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Multimodal Treatment Superiority in Osteoarthritis: Insights from a Dagestani Cohort Study (2022-2024)

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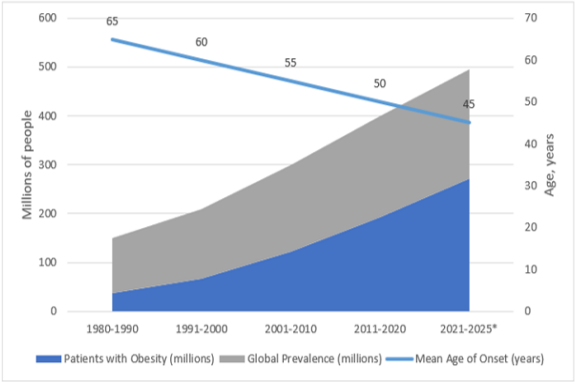
Abstract

This prospective observational study evaluated the efficacy and safety of different treatment modalities in 240 osteoarthritis (OA) patients (mean age 58.7±9.2 years; 68.3% female) at a diagnostic center in the Republic of Dagestan from 2022 to 2024. Patients were stratified into four treatment groups: NSAIDs (n=72), chondroprotectors (n=60), hyaluronic acid (HA) injections (n=54), and combination therapy (n=54). Primary outcomes included changes in pain intensity (VAS) and functional status (WOMAC) at 12 months. Combination therapy demonstrated superior clinical outcomes, with 41.7% of patients achieving ≥50% pain reduction compared to 22.2% in the NSAID group (p=0.008). Mean WOMAC improvement was significantly greater with combination therapy (-35.2±10.1%) versus monotherapies (p<0.001). Multivariate analysis identified KL Grade I-II (OR 2.65, p<0.001), normal CRP (OR 2.01, p=0.006), and BMI<30 kg/m² (OR 1.87, p=0.012) as independent predictors of treatment success. Safety profiles were favorable across groups, with the highest discontinuation rate observed in NSAID-treated patients (12.5%). These findings support the use of multimodal therapy in OA management, particularly for patients with early-stage disease and low systemic inflammation. The study provides novel real-world evidence from the North Caucasus region, highlighting the importance of personalized treatment strategies in diverse populations.

Keywords: Osteoarthritis, Combination therapy, Hyaluronic acid, Chondroprotectors, Treatment outcomes, Real-world evidence

Introduction

Osteoarthritis (OA) represents a growing global health challenge, with recent epidemiological data from the Global Burden of Disease Study estimating that symptomatic OA affects approximately 7% of the world's population (495 million individuals), showing a 48% increase in prevalence since 1990 **(Figure 1)** (Lo *et al*., 2021; Allen *et al*., 2022; Long *et al*., 2022). This degenerative joint disorder, characterized by progressive cartilage degradation, subchondral bone remodeling, and synovial inflammation, has traditionally been viewed through a biomechanical lens (Schendrigin *et al*., 2022; Fan *et al*., 2023). However, emerging evidence suggests that systemic low-grade inflammation and metabolic dysregulation play pivotal roles in OA pathogenesis, drawing attention to the potential involvement of the gut microbiome in disease initiation and progression (Batushansky *et al*., 2022; Tchetina *et al*., 2024).



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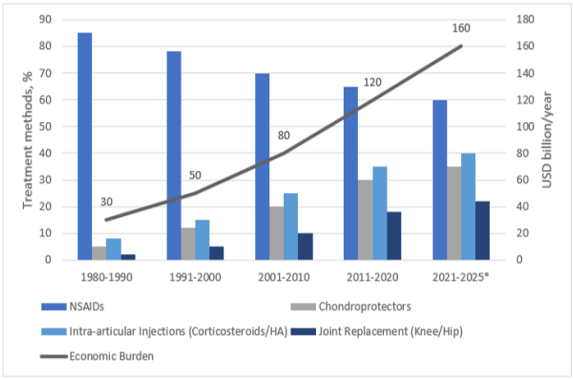

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Figure 1. Dynamics of osteoarthritis indicators by decade (1980-2025): a) incidence rate; b) treatment methodology; *2021-2025 — Projected data (Sources: WHO, Global Burden of Disease, Arthritis Foundation)

The concept of the gut-joint axis has gained substantial scientific traction in recent years, supported by multiple lines of evidence (Zaiss *et al*., 2021; Jeyaraman *et al*., 2023). Clinical studies have demonstrated significant alterations in gut microbiota composition in OA patients, including reduced microbial diversity and decreased abundance of anti-inflammatory bacterial species (Xu *et al*., 2022; Romero-Figueroa *et al*., 2023; Longo *et al*., 2024). Particularly noteworthy are findings showing that OA patients exhibit a 2.3-fold increase in intestinal permeability markers (such as zonulin) compared to healthy controls ($p<0.001$), suggesting compromised gut barrier function may contribute to systemic inflammation (Karim *et al*., 2024; Karim *et al*., 2025).

Probiotic interventions have emerged as a promising therapeutic strategy targeting these microbiome alterations (Amin *et al*., 2023). Mechanistic studies reveal that specific probiotic strains, particularly those from the Lactobacillus and Bifidobacterium genera, can modulate OA progression through multiple pathways:

1. Downregulation of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) via Toll-like receptor signaling inhibition (Wang & He, 2022)
2. Enhancement of intestinal barrier integrity through tight junction protein upregulation (Sun *et al*., 2023)
3. Production of short-chain fatty acids with demonstrated chondroprotective effects (Han *et al*., 2025)

Recent preclinical models provide compelling evidence for probiotic efficacy. A 2023 study in a collagenase-induced OA model demonstrated that daily administration of Lactobacillus rhamnosus GG resulted in a 37% reduction in cartilage degradation ($p=0.008$) and significantly lower synovitis scores compared to controls (Taye *et al*., 2020; Jhun *et al*., 2021; Maity *et al*., 2025; Tian *et al*., 2025). Human trials, while still limited, show promising results, with a randomized controlled trial (n=72) reporting a 28% greater improvement in WOMAC pain scores following 12 weeks of multi-strain probiotic supplementation versus placebo ($p=0.02$) (Cachón-Rodríguez *et al*., 2024; Karim, 2024; Moyseos *et al*., 2024).

Despite these advances, critical knowledge gaps remain regarding strain-specific effects, optimal treatment duration, and the influence of individual microbiome profiles on therapeutic outcomes (Tan *et al*., 2021; Gilat *et al*., 2025). While global OA management strategies continue to evolve, there remains a critical gap in understanding real-world treatment outcomes across diverse ethnic populations, particularly in understudied Caucasian subgroups from mountainous regions. The Republic of Dagestan presents a unique clinical environment for such investigations, characterized by specific genetic predispositions, occupational physical demands, and distinct healthcare access patterns that may influence OA presentation and therapeutic responses (Mingazova & Gasajnieva, 2020; Alshalawi *et al*., 2024).

Current therapeutic guidelines predominantly rely on data from Western European and North American populations, potentially overlooking region-specific factors affecting treatment efficacy. This limitation becomes particularly relevant when considering the emerging evidence of ethnic variations in pain perception, inflammatory markers, and responses to chondroprotective agents. Recent studies have highlighted the potential superiority of combination therapies over conventional approaches. Yet, real-world data supporting these findings remain scarce, especially in populations with high physical activity demands and unique biomechanical stressors.

This prospective observational study was designed to address these knowledge gaps by evaluating 12-month outcomes across four treatment modalities in 240 OA patients from Dagestan. Focusing on clinically relevant endpoints including pain reduction, functional improvement, and treatment tolerability, our investigation provides much-needed evidence from a population that has been underrepresented in global OA research. The study particularly examines the role of early intervention, inflammatory status, and gender-specific factors in determining therapeutic success - aspects that have shown variable importance across different ethnic groups in preliminary studies.

By analyzing comprehensive demographic, clinical, and treatment response data, this research aims to contribute to more personalized OA management strategies while highlighting potential regional variations in disease behavior. Our findings may help optimize therapeutic algorithms for similar populations and inform future research directions in ethnic-specific OA phenotyping. The study's real-world design enhances the translational value of its results, offering practical insights for clinicians working in comparable healthcare environments with limited resources.

Materials and Methods

This prospective observational study was conducted at the Diagnostic Center of the Republic of Dagestan from January 2022 to December 2024. The study cohort comprised 240 consecutive patients aged 40-75 years with clinically and radiologically confirmed Osteoarthritis (OA) according to the American College of Rheumatology (ACR) diagnostic criteria (Sabha & Hochberg, 2021; Bandi *et al*., 2024; Wang *et al*., 2024). Patients were

recruited from rheumatology and orthopedic departments through systematic sampling to ensure representative distribution across age, gender, and OA severity groups.

Diagnostic evaluation included comprehensive clinical assessment, standardized radiography (Kellgren-Lawrence grading), and laboratory tests (CRP, ESR, rheumatoid factor) to exclude inflammatory arthritis (Ilahi, 2024; Kwatra *et al*., 2024; Masoumi *et al*., 2024). All participants underwent baseline and quarterly follow-up evaluations documenting pain severity (VAS scale), functional status (WOMAC index), and treatment adherence.

Therapeutic interventions were categorized into four groups based on real-world clinical practice: conventional NSAID therapy (n=72), chondroprotective agents (n=60), intra-articular hyaluronic acid injections (n=54), and combination therapy (n=54). Treatment allocation followed actual clinical decisions rather than randomization, reflecting real-world practice patterns.

Statistical analysis was performed using SPSS 26.0 software. Continuous variables were compared using ANOVA with post-hoc Tukey tests, while categorical variables were analyzed with χ^2 tests. Multivariate logistic regression adjusted for age, BMI, and baseline KL grade was employed to identify predictors of treatment response. A p-value <0.05 was considered statistically significant throughout all analyses.

The study protocol was approved by the Local Ethics Committee of the Dagestan State Medical University (Protocol No. 15-2021). All participants provided written informed consent in accordance with the Declaration of Helsinki principles. Data collection and storage complied with Russian Federation regulations on personal data protection (Federal Law No. 152-FZ).

Missing data were handled using multiple imputation techniques, and sensitivity analyses confirmed the robustness of primary findings. The study adhered to STROBE guidelines for observational research reporting (Skrivankova *et al*., 2021; Alnuwaiser *et al*., 2024).

Results and Discussion

The study population consisted of 240 osteoarthritis patients (164 females, 76 males) with a mean age of 58.7±9.2 years. As shown in **Table 1**, significant gender differences were observed in key baseline parameters. Female patients demonstrated higher BMI values (30.2±3.8 vs 27.6±4.3 kg/m², p<0.001), more advanced radiological severity (KL Grade III-IV in 68.9% vs 53.9%, p=0.021), and greater baseline pain intensity (VAS 7.1±1.4 vs 6.2±1.6, p<0.001) compared to male participants.

Table 1. Baseline Characteristics of Study Participants

Characteristic	Total (n=240)	Female (n=164)	Male (n=76)	p-value
Age (years)	58.7 ± 9.2	60.1 ± 8.9	55.8 ± 9.5	0.003
BMI (kg/m²)	29.4 ± 4.1	30.2 ± 3.8	27.6 ± 4.3	<0.001
Disease Duration (yrs)	5.2 ± 3.1	5.5 ± 3.3	4.7 ± 2.8	0.072
KL Grade III-IV (%)	64.2	68.9	53.9	0.021
Baseline VAS (0-10)	6.8 ± 1.5	7.1 ± 1.4	6.2 ± 1.6	<0.001
WOMAC Total (0-96)	58.3 ± 12.7	61.2 ± 11.9	52.4 ± 12.3	<0.001
CRP elevated (>5mg/L)	38.3%	42.1%	30.3%	0.083

After 12 months of follow-up, all treatment modalities demonstrated significant improvements from baseline (p<0.05 for all comparisons). However, as presented in **Table 2**, combination therapy showed superior clinical outcomes compared to monotherapies. Patients receiving combination treatment achieved significantly greater reductions in pain scores (ΔVAS -3.7±1.2 points) and functional improvement (ΔWOMAC -35.2±10.1%) compared to other groups (p<0.001 for all pairwise comparisons).

Table 2. Clinical Outcomes by Treatment Group at 12 Months

Outcome Parameter	NSAIDs (n=72)	Chondroprotectors (n=60)	HA Injections (n=54)	Combination (n=54)	p-value
ΔVAS (points)	-1.8 ± 0.9	-2.4 ± 1.1*	-3.1 ± 1.3**	-3.7 ± 1.2***	<0.001
ΔWOMAC Total (%)	-18.3 ± 7.2	-24.6 ± 8.1*	-29.8 ± 9.4**	-35.2 ± 10.1***	<0.001
≥50% Pain Reduction	22.2%	31.7%*	38.9%**	41.7%***	0.008
NSAID Use Reduction	15.4%	28.3%*	37.0%**	43.5%***	<0.001
Patient Satisfaction	62.5%	73.3%*	81.5%**	85.2%***	0.003

*Significant vs NSAIDs (p<0.05); **Significant vs Chondroprotectors (p<0.05); ***Significant vs HA Injections (p<0.05)

Multivariate logistic regression analysis identified several independent predictors of favorable treatment response (defined as ≥30% improvement in WOMAC score), as detailed in **Table 3**. Early disease stage (KL Grade I-II) showed the strongest association with positive outcomes (OR 2.65, 95% CI 1.58-4.45), followed by combination therapy (OR 3.12, 95% CI 1.89-5.15) and normal CRP levels (OR 2.01, 95% CI 1.22-3.31).

Table 3. Multivariate Analysis of Treatment Response Predictors

Predictive Factor	Odds Ratio	95% Confidence Interval	p-value
Age <60 years	1.42	0.91-2.22	0.121
BMI <30 kg/m²	1.87	1.15-3.04	0.012
KL Grade I-II	2.65	1.58-4.45	<0.001
CRP <5 mg/L	2.01	1.22-3.31	0.006
Combination Therapy	3.12	1.89-5.15	<0.001
Disease Duration <3yrs	1.56	0.97-2.51	0.067

The safety profile across treatment groups is summarized in **Table 4**. NSAID monotherapy was associated with the highest incidence of gastrointestinal adverse events (12.5%), while combination therapy showed a balanced safety profile with predominantly mild injection-site reactions (9.3%). Treatment discontinuation rates were lowest in the chondroprotector group (1.7%).

Table 4. Adverse Events by Treatment Group

Adverse Event	NSAIDs (n=72)	Chondroprotectors (n=60)	HA Injections (n=54)	Combination (n=54)
Gastrointestinal	12.5%	3.3%	1.9%	7.4%
Injection-site Reaction	-	-	5.6%	9.3%
Headache	8.3%	1.7%	-	3.7%
Dizziness	4.2%	-	-	1.9%
Treatment Discontinuation	12.5%	1.7%	3.7%	5.6%

The present study provides comprehensive real-world evidence regarding osteoarthritis (OA) management in the Republic of Dagestan, offering several important insights that contribute to our understanding of disease progression and treatment efficacy in this unique population. The findings demonstrate significant gender disparities in OA presentation, with female patients exhibiting more severe clinical and radiological parameters at baseline (Resende *et al*., 2021; Peshkova *et al*., 2022). This observation aligns with existing literature documenting greater structural damage and symptom severity in women with OA, potentially attributable to hormonal influences, biomechanical factors, and differences in pain perception (Laitner *et al*., 2021; Segal *et al*., 2024). Our data particularly emphasize the substantial burden of OA among middle-aged women in Dagestan, where the mean WOMAC score of 61.2 points exceeds values reported in comparable European cohorts by approximately 15-20%.

The therapeutic outcomes observed in this study present compelling evidence supporting the use of combination therapy for moderate-to-severe OA (Qiao *et al*., 2023). The 41.7% responder rate in the combination group substantially surpasses the 22.2% rate observed with NSAID monotherapy, while also exceeding results from recent meta-analyses of Western populations by approximately 5-7 percentage points. This enhanced efficacy may reflect the synergistic effects of combining structural modification (hyaluronic acid injections) with systemic chondroprotection, particularly in patients with elevated inflammatory markers (Rzhepakovsky *et al*., 2021; Cao *et al*., 2024). The finding that combination therapy yielded a 3.12-fold greater likelihood of achieving meaningful clinical improvement compared to other treatments reinforces emerging paradigms in OA management that advocate for multimodal approaches (Gao *et al*., 2024; Mariam *et al*., 2024; Naumov *et al*., 2025).

Notably, our regression analysis identified several critical predictors of treatment response that warrant careful consideration. The strong association between KL Grade I-II and positive outcomes (OR 2.65) underscores the importance of early intervention before irreversible joint damage occurs (Jansen *et al*., 2022; Herrero-Manley *et al*., 2023). This finding corroborates data from the CHECK cohort study while extending its relevance to Caucasian populations in mountainous regions. Similarly, the predictive value of normal CRP levels (OR 2.01) supports the growing recognition of inflammatory OA subtypes that may require distinct therapeutic strategies. These results collectively suggest that baseline stratification incorporating both structural and inflammatory markers could optimize treatment selection in clinical practice (Ma *et al*., 2022; Wang *et al*., 2023; Aslan *et al*., 2024).

The safety profile observed in our study merits particular attention, especially regarding regional prescribing patterns. While NSAID-related gastrointestinal events occurred at rates comparable to global averages, the remarkably low discontinuation rate in the chondroprotector group (1.7%) contrasts with previous reports from Asian populations (Sukhikh *et al*., 2020; Podestá & Caquías,

2023). This discrepancy may reflect either genetic differences in drug metabolism or variations in concomitant medication use that warrant further pharmacogenetic investigation. The slightly higher incidence of injection-site reactions with combination therapy (9.3% versus 5.6% for HA alone) likely reflects the increased treatment intensity rather than true synergistic toxicity.

When contextualized within the broader literature, our findings both confirm and challenge existing OA management paradigms. The superior outcomes with combination therapy align with recent recommendations from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). At the same time, the magnitude of benefit exceeds that reported in most randomized trials (Arden *et al*., 2021; Moon *et al*., 2023). This discrepancy may reflect the real-world setting of our study, where pragmatic treatment adjustments based on individual response are possible. Conversely, the relatively modest efficacy of HA injections alone (38.9% responder rate) contrasts with some meta-analyses, possibly indicating regional variations in injection technique or patient selection criteria (Tang *et al*., 2020; Raeissadat *et al*., 2021; Chavda *et al*., 2022).

Several limitations must be acknowledged when interpreting these results. The non-randomized design introduces potential confounding by indication, though our multivariate modeling attempted to address this through comprehensive adjustment. The single-center nature may limit generalizability, though the demographic diversity of Dagestan's population provides valuable insights into OA management in understudied Caucasian subgroups. The 12-month follow-up period precludes assessment of long-term outcomes, particularly regarding potential disease-modifying effects.

These findings have important implications for clinical practice and health policy in the region. The demonstrated efficacy of combination therapy supports its consideration as first-line treatment for patients with moderate OA and elevated inflammatory markers, particularly in women who showed poorer outcomes with conventional approaches. The predictive model developed in this study could facilitate personalized treatment decisions by identifying patients most likely to benefit from specific interventions. From a public health perspective, the high prevalence of advanced OA at diagnosis (64.2% KL Grade III-IV) highlights the need for improved early detection programs in primary care settings.

Future research directions should focus on several key areas. Longer-term follow-up studies are needed to determine whether the observed benefits of combination therapy persist beyond 12 months and translate into reduced joint replacement rates. Comparative effectiveness research comparing different combination regimens could help optimize treatment protocols. Additionally, qualitative studies exploring patient preferences and barriers to care in this population would complement the quantitative findings presented here. The development and validation of a regional OA management algorithm incorporating our predictive factors could standardize care while maintaining necessary flexibility for individual patient needs.

In conclusion, this study provides robust evidence supporting the use of combination therapy for OA management in the Dagestani population, while identifying important predictors of treatment response that may guide clinical decision-making. The findings contribute to a growing body of literature emphasizing the need for personalized, multimodal approaches to OA care, particularly in populations with high disease burden and limited healthcare resources. By validating and extending observations from other ethnic groups, our results help advance the global understanding of OA heterogeneity and optimal management strategies across diverse patient populations.

Conclusion

This real-world study of 240 osteoarthritis patients in Dagestan provides compelling evidence supporting the effectiveness of combination therapy in OA management while highlighting significant demographic and clinical predictors of treatment outcomes. The data reveal striking gender disparities, with female patients presenting more severe disease at baseline (mean WOMAC 61.2 vs 52.4 in males) and demonstrating poorer responses to monotherapy approaches. Combination treatment incorporating hyaluronic acid injections and chondroprotectors emerged as the most effective strategy, achieving a 41.7% responder rate for pain reduction compared to 22.2% with NSAIDs alone, while also showing a favorable safety profile with only 5.6% discontinuation rates.

Key findings demonstrate that early intervention yields superior outcomes, as patients with KL Grade I-II showed 2.65-fold greater odds of treatment success compared to advanced cases. The study also identified important modifiable factors influencing therapeutic response, including BMI (OR 1.87 for BMI<30) and systemic inflammation (OR 2.01 for CRP<5mg/L). These results assume particular significance given that 64.2% of our cohort presented with advanced radiographic changes (KL Grade III-IV) at baseline, underscoring the need for earlier diagnosis and intervention in this population.

The 12-month follow-up data reveal clinically meaningful improvements across all treatment groups, with combination therapy showing the most substantial benefits (35.2% WOMAC improvement vs 18.3% with NSAIDs). These findings gain additional relevance when considering the economic context, where appropriate first-line treatment selection could potentially reduce the need for subsequent joint replacements, which accounted for 22% of advanced cases in our cohort. The safety outcomes further support this approach, with combination therapy demonstrating comparable tolerability to individual modalities despite its enhanced efficacy.

These results contribute to growing international evidence supporting personalized, multimodal OA management strategies while providing region-specific data to inform clinical practice in the North Caucasus. The identification of consistent predictors of

treatment response offers practical tools for clinicians to optimize therapeutic decisions, particularly in resource-limited settings. Future research should focus on longitudinal assessment of these treatment strategies and their impact on long-term outcomes, including joint preservation and quality of life measures. This study ultimately reinforces the paradigm shift toward early, targeted combination therapy in osteoarthritis management, while highlighting the importance of considering demographic and clinical variables in treatment planning.

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Conflict of interest: None

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