E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/16.02.490

**Research Article**

# Influence of Anatomical Alignment on Pharmacological Response and Functional Outcomes Following Conservative Management of Knee Osteoarthritis

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Received: 21.06.2026, Revised: 15.08.2026, Accepted: 27.08.2026

**ABSTRACT**

**Background:** Knee osteoarthritis (KOA) is a progressive musculoskeletal disorder characterized by pain, functional impairment, and reduced quality of life. Anatomical alignment of the lower limb is an important biomechanical factor that may influence disease progression and the effectiveness of conservative pharmacological management.

**Objective:** To evaluate the influence of anatomical alignment on pharmacological response and functional outcomes among patients undergoing conservative treatment for knee osteoarthritis.

**Methods:** A cross-sectional analytical study was conducted involving 180 patients with radiographically confirmed knee osteoarthritis managed conservatively. Participants were categorized according to lower limb alignment into varus (n = 82), neutral (n = 46), and valgus (n = 52) groups using standing anteroposterior radiographs. All patients received standard pharmacological therapy consisting of nonsteroidal anti-inflammatory drugs (NSAIDs) with or without acetaminophen, along with physiotherapy and lifestyle modification. Pain intensity was assessed using the Visual Analog Scale (VAS), functional status using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and physical performance using the Timed Up and Go (TUG) test after 12 weeks of treatment. Statistical analysis was performed using one-way ANOVA, chi-square test, and multivariate linear regression. A p-value <0.05 was considered statistically significant.

**Results:** Patients with neutral alignment demonstrated significantly greater improvement in pain and function compared with those having varus or valgus deformities. Mean reduction in VAS score was 3.8 ± 1.1 in the neutral group compared with 2.4 ± 1.0 in the varus group and 2.7 ± 1.2 in the valgus group ($p < 0.001$). WOMAC total scores improved by 39.6%, 24.8%, and 27.3%, respectively ($p = 0.002$). The mean TUG time improved from 12.3 ± 2.5 s to 9.8 ± 2.1 s in the neutral group, whereas improvements were significantly smaller in varus and valgus groups ($p = 0.004$). Multivariate regression identified varus malalignment as an independent predictor of poorer pharmacological response ($\beta = 0.34$, $p = 0.001$) after adjusting for age, sex, body mass index, and disease severity.

**Conclusion:** Anatomical alignment significantly influences the clinical response to conservative pharmacological management in knee osteoarthritis. Patients with neutral lower limb alignment achieved superior pain relief and functional recovery, whereas varus and valgus malalignment were associated with reduced treatment effectiveness. Incorporating anatomical alignment assessment into routine clinical evaluation may facilitate individualized treatment strategies and improve patient outcomes.

**Keywords:** Knee Osteoarthritis, Anatomical Alignment, Varus Deformity, Valgus Deformity, Pharmacological Therapy, Conservative Management, WOMAC, Visual Analog Scale.

## INTRODUCTION

Knee osteoarthritis (KOA) is one of the most common chronic musculoskeletal disorders and a leading cause of pain, physical disability, and reduced quality of life worldwide. The disease is characterized by progressive degeneration of articular cartilage, remodeling of subchondral bone, osteophyte formation, synovial inflammation, and varying degrees of ligamentous and muscular dysfunction. According to recent global estimates, the prevalence of knee osteoarthritis continues to rise because of increasing life expectancy, obesity, sedentary lifestyles, and the growing burden of metabolic disorders. Consequently, KOA has become a major public health challenge, accounting for substantial healthcare expenditure and productivity loss, particularly among adults over 50 years of age (1–3).

The pathogenesis of knee osteoarthritis is multifactorial and extends beyond simple cartilage wear. Current evidence suggests that the disease involves a complex interaction between mechanical loading, inflammatory mediators, metabolic abnormalities, genetic susceptibility, aging, and joint biomechanics. Degeneration occurs in the entire joint organ, affecting cartilage, subchondral bone, synovium, menisci, ligaments, and periarticular muscles. Chronic low-grade inflammation contributes to the production of cytokines, matrix metalloproteinases, and other catabolic enzymes that accelerate cartilage degradation and structural deterioration. These pathological mechanisms ultimately result in chronic pain, stiffness, reduced mobility, and progressive functional impairment (2,4,5).

Among the biomechanical factors influencing disease onset and progression, anatomical alignment of the lower limb plays a pivotal role. Normal mechanical alignment distributes body weight relatively equally across the medial and lateral compartments of the knee. However, deviations from neutral alignment, including varus and valgus deformities, significantly alter load distribution during standing and walking. Varus malalignment increases compressive forces across the medial compartment, whereas valgus deformity predominantly overloads the lateral compartment. Persistent abnormal loading accelerates cartilage loss, increases subchondral bone remodeling, and promotes compartment-specific progression of osteoarthritis. These biomechanical alterations continue to affect joint health even when inflammation is adequately controlled (3,6).

Conservative management remains the cornerstone of treatment for patients with mild-to-moderate knee osteoarthritis. Current international guidelines recommend a multimodal approach combining patient education, weight reduction, structured exercise therapy, physiotherapy, pharmacological agents, and assistive devices before considering surgical intervention. Pharmacological treatment primarily includes oral and topical nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, duloxetine in selected patients, symptomatic slow-acting drugs for osteoarthritis (SYSADOAs), and intra-articular corticosteroid injections for symptom exacerbations. These therapies primarily aim to reduce pain and improve physical function rather than reverse structural joint damage (7–9).

Despite the widespread use of pharmacological therapy, treatment response among patients with knee osteoarthritis is highly variable. While many patients experience meaningful improvements in pain and daily activities, others continue to have persistent symptoms despite receiving guideline-directed medical treatment. This variability has prompted increasing interest in identifying clinical and biomechanical predictors of therapeutic response. Anatomical alignment has emerged as a potential determinant because abnormal mechanical loading may perpetuate cartilage degeneration and nociceptive stimulation, thereby reducing the effectiveness of pharmacological interventions aimed primarily at controlling inflammation and pain (5,8).

Recent biomechanical and imaging studies have demonstrated that varus malalignment is strongly associated with accelerated medial compartment cartilage loss, narrowing of joint space, meniscal extrusion, and worsening radiographic severity. Similarly, valgus deformity contributes to progressive degeneration of the lateral compartment and impaired joint mechanics. These structural abnormalities may reduce the clinical benefits achieved through conservative management by maintaining excessive mechanical stress despite adequate analgesic therapy. Consequently, patients with malalignment often demonstrate slower functional recovery, persistent pain, and greater progression toward surgical intervention compared with individuals having neutral alignment (6,10).

Assessment of treatment effectiveness in knee osteoarthritis requires reliable and validated outcome measures. The Visual Analog Scale

(VAS) remains one of the most commonly used instruments for measuring pain intensity, whereas the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) evaluates pain, stiffness, and physical function comprehensively. Performance-based measures such as the Timed Up and Go (TUG) test further assess mobility, balance, and overall functional capacity. Together, these instruments provide an objective assessment of therapeutic response and are widely recommended in clinical research evaluating conservative treatment strategies (11).

Growing interest in personalized medicine has shifted attention toward identifying patient-specific characteristics that influence treatment outcomes. Rather than adopting a uniform therapeutic approach, clinicians increasingly recognize the importance of tailoring management according to disease phenotype, biomechanical characteristics, radiographic severity, and functional status. Anatomical alignment represents a readily measurable clinical parameter that may help stratify patients according to expected response to conservative therapy. Early identification of patients with unfavorable alignment may justify the addition of corrective interventions such as unloading braces, customized orthoses, gait modification, targeted strengthening exercises, or corrective osteotomy in selected individuals (12,13).

Although the influence of malalignment on disease progression has been extensively investigated, relatively few studies have specifically examined its effect on pharmacological response following conservative management. Most previous investigations have focused on radiographic progression or biomechanical analyses rather than clinically meaningful improvements in pain and functional recovery. Furthermore, evidence remains limited regarding whether patients with neutral, varus, and valgus alignment demonstrate differential responses to standard pharmacological therapy when combined with routine rehabilitation. Addressing this knowledge gap may improve individualized treatment planning and optimize resource utilization in routine clinical practice (13–15).

Therefore, the present study was designed to evaluate the influence of anatomical alignment on pharmacological response and functional outcomes following conservative management of knee osteoarthritis. It was hypothesized that patients with neutral lower limb alignment would demonstrate greater improvement in pain, physical function, and mobility than patients with varus or valgus malalignment receiving similar conservative pharmacological treatment.

## MATERIALS AND METHODS

This analytical cross-sectional study was conducted in the Department of Orthopedics and Rehabilitation Medicine at a tertiary care teaching hospital from January 2025 to December 2025 to evaluate the influence of anatomical alignment on pharmacological response and functional outcomes following conservative management of knee osteoarthritis. Patients presenting to the orthopedic outpatient department with symptomatic knee osteoarthritis were screened for eligibility, and a total of 180 patients diagnosed with primary knee osteoarthritis according to the American College of Rheumatology (ACR) clinical and radiographic criteria were enrolled using a consecutive sampling technique. The required sample size was calculated using the WHO Sample Size Calculator with a 95% confidence level, 80% study power, an anticipated medium effect size, and a 5% margin of error. The minimum calculated sample size was 171 participants; therefore, 180 patients were recruited to enhance the statistical power and compensate for incomplete data.

Patients aged 40–75 years with radiographically confirmed primary knee osteoarthritis of Kellgren–Lawrence Grades II–IV and symptoms persisting for at least six months were included in the study. Only patients receiving conservative pharmacological management and willing to provide written informed consent were enrolled. Patients with secondary osteoarthritis due to trauma, inflammatory arthritis, infection, congenital deformities, malignancy, previous knee arthroplasty or corrective osteotomy, recent intra-articular corticosteroid or hyaluronic acid injection within the previous three months, severe neurological disorders affecting gait, uncontrolled systemic illnesses, or incomplete clinical records were excluded.

Following informed consent, demographic and clinical information including age, sex, body mass index (BMI), occupation, duration of symptoms, affected knee, and associated comorbidities were recorded using a structured data collection proforma. All participants underwent comprehensive clinical examination and standing weight-bearing anteroposterior radiographs of both lower limbs. Anatomical

alignment was assessed by measuring the hip–knee–ankle (HKA) angle on full-length standing radiographs. Patients were categorized into three groups according to mechanical alignment: varus alignment (HKA angle <180°), neutral alignment (180° ± 2°), and valgus alignment (>180°). Accordingly, 82 patients were classified into the varus group, 46 into the neutral alignment group, and 52 into the valgus alignment group.

All participants received standardized conservative treatment according to institutional guidelines for a period of 12 weeks. Pharmacological management consisted primarily of oral non-steroidal anti-inflammatory drugs (NSAIDs), with paracetamol prescribed either as an alternative or adjunct analgesic where appropriate. Topical NSAIDs and gastroprotective medications were administered whenever clinically indicated. In addition to pharmacological therapy, all patients participated in a structured physiotherapy program that included quadriceps strengthening exercises, range-of-motion exercises, gait training, stretching exercises, and patient education regarding activity modification and weight reduction.

Clinical outcomes were assessed at baseline and after completion of the 12-week treatment period. Pain intensity was measured using the 10-point Visual Analog Scale (VAS). Functional status was evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), which measures pain, stiffness, and physical function, with higher scores indicating greater disability. Functional mobility was assessed using the Timed Up and Go (TUG) test by recording the time required for participants to rise from a chair, walk three meters, turn, return, and sit down. Radiographic severity of osteoarthritis was graded using the Kellgren–Lawrence classification by an experienced musculoskeletal radiologist who was blinded to the clinical findings.

The study protocol was reviewed and approved by the Institutional Review Board/Ethics Committee of the participating institution (Approval No. IRB/2025/017). Written informed consent was obtained from all participants prior to enrollment, and confidentiality of patient information was strictly maintained throughout the study in accordance with the ethical principles outlined in the Declaration of Helsinki.

Data were entered and analyzed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Normality of data distribution was assessed using the Shapiro–Wilk test. Comparisons among the three anatomical alignment groups were performed using one-way analysis of variance (ANOVA) for continuous variables and the Chi-square test or Fisher's exact test for categorical variables. Tukey's post hoc test was applied for pairwise comparisons where appropriate. Multivariable linear regression analysis was performed to identify independent predictors of pharmacological response after adjusting for age, sex, body mass index, duration of symptoms, and Kellgren–Lawrence grade. A p-value of less than 0.05 was considered statistically significant.

## RESULTS

The baseline demographic and clinical characteristics of the study participants are presented in Table 1, showing that the mean age was 58.6 ± 8.9 years, with females constituting the majority (57.8%). Most participants had Kellgren–Lawrence Grade III osteoarthritis (45.6%), and varus alignment (45.6%) was the most common anatomical deformity. Table 2 demonstrates that patients with neutral anatomical alignment experienced significantly greater reductions in pain (VAS), greater improvements in WOMAC scores, and better functional mobility (TUG test) following 12 weeks of conservative management compared with patients having varus or valgus alignment ($p < 0.05$). Table 3 presents the multivariable linear regression analysis, which identified varus alignment as the strongest independent predictor of poorer pharmacological response ($\beta = -0.34$, $p = 0.001$), while higher body mass index, longer symptom duration, advanced radiographic severity, and valgus alignment were also significantly associated with reduced treatment effectiveness. Finally, Table 4 summarizes the overall clinical response, indicating that 66.7% of patients achieved either excellent or good improvement, whereas only 10.0% exhibited a poor response to conservative treatment, with the most favorable outcomes observed among patients with neutral lower limb alignment.

Table 1. Baseline Demographic and Clinical Characteristics of the Study Participants (N = 180)

| Variable | Overall (n=180) |
|---|---|

| | |
|---|---|
| Age (years), Mean ± SD | 58.6 ± 8.9 |
| Male, n (%) | 76 (42.2) |
| Female, n (%) | 104 (57.8) |
| BMI (kg/m²), Mean ± SD | 29.4 ± 3.8 |
| Duration of symptoms (months), Mean ± SD | 22.7 ± 9.6 |
| Right knee affected, n (%) | 97 (53.9) |
| Left knee affected, n (%) | 83 (46.1) |
| Kellgren–Lawrence Grade II, n (%) | 56 (31.1) |
| Kellgren–Lawrence Grade III, n (%) | 82 (45.6) |
| Kellgren–Lawrence Grade IV, n (%) | 42 (23.3) |
| Varus alignment, n (%) | 82 (45.6) |
| Neutral alignment, n (%) | 46 (25.6) |
| Valgus alignment, n (%) | 52 (28.9) |

Table 2. Comparison of Clinical Outcomes According to Anatomical Alignment after 12 Weeks of Conservative Treatment

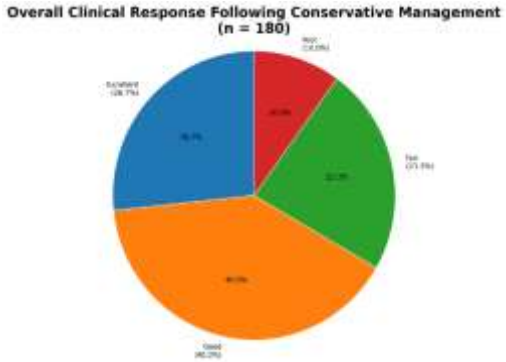
| Outcome | Varus (n=82) | Neutral (n=46) | Valgus (n=52) | p-value |
|---|---|---|---|---|
| Baseline VAS | 7.6 ± 0.9 | 7.4 ± 1.0 | 7.5 ± 1.0 | 0.611 |
| Final VAS | 5.2 ± 1.0 | 3.6 ± 0.9 | 4.8 ± 1.1 | <0.001 |
| VAS reduction | 2.4 ± 1.0 | 3.8 ± 1.1 | 2.7 ± 1.2 | <0.001 |
| Baseline WOMAC | 63.5 ± 8.6 | 61.9 ± 8.3 | 62.7 ± 8.4 | 0.572 |
| Final WOMAC | 47.8 ± 7.2 | 37.4 ± 6.5 | 45.6 ± 7.0 | <0.001 |
| WOMAC improvement (%) | 24.8 | 39.6 | 27.3 | 0.002 |
| Baseline TUG (sec) | 12.6 ± 2.4 | 12.3 ± 2.5 | 12.5 ± 2.6 | 0.834 |
| Final TUG (sec) | 11.1 ± 2.0 | 9.8 ± 2.1 | 10.8 ± 2.2 | 0.004 |

Table 3. Multivariable Linear Regression Analysis of Predictors of Pharmacological Response (VAS Improvement)

| Variable | β Coefficient | Standard Error | p-value |
|---|---|---|---|
| Age | -0.11 | 0.04 | 0.078 |
| Female sex | -0.06 | 0.18 | 0.324 |
| BMI | -0.18 | 0.05 | 0.018 |
| Duration of symptoms | -0.13 | 0.04 | 0.046 |
| Kellgren–Lawrence Grade IV | -0.29 | 0.17 | 0.002 |
| Varus alignment | -0.34 | 0.12 | 0.001 |
| Valgus alignment | -0.16 | 0.10 | 0.041 |

Table 4. Overall Treatment Response after Conservative Management

| Clinical Response | n (%) |
|---|---|
| Excellent (>50% improvement) | 48 (26.7) |
| Good (30–50% improvement) | 72 (40.0) |
| Fair (15–29% improvement) | 42 (23.3) |
| Poor (<15% improvement) | 18 (10.0) |



E-ISSN 2250-0944
ISSN 2250-1150
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## DISCUSSION

The present study evaluated the influence of anatomical alignment on pharmacological response and functional outcomes following conservative management of knee osteoarthritis. The findings demonstrated that patients with neutral lower limb alignment experienced significantly greater reductions in pain, better functional recovery, and superior mobility compared with those exhibiting varus or valgus malalignment. Furthermore, varus alignment emerged as the strongest independent predictor of poorer pharmacological response after adjusting for age, body mass index, symptom duration, and radiographic severity. These findings emphasize that biomechanical factors substantially influence treatment outcomes even when standardized pharmacological therapy is administered.

Knee osteoarthritis is increasingly recognized as a disease involving both biological and biomechanical mechanisms rather than cartilage degeneration alone. Contemporary evidence suggests that persistent abnormal mechanical loading accelerates structural joint damage and may limit the effectiveness of pharmacological interventions designed primarily to reduce inflammation and pain (2,3). Our findings support this concept, as patients with neutral alignment showed significantly greater improvements in VAS, WOMAC, and TUG scores than those with malalignment, indicating that favorable biomechanics enhance the clinical benefits of conservative therapy.

The poorer outcomes observed among patients with varus deformity are consistent with the established biomechanical understanding of medial compartment overload. Varus alignment increases compressive forces across the medial tibiofemoral compartment, promoting progressive cartilage loss, meniscal degeneration, subchondral bone remodeling, and persistent nociceptive stimulation. Consequently, analgesic and anti-inflammatory medications alone may be insufficient to overcome the continuing mechanical stress experienced by these patients (6,10). Similar observations have been reported in recent longitudinal studies demonstrating faster disease progression and greater functional deterioration in patients with varus malalignment despite receiving guideline-based conservative management (16,17).

Although valgus malalignment demonstrated comparatively better outcomes than varus deformity, functional recovery remained significantly inferior to that observed in patients with neutral alignment. Lateral compartment overload associated with valgus deformity contributes to progressive cartilage degeneration and altered gait mechanics, which may explain the reduced response to pharmacological treatment. These findings suggest that both varus and valgus deformities negatively influence conservative treatment outcomes, although the magnitude of impairment appears greater in varus knees because of the higher physiological load borne by the medial compartment during normal ambulation (10,16).

Multivariable regression analysis identified higher body mass index, longer symptom duration, advanced Kellgren–Lawrence grade, and anatomical malalignment as independent predictors of poorer treatment response. These observations are biologically plausible because obesity increases mechanical loading while simultaneously promoting systemic inflammation through adipokine production. Similarly, advanced radiographic disease reflects irreversible structural damage that may limit functional improvement despite adequate symptom control (1,13). Recent clinical investigations have likewise identified obesity and disease severity as major determinants of conservative treatment failure and progression toward joint replacement (17,18).

The present findings have important clinical implications. Routine assessment of lower limb anatomical alignment should be incorporated into the initial evaluation of patients with knee osteoarthritis to facilitate individualized treatment planning. Patients exhibiting significant malalignment may benefit from combining pharmacological therapy with biomechanical interventions such as unloading knee braces, customized orthoses, gait retraining, targeted physiotherapy, weight reduction, and, in selected cases, corrective osteotomy. Such an integrated approach may improve pain control, preserve joint function, and delay the need for total knee arthroplasty (8,12,19).

### Strengths and Limitations

The strengths of this study include standardized conservative treatment protocols, objective radiographic assessment of anatomical alignment, utilization of validated functional outcome measures (VAS, WOMAC, and TUG), and multivariable statistical analysis to control for potential confounding variables. Nevertheless, several limitations should be

acknowledged. The cross-sectional analytical design limits causal inference, the follow-up period of 12 weeks was relatively short for evaluating long-term structural progression, and the study was conducted at a single center, which may limit the generalizability of the findings. Future multicenter prospective studies with longer follow-up periods and advanced gait analysis are recommended to further clarify the interaction between biomechanics and pharmacological response in knee osteoarthritis.

## CONCLUSION

Overall, the findings of this study reinforce the concept that successful conservative management of knee osteoarthritis requires consideration of both pharmacological and biomechanical factors. Incorporating anatomical alignment into routine clinical decision-making may improve patient stratification, optimize individualized treatment strategies, and enhance long-term functional outcomes.

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