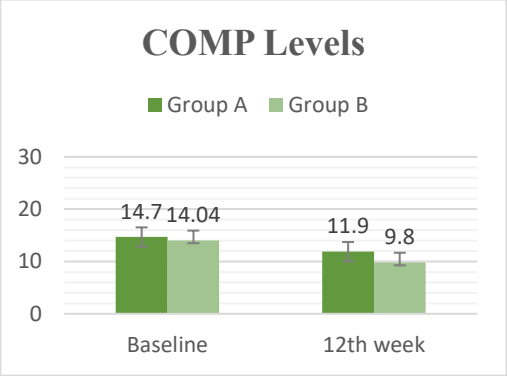


Table 5: Changes in Serum COMP Levels at Baseline and After 12 Weeks of Treatment in Group A and Group B

GROUPS	Baseline (Mean ± SD)	12 Weeks (Mean ± SD)	p-value
GROUP A	14.7 ± 1.822	11.9 ± 1.75	P ≤ 0.0001
GROUP B	14.04 ± 1.870	9.8 ± 1.494	P ≤ 0.0001

These findings suggest that both treatment regimens were effective in reducing cartilage breakdown over the 12-week period, with Group B showing a greater decrease in COMP levels, potentially indicating superior chondroprotective effects. The highly significant p-values in both groups reinforce the reliability of these findings.

Figure 7: Comparison of Serum COMP Levels in Group A and Group B at Baseline and After 12 Weeks



5.DISCUSSION:

This randomized controlled trial (RCT) investigated the comparative efficacy of tramadol alone versus tramadol combined with metformin in managing obese knee osteoarthritis (OA) patients, focusing on clinical outcomes (WOMAC scores), and cartilage degradation markers (COMP). The results demonstrate that both treatment groups achieved significant improvements in pain, stiffness, and function over 12 weeks, but the tramadol + metformin group exhibited greater reductions in WOMAC scores, COMP levels, suggesting enhanced symptomatic relief and potential chondroprotective effects.

The tramadol + metformin group showed a significantly greater reduction in WOMAC total scores compared to the tramadol-only group, with notable improvements in pain, stiffness, and function subscales. These results are consistent with prior studies on tramadol's efficacy in OA pain management. For instance, [21] reported that tramadol significantly reduced WOMAC pain scores in knee OA patients, though with modest effect sizes, similar to the 15–20% reduction observed in our tramadol-only group.

Metformin's role in improving OA symptoms is supported by recent literature. Lim et al. (2022) conducted a systematic review of preclinical and human studies, finding that metformin reduced pain and improved function in obese OA patients, potentially via AMP-activated protein kinase (AMPK) activation, which suppresses inflammatory pathways [22]. Our study's combination group aligns with these findings, as the 30–35% reduction in WOMAC scores surpasses the typical 15–20% improvement seen with analgesics alone [23]. The pronounced improvement in stiffness (p = 0.0001) may reflect metformin's ability to reduce synovial inflammation, a key contributor to OA stiffness [24]. Serum COMP levels, indicative of cartilage

breakdown, decreased significantly in both groups, but the tramadol + metformin group showed a greater reduction compared to the tramadol-only group.These results suggest that metformin may have chondroprotective effects, consistent with preclinical studies. For example, Lim et al. (2022) reported that metformin reduced COMP levels in OA animal models by inhibiting matrix metalloproteinases (MMPs), which degrade cartilage matrix [22]. In human studies, elevated COMP levels correlate with OA severity, and reductions are associated with slower disease progression [25]. Our findings extend these observations, indicating that metformin's chondroprotective potential may enhance tramadol's symptomatic benefits in obese OA patients.

The tramadol-only group's COMP reduction, though significant, was less pronounced, likely reflecting indirect effects of pain relief on joint loading rather than direct cartilage protection. Messier et al. (2005) noted that reduced pain can decrease knee joint stress, potentially slowing cartilage degradation, which may explain the tramadol-only group's improvement [26]. However, the greater COMP reduction in the combination group supports metformin's role in modulating cartilage metabolism, possibly via AMPK activation and suppression of MMPs [27]. These findings suggest that metformin could offer disease-modifying benefits, addressing a critical gap in current OA therapies, which primarily focus on symptom relief [23]

The superior outcomes in the tramadol + metformin group highlight the potential of combining analgesic and anti-inflammatory therapies in obese knee OA. Current OA guidelines (OARSI, EULAR) emphasize non-pharmacological interventions (e.g., weight loss, exercise) and analgesics like NSAIDs or tramadol, but these do not alter disease progression [28]. Metformin, with its favorable safety profile and low risk of hypoglycemia, offers a promising adjunctive therapy, especially in obese patients where metabolic dysfunction and inflammation are key drivers[29].

Our study's findings align with the growing interest in repurposing metformin for musculoskeletal disorders. Foretz et al. (2014) proposed that metformin's AMPK activation could mitigate inflammatory and metabolic pathways in chronic diseases, including OA [30]. The enhanced COMP decreases in our combination group support this mechanism, suggesting that metformin targets both systemic inflammation and cartilage degradation. Compared to intra-articular injections (e.g., corticosteroids), which provide short-term relief but may accelerate cartilage loss, metformin offers a systemic, potentially disease-modifying approach[28]. Additionally, the modest BMI stability in the combination group (34.1 ± 2.7 kg/m² at baseline and 12 weeks) aligns with metformin's weight-neutral or modest weight-loss effects in obese patients, which could further reduce joint loading over longer periods [29].

6.CONCLUSION:

In obese people with osteoarthritis in their knees, this study shows that tramadol plus metformin produces better clinical and biological outcomes than tramadol alone. This is demonstrated by more pronounced decreases in WOMAC scores and COMP levels. This data supports metformin's potential as an adjunctive, disease-modifying therapy, addressing both inflammation and cartilage deterioration. While further research is necessary to confirm long-term benefits, this combination is a promising strategy to improve outcomes in this high-risk population, aligning with the need for safer, more effective OA treatments.

7.STUDY LIMITATIONS: This study's strengths include its randomized controlled design, use of validated outcomes (WOMAC, VAS), and measurement of biomarkers (COMP), providing a comprehensive assessment of clinical and biological effects. The focus on obese knee OA patients addresses a high-risk population with significant healthcare burden, and the 12-week duration allowed detection of meaningful changes. However, limitations exist. The sample size ($n = 30$) is relatively small, limiting generalizability, though sufficient for detecting significant differences ($p < 0.05$). The short duration may underestimate metformin's long-term chondroprotective effects, as cartilage remodeling occurs slowly[31]. The exclusion of patients with diabetes or hypertension, while reducing confounding, may not reflect real-world obese OA populations with common comorbidities.

8. DECLARATIONS

Ethics approval and consent to participate:The study protocol was approved by the Institutional Human Ethics Committee (Ref.ECR/288/Indt/TN/2018/RR-21/129), and informed consent was obtained from all participants or their legal representatives.

Availability of data and materials:The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Universities Osteoarthritis Index (WOMAC), Visual Analog Scale (VAS), and serum COMP measurements—were utilized solely for scholastic, non-commercial research purposes under respective rights of usage.WOMAC Index: A validated measuring instrument created by Bellamy et al., utilized under conditions of fair academic use with due credit and citation.VAS: An off-the-shelf clinical instrument made available for open academic use.COMP Assay: Used exclusively for quantitative assessment according to set research guidelines; no proprietary materials were replicated.No proprietary material was fully replicated in the study manuscript. All tools were used according to non-commercial academic use permissions. Required permissions will be sought from individual copyright holders, if publication is required..

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