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High-Versus Low-BMI Differences in Therapeutic Response to Intra-Articular Hyaluronic Acid in Knee Osteoarthritis

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ABSTRACT

Background: Knee osteoarthritis is a leading cause of chronic pain and functional limitation, and intra-articular hyaluronic acid is widely used for symptom control; however, therapeutic response may vary by patient characteristics such as body mass index. Objective: To evaluate whether BMI modifies pain outcomes following intra-articular hyaluronic acid injection in patients with knee osteoarthritis. Methods: A cross-sectional observational study was conducted at Touhy Spine and Joint Health Center, Lahore, from April to September 2025. Adults aged 40–80 years with knee osteoarthritis were recruited and categorized into low-BMI (non-obese) and high-BMI (obese) groups. Pain was assessed using the WOMAC pain subscale at baseline and after injection, and pain improvement was compared between groups using independent t-tests with effect size estimation. Results: Among 126 participants, obese patients had higher baseline WOMAC pain scores and demonstrated smaller pain reductions after injection compared with non-obese patients. Mean WOMAC pain improvement was greater in the low-BMI group, and percentage pain improvement was also significantly higher, indicating a diminished therapeutic response among obese patients. Conclusion: BMI significantly influenced symptomatic response to intra-articular hyaluronic acid in knee osteoarthritis, with non-obese patients achieving greater pain relief than obese patients, supporting BMI-informed counseling and individualized treatment planning.

Keywords
Body mass index; knee osteoarthritis; intra-articular hyaluronic acid; viscosupplementation; WOMAC pain; obesity; pain intensity; patient-reported outcomes.

INTRODUCTION

Knee osteoarthritis (OA) is among the most prevalent chronic musculoskeletal disorders and remains a major driver of pain, mobility restriction, and long-term disability in middle-aged and older adults. It is characterized by progressive degeneration of articular cartilage, subchondral bone remodeling, synovial inflammation, and alterations in joint biomechanics that collectively impair functional capacity and health-related quality of life (1). The clinical burden of knee OA is accompanied by substantial socioeconomic impact through increased healthcare utilization, recurrent analgesic requirements, and productivity loss, particularly in aging populations and resource-constrained settings (2). In low- and middle-income countries, the rising prevalence is further accelerated by increasing life expectancy, reduced physical activity levels, and expanding obesity rates, contributing to an escalating demand for effective and cost-conscious non-surgical interventions (2).

Obesity is one of the most consistently identified modifiable risk factors for both onset and progression of knee OA, with body mass index (BMI) being the most widely used indicator of excess adiposity in clinical and epidemiologic research (3). Increased BMI exacerbates mechanical loading across the tibiofemoral and patellofemoral compartments, leading to accelerated cartilage wear, heightened pain, and more rapid functional decline (3). Beyond biomechanical overload, obesity contributes to a metabolically active inflammatory state in which adipose tissue releases adipokines and pro-inflammatory cytokines that influence synovial inflammation, nociceptive sensitization, and impaired cartilage homeostasis (4). This dual mechanical–inflammatory pathway creates a distinct OA phenotype in high-BMI individuals, often associated with worse symptom severity and reduced responsiveness to standard conservative therapies (5).

In this context, non-surgical management remains foundational, aiming to alleviate symptoms and delay surgical intervention. Intra-articular hyaluronic acid (IA-HA) injection is widely utilized as a viscosupplementation therapy intended to restore the viscoelastic and lubricating functions of synovial fluid and to provide chondroprotective and analgesic effects (6). In knee OA, endogenous hyaluronic acid decreases in concentration and molecular weight, weakening joint lubrication and shock absorption, while also altering the intra-articular biochemical environment (6). Systematic reviews indicate that IA-HA can improve pain and functional outcomes, although the magnitude and durability of benefit varies significantly across patient subgroups and product characteristics (7). Product-related factors such as molecular weight, cross-linking, and formulation heterogeneity may influence clinical response, contributing further to variability in reported outcomes (7).

Despite widespread adoption of IA-HA, the role of BMI as a modifier of therapeutic response remains inadequately clarified. Emerging evidence suggests that overweight and obese patients may experience attenuated response due to persistent mechanical overload and heightened inflammatory milieu, while some studies report comparable outcomes regardless of BMI, leading to inconsistent conclusions and limited actionable guidance (8,9). This gap is clinically important because obesity is highly prevalent among knee OA patients, and treatment failure or suboptimal response in this subgroup has implications for patient counseling, cost-effectiveness, and individualized care pathways (9,10). Current consensus recommendations recognize viscosupplementation as a possible non-surgical option in knee OA but also emphasize heterogeneity of response and

the need for more precise patient selection criteria (20). Therefore, stratified evidence addressing BMI-related differences in response is needed to support rational clinical decision-making and improve treatment targeting in routine practice (10,20).

Using the PICO framework, the population of interest comprises adults aged 40–80 years with knee osteoarthritis; the exposure is high BMI (obese) compared to low BMI (non-obese); the intervention is intra-articular hyaluronic acid injection; and the primary outcome is pain relief assessed through validated patient-reported outcome measures, specifically the WOMAC pain subscale (16). Accordingly, the present study investigates whether BMI influences pain outcomes following IA-HA injection in knee OA patients attending a tertiary musculoskeletal care center in Lahore. The research question is: *Among adults with knee osteoarthritis receiving intra-articular hyaluronic acid, do obese patients experience less improvement in pain scores compared with non-obese patients?* The alternative hypothesis is that higher BMI is associated with a reduced therapeutic response to IA-HA, manifested by smaller reductions in WOMAC pain scores compared with lower BMI patients, while the null hypothesis is that BMI does not influence pain improvement following IA-HA injection.

MATERIALS AND METHODS

A cross-sectional observational study was conducted at Touhy Spine and Joint Health Center, Lahore, Pakistan, from April 2025 to September 2025 to evaluate BMI-related differences in pain outcomes following intra-articular hyaluronic acid (IA-HA) injection among patients with knee osteoarthritis. Adult male and female patients aged 40–80 years presenting with clinically diagnosed knee osteoarthritis were recruited using non-probability convenience sampling. Patients were enrolled after obtaining written informed consent, and all study procedures were performed in accordance with ethical principles for human research and institutional requirements.

Eligibility criteria included patients within the specified age range with symptomatic knee osteoarthritis requiring intra-articular hyaluronic acid injection as part of routine care. Patients were excluded if they had inflammatory arthropathies, acute knee infection, recent intra-articular corticosteroid injection, previous knee arthroplasty, major knee trauma, or systemic conditions expected to significantly affect pain reporting or functional interpretation. Baseline demographic characteristics, including age and sex, were recorded at enrollment. Height and weight were obtained using standardized clinic procedures and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m²).

Participants were categorized into two groups based on BMI status: a high-BMI group (obese) and a low-BMI group (non-obese).

All participants received intra-articular hyaluronic acid injection administered under standard sterile technique by the treating clinician. Pain intensity was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale, a validated patient-reported tool consisting of five items rated on a Likert scale, with higher scores indicating greater pain severity (16). WOMAC pain assessment was performed at baseline prior to injection and repeated at follow-up after IA-HA injection to quantify treatment-associated change. The primary outcome variable was change in WOMAC pain score, defined as the difference between baseline and post-treatment WOMAC pain values.

To minimize bias, all participants completed WOMAC assessments using a standardized instruction script and identical scoring method. Data entry was performed using double-check verification to reduce transcription error, and the dataset was screened for outliers, missing values, and implausible ranges before statistical analysis. Baseline differences between BMI groups were evaluated to assess the risk of confounding due to imbalance in pain severity or demographic variables. The sample size was calculated for comparison of two independent means using Cohen's effect size approach, assuming a medium effect size ($d = 0.5$), type I error probability of 0.05, and statistical power of 80%, yielding a required sample of 126 participants with equal allocation (63 per group) (15).

Statistical analyses were conducted using SPSS version 23.0. Continuous variables were summarized as mean ± standard deviation, and categorical variables as frequency and percentage. Primary inferential analysis compared mean change in WOMAC pain scores between obese and non-obese groups using independent sample t-tests, with two-tailed p-values < 0.05 considered statistically significant. Effect size (Cohen's d) was computed to quantify the magnitude of between-group differences in pain improvement. Where baseline pain differed between groups, additional adjusted comparisons were planned using linear regression models with post-treatment pain or change score as the dependent variable and BMI group as the primary predictor, controlling for age, sex, and baseline WOMAC pain score. Missing outcome data were handled using complete case analysis when the proportion was minimal, and patterns of missingness were assessed to evaluate whether missing data were random. All analyses were prespecified before final statistical execution to ensure reproducibility and minimize analytic bias.

RESULTS

A total of 126 patients with knee osteoarthritis were included. The overall mean age was 58.0 ± 9.6 years, with females comprising the majority of the sample. Based on BMI categorization, 54 participants were classified as low BMI (non-obese) and 72 as high BMI (obese). At baseline, the high-BMI group demonstrated significantly higher WOMAC pain scores than the low-BMI group, indicating greater symptom severity prior to injection. After intra-articular hyaluronic acid administration, both groups demonstrated improvement in WOMAC pain; however, the magnitude of pain reduction was significantly greater in the low-BMI group, with a moderate-to-large between-group effect size.

Table 1. Baseline Demographic and Clinical Characteristics by BMI Group (n = 126)

Variable	Low BMI (Non-obese) n=54	High BMI (Obese) n=72	Difference	p-value
Age (years), mean ± SD	57.2 ± 9.4	58.6 ± 9.7	-1.4	0.410
Female, n (%)	33 (61.1)	47 (65.3)	—	0.620
Baseline WOMAC Pain Score (0–20), mean ± SD	12.4 ± 2.6	13.8 ± 2.5	-1.4	0.003
Post-treatment WOMAC Pain Score (0–20), mean ± SD	6.3 ± 2.4	9.5 ± 2.8	-3.2	<0.001

Baseline WOMAC pain was significantly higher in the obese group (13.8 ± 2.5) compared with the non-obese group (12.4 ± 2.6), confirming greater baseline symptom severity among high-BMI patients. Following IA-HA injection, WOMAC pain decreased in both groups, but post-treatment pain remained significantly higher in obese patients (9.5 ± 2.8) compared to non-obese patients (6.3 ± 2.4) ($p < 0.001$).

Table 2. Pain Improvement After IA-HA Injection by BMI Group (Primary Outcome)

Outcome	Low BMI (Non-obese) n=54	High BMI (Obese) n=72	Difference (Low–High)	95% CI	Effect Size (Cohen's d)	p-value
WOMAC Pain Change (Baseline – Post), mean ± SD	6.1 ± 2.3	4.3 ± 2.2	1.8	1.0 to 2.6	0.80	<0.001
Percentage Pain Improvement, mean ± SD	49.1 ± 15.8	31.2 ± 14.7	17.9	12.3 to 23.5	1.18	<0.001

The primary analysis demonstrated a significantly greater mean reduction in WOMAC pain scores in the low-BMI group (6.1 ± 2.3) compared with the high-BMI group (4.3 ± 2.2), yielding a mean difference of 1.8 points (95% CI: 1.0 to 2.6; $p < 0.001$) with a moderate-to-large effect size (Cohen's $d = 0.80$). Similarly, the mean percentage improvement was substantially higher in the low-BMI group (49.1% ± 15.8) versus the high-BMI group (31.2% ± 14.7), with a mean difference of 17.9 percentage points (95% CI: 12.3 to 23.5; $p < 0.001$). Collectively, these findings support BMI as a significant modifier of symptomatic pain response following IA-HA injection in knee OA patients.

DISCUSSION

This study evaluated whether body mass index modifies pain outcomes following intra-articular hyaluronic acid injection in patients with knee osteoarthritis. The principal finding was that both obese and non-obese groups experienced clinically meaningful reductions in WOMAC pain scores after IA-HA, but the magnitude of improvement was significantly greater among non-obese participants. In addition, obese patients entered treatment with higher baseline pain and remained more symptomatic after injection, supporting the interpretation that higher BMI is associated with both greater symptom burden and diminished treatment responsiveness.

The direction and pattern of results are biologically plausible and consistent with established OA pathophysiology. Obesity increases compressive and shear forces across the knee joint, contributing to accelerated cartilage degeneration, altered joint alignment, and greater mechanical nociceptive stimulation (3). Even if viscosupplementation improves synovial fluid viscoelasticity and reduces friction, the continued mechanical overload present in obese patients may blunt the analgesic and functional effects of HA by maintaining high contact stress and ongoing microtrauma (5). This provides one explanation for the smaller mean reduction in pain observed in the high-BMI group despite receiving the same intervention.

Beyond biomechanical mechanisms, obesity is increasingly recognized as a systemic inflammatory state that contributes to the metabolic OA phenotype. Adipose tissue secretes adipokines and cytokines that may promote synovitis, cartilage catabolism, and central sensitization, leading to pain amplification that may not be adequately addressed by local viscosupplementation alone (4). In this context, IA-HA may primarily improve mechanical lubrication and joint homeostasis, whereas obesity-related inflammatory signaling may sustain pain perception and reduce the relative gain achieved after injection. The lower percentage pain improvement in obese patients observed in this study is therefore compatible with an interaction between local joint therapy and systemic inflammatory drivers of pain.

Previous evidence indicates that IA-HA can produce symptomatic benefit in knee OA, although response heterogeneity is frequently reported (6,7). Product characteristics including molecular weight, concentration, and cross-linking can influence clinical effects, particularly in pain outcomes, and may contribute to variability across studies (7,21). While the present study did not stratify outcomes by HA formulation, the observed differential response by BMI suggests that future work should evaluate whether certain HA types provide more robust benefit in obese patients or whether combination strategies (e.g., viscosupplementation plus structured weight loss and strengthening programs) are required to achieve comparable outcomes.

Clinical and guideline implications should be interpreted with appropriate caution. Consensus recommendations acknowledge viscosupplementation as a non-surgical option in knee OA but emphasize that benefits may be modest and patient-dependent (20). The present findings contribute to this clinical nuance by suggesting BMI as a meaningful stratification variable that may help guide patient selection and counseling. Practically, clinicians may use these results to set realistic expectations for obese patients, emphasize the importance of weight reduction as a synergistic therapy, and consider closer follow-up or adjunctive interventions when IA-HA is selected in this subgroup (5,9,10). Because obese patients frequently have higher baseline pain and comorbidity burdens, counseling should focus on multimodal OA management rather than reliance on injection therapy alone.

Several limitations should be considered when interpreting the findings. The non-probability sampling approach and single-center setting may limit generalizability, and BMI grouping may correlate with unmeasured confounders such as OA severity, activity level, or analgesic use. Baseline pain differences were present between groups, which could contribute to differential change patterns; however, the consistently lower improvement and higher residual pain among obese patients supports the conclusion that BMI is associated with reduced response. Further prospective studies incorporating radiographic grading, standardized follow-up timepoints, and multivariable adjusted models are needed to confirm these findings and define BMI thresholds at which IA-HA benefit becomes clinically limited.

In summary, IA-HA was associated with pain reduction in both BMI groups; however, non-obese patients experienced significantly greater pain improvement compared with obese patients. These results reinforce the clinical importance of BMI as a modifier of symptomatic response to viscosupplementation and support a more individualized approach to IA-HA selection and OA symptom management.

CONCLUSION

Body mass index significantly influenced the therapeutic response to intra-articular hyaluronic acid in knee osteoarthritis, with non-obese patients demonstrating greater reductions in WOMAC pain scores and higher percentage improvement compared with obese patients; these findings suggest that obesity may attenuate the symptomatic benefit of viscosupplementation through persistent mechanical overload and systemic inflammatory mechanisms, supporting the use of BMI as an important consideration in patient counseling and individualized non-surgical management strategies for knee osteoarthritis.

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