International Journal of Research and Review
[Indexed, Peer-Reviewed Journal]
Volume 13; Issue: 6; June 2026
Website: www.ijrrjournal.com
Research Paper *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

The Differences in Cartilaginous Oligomeric Matrix Protein Levels and Womac Scores in Knee OA Patients 3 Months After Mesenchymal Stem Cell Secretome Injection Compared with Hyaluronic Acid Injection

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DOI: https://doi.org/10.52403/ijrr.20260652

ABSTRACT

Current management of knee osteoarthritis (OA) remains limited in its ability to halt disease progression. Emerging regenerative therapies, particularly mesenchymal stem cell (MSC)-derived secretome injections, aim to reduce joint degeneration and delay the need for knee arthroplasty. This study aimed to compare the clinical and biochemical outcomes of intra-articular MSC secretome injections versus hyaluronic acid (HA) viscosupplementation in patients with grade II–III knee OA. A prospective cohort study was conducted involving 37 patients diagnosed with grade II–III knee OA. Participants were allocated into two groups based on treatment received: intra-articular hyaluronic acid or MSC secretome injection. Clinical outcomes were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), while biochemical changes were evaluated by measuring synovial fluid cartilaginous oligomeric matrix protein (COMP) levels. Assessments were performed at baseline and 3 months post-intervention. Statistical analysis was conducted using SPSS version 29.0. Both groups demonstrated improvement in clinical and biochemical parameters; however, patients receiving MSC secretome injections showed a significantly greater reduction in WOMAC scores and synovial COMP levels compared to the hyaluronic acid group ($p < 0.05$). Intra-articular MSC secretome injections resulted in superior clinical and biochemical outcomes compared to hyaluronic acid in patients with grade II–III knee osteoarthritis. These findings suggest that MSC secretome may serve as a promising regenerative therapy to alleviate symptoms and potentially slow disease progression.

Keywords: COMP level, hyaluronic acid, MSC secretome, Osteoarthritis, WOMAC score

INTRODUCTION

Osteoarthritis (OA) of the knee is a degenerative joint disease that is a global health burden with a cumulative prevalence reaching 16.0% in the population aged over 15 years and increasing to 22.9% in the population aged over 40 years [1]. This disease begins with damage to the articular cartilage, followed by progressive degeneration of the cartilage, hypertrophy and remodeling of the subchondral bone,

and secondary inflammation of the knee synovial membrane [2]. Osteoarthritis grades 2 and 3 are intermediate degrees characterized by marked joint space narrowing, osteophyte formation, and the beginning of significant structural changes in the subchondral bone. At this stage, patients experience mechanical pain, joint stiffness, and varying functional limitations. Therefore, the management of OA grades 2 and 3 is carried out through conservative therapy and pharmacology. A comprehensive understanding of the disease course at each stage is crucial to determine the optimal treatment strategy, prevent disease progression, and improve patient clinical outcomes.

Based on the 2021 American Academy of Orthopaedic Surgeons (AAOS) guidelines, intra-articular hyaluronic acid (HA) injection is a non-operative treatment modality for mild to moderate knee OA [3]. HA injection functions as a viscosupplement that plays a role in chondroprotection and proteoglycan synthesis, thereby improving joint function, relieving pain, and reducing the need for pain medication [4]. As regenerative therapies develop, the secretome of mesenchymal stem cells (MSCs) is attracting attention as a potential non-cellular approach to addressing the pathogenic processes of OA. The secretome is a collection of bioactive molecules, including cytokines, growth factors, extracellular matrix proteins, and extracellular vesicles, released by MSCs into the extracellular environment and capable of modulating the joint tissue microenvironment. Various studies have shown that secretome has anti-inflammatory, anti-catabolic, and pro-anabolic effects on degenerating joint tissue in OA, with the ability to suppress inflammatory pathways triggered by TNF-α and IL-1β cytokines and reduce the activity of matrix degradation enzymes such as metalloproteinases. In addition, secretome has been shown to increase the expression of genes and proteins involved in cartilage matrix synthesis, such as COL2A1, aggrecan, and SOX9, which are important in the regeneration and maintenance of chondrocyte phenotype in vitro [5,6]. Secretome has the advantage of overcoming the shortcomings of cell-based therapies, such as unwanted differentiation and the potential activation of allogeneic immune responses, while its therapeutic effect depends on the ability to reach target cells and deliver genetic material, growth factors, and immunomodulators [6]. Cartilage Oligomeric Matrix Protein (COMP) plays a crucial role in cell proliferation and apoptosis as well as in the regulation of cell movement and attachment in cartilage tissue, so serum COMP levels can be used as a diagnostic marker for OA while providing prognostic information for patients at risk of developing joint disease [7].

Several studies have been conducted on the administration of MSC secretome or hyaluronic acid to patients with grade 2 and 3 knee OA in various regions, but the results have been inconsistent. This prompted researchers to observe the effects of both exposures and their outcomes, particularly on synovial fluid COMP levels and WOMAC scores in knee OA patients three months after injection.

MATERIALS & METHODS

Research Design

This is an observational analytical study with a prospective cohort study design. The independent variables, exposure to intra-articular injection of MSC and HA secretome, were not administered by the researchers but were obtained from medical records. Outcome data, including COMP levels and WOMAC scores at three months, were collected based on these medical records. The study was conducted at Ngoerah Hospital, Denpasar, from July 2025 to December 2025.

Study Population

The target population of this study was grade 2 and 3 knee OA patients who had received exposure in the form of intra-articular injection of MSC and HA secretome. The accessible population was knee OA patients with such exposure whose data were obtained from the medical records of the Orthopedic and Traumatology Polyclinic of Ngoerah Hospital in the period July 2025 to December 2025. The study sample was taken from the accessible population that met the inclusion and exclusion criteria, using a consecutive sampling technique, with all data of subjects who met the criteria included until the minimum sample size was met. The minimum sample size was calculated using an unpaired numerical analytical formula with a type I error of 5% and a type II error of 20%, resulting in 11.3, which was rounded up to 12 subjects per group; an additional 10% to anticipate drop-outs resulted in a sample size of 14 subjects per group with a total of 28 samples.

Eligibility Criteria

The inclusion criteria for this study included patients with grade 2 and 3 primary knee OA based on the American College of Rheumatology clinical and radiological diagnostic criteria, aged 40 to 70 years, and patients who agreed to have their data included in the study. Exclusion criteria included patients with knee joint deformities due to trauma, congenital knee joint deformities, patients who refused to participate in the study, and incomplete medical records.

Research Variables

The independent variables in this study were exposure in the form of intra-articular injection of MSC secretome and intra-articular injection of HA. The dependent variables were the COMP levels of knee synovial fluid and the WOMAC score assessed three months after the injection based on medical record data review. Confounding variables included patient age, gender, obesity, congenital deformity of the knee joint, and corticosteroid use, which were controlled through the application of strict inclusion and exclusion criteria. The degree of knee OA was assessed based on radiographic examination according to the Kellgren-Lawrence criteria, with grade 2 indicating joint space narrowing and minimal osteophytes, while grade 3 indicated moderate multiple osteophytes, marked joint space narrowing, sclerosis, and possible bone contour deformity. The WOMAC score was assessed based on three domains: pain, joint stiffness, and physical function, with a score range of 0 to 96 indicating the severity of knee joint symptoms. COMP levels of synovial fluid were measured using an ELISA technique with a Quantikine kit from R&D System, Inc., catalog number DCMP0, at the Clinical Laboratory of the Faculty of Medicine, Udayana University.

Data Collection Procedure

All grade 2 and 3 knee OA patients at the Orthopedic Polyclinic of Prof. Dr. I.G.N.G. Ngoerah General Hospital between July 2025 and December 2025 who met the inclusion and exclusion criteria were used as the study sample. Initial data in the form of serum COMP levels and knee plain radiographs were collected from medical records. Patients received knee OA therapy management in the form of MSC secretome injections in the treatment group and HA injections in the control group. The second data collection was carried out at a three-month follow-up after the injection through examination of joint fluid COMP levels and WOMAC scores, and then the data were collected for statistical analysis.

Data Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 29.0. Descriptive analysis was performed to determine the proportion and baseline characteristics of patients in each group. Numerical data are presented as

means and standard deviations if normally distributed, or medians and ranges if not normally distributed, while categorical data are presented as percentages. Data normality testing was performed using the Shapiro-Wilk test because the sample size was less than 50. Hypothesis analysis for unpaired numerical data between two groups was performed using the independent t-test if the data were normally distributed, and the Mann-Whitney test if the data were not normally distributed.

RESULT

Sample Characteristics

Characteristics of grade 2 and 3 OA patients who received intra-articular HA injection were found to be male (4 people) (20.0%) and female (16 people) (80.0%), with an average age of 59.65 ± 7.42 years. In the group of patients who received intra-articular MSC secretome injection, there were 3 males (17.6%) and 14 females (82.4%) with an average age of 58.88 ± 7.63 years. The age group of patients who received intra-articular HA injection was found to be 2 patients (10%) aged 40-50 years, 8 patients (40%) aged 51-60 years, and 10 patients (50%) aged >60 years. The age group of patients who received intra-articular injection of MSC secretome was found to be 3 patients (17.6%) in the 40-50 years age group, 7 patients (41.2%) in the 51-60 years age group, and 7 patients (41.2%) in the >60 years age group. The group of patients who received intra-articular injection of HA was found to be 12 patients (60%) with the right foot and 8 patients (40%) with the left foot. The group of patients who received intra-articular injection of MSC secretome was found to be 12 patients (60%) with the right foot and 8 patients (40%) with the left foot. The group of patients who received intra-articular injection of HA was found to be 10 patients (50%) with OA grade 2, and 10 patients (50%). The group of patients who received intra-articular injection of MSC secretome was found to be 9 patients (52.9%) with OA grade 2 and 8 patients (47.1%). In the groups of patients who received intra-articular HA injections and those who received intra-articular MSC secretome injections, there were no significant differences in age (years) or gender. Patient characteristics are shown in Table 1.

Table 1. Patient Characteristics

Characteristic	Total n=37 (%)	HA n=20 (%)	Secretome MSC n=17 (%)	P-value
Sex				0.855*
Male	7 (18.9)	4 (20.0)	3 (17.6)	
Female	30 (81.1)	16 (80.0)	14 (82.4)	
Age group				0.556*
40–50 years	5 (13.5)	2 (10.0)	3 (17.6)	
51–60 years	15 (40.5)	8 (40.0)	7 (41.2)	
> 60 years	17 (45.9)	10 (50.0)	7 (41.2)	
Affected side				0.942*
Right	22 (59.5)	12 (60.0)	10 (58.8)	
Left	15 (40.5)	8 (40.0)	7 (41.2)	
Osteoarthritis grade				0.855*
Grade 2	19 (51.4)	10 (50.0)	9 (52.9)	
Grade 3	18 (48.6)	10 (50.0)	8 (47.1)	
Age, years (mean ± SD)	59.29 ± 7.42	59.65 ± 7.42	58.88 ± 7.63	0.759**

**Chi-square test, **Independent t-test, HA: hyaluronic acid; MSC: mesenchymal stem cell; SD: standard deviation.*

Analysis of differences in COMP levels in knee synovial fluid between patients receiving MSC and HA secretome injections

The mean COMP levels in patients receiving intra-articular HA injections were higher than those in the group receiving intra-articular MSC secretome injections.

Furthermore, Levene's heterogeneity test showed homogeneity (p=0.299). A parametric independent t-test revealed a statistically significant difference in mean COMP levels between the HA and MSC secretome injections (p<0.001). The results are presented in Table 2.

Table 2. Comparison of Synovial Fluid COMP Levels Between Groups

Patient group	Mean ± SD (ng/mL)	p-value	Mean Difference (95% CI)
HA (n=20)	1546.92 ± 486.18	<0.001	555.86 (255.69–856.03)
Secretome MSC (n=17)	991.05 ± 398.46		

Independent t-test; SD: standard deviation; CI: confidence interval; COMP: Cartilage Oligomeric Matrix Protein; HA: hyaluronic acid; MSC: mesenchymal stem cell.

Analysis of WOMAC Score Differences between Patients Who Received MSC and HA Secretome Injections

The mean WOMAC score in patients receiving intra-articular HA injection was higher than in the group receiving intra-articular MSC secretome injection. Furthermore, Levene's heterogeneity test showed heterogeneity (p < 0.001). The parametric independent t-test showed a statistically significant difference in the mean WOMAC score between the HA and MSC secretome injection groups (p=<0.001). The results are presented in Table 3.

Table 3. Comparison of WOMAC Scores Between Groups

Patient group	Mean ± SD	p-value	Mean Difference (95% CI)
HA (n=20)	54.45 ± 12.85	<0.001	38.50 (32.19–44.81)
Secretome MSC (n=17)	15.94 ± 4.26		

Independent t-test; SD: standard deviation; CI: confidence interval; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; HA: hyaluronic acid; MSC: mesenchymal stem cell.

DISCUSSION

This study involved 37 subjects with grade 2 and 3 knee OA who received MSC or HA secretome injections at Ngoerah General Hospital, consisting of 20 patients in the HA group and 17 patients in the MSC secretome group. There were no statistically significant differences in the mean or proportion of age, gender, side of knee pain, and OA grade characteristics between the two groups of subjects, so that control of confounding variables carried out through strict inclusion and exclusion criteria can be said to have succeeded in forming an equivalent comparison group.

The results of the parametric independent t-test showed a significant difference (p<0.001) in joint fluid COMP levels between patients receiving MSC and HA secretome injections, with COMP levels tending to be lower in the MSC secretome group. The increase in COMP levels can be interpreted as an indicator of a more significant cartilage degradation process, which may be caused by a longer period of inflammation. These results are in line with the findings of Partan et al. who reported significant differences in MMP-3 and TGF-β1 biomarkers between patients receiving repeated injections of MSC and HA secretome, with modulation of inflammation and cartilage tissue repair in the form of a decrease in MMP-3 as a catabolic enzyme related to cartilage matrix degradation and an increase in TGF-β1 as a growth factor that supports regeneration [8]. MSC secretome was also found to trigger an increase in TGF-β1, aggrecan, SOX-9, and type II collagen levels, which are key components of the cartilage repair pathway [8]. The potential of MSC secretome in enhancing cartilage regeneration and reducing joint inflammation is also supported by the study of D'arrigo et al. and Klaymook et al., who reported that MSCs increased proteoglycan synthesis and

reduced levels of cartilage-damaging metalloproteinases [5,6], and Giannasi et al., who encouraged clinical consideration of the use of MSC secretome injections to reduce the risk of further cartilage damage [9]. An animal study by Lubis et al., which compared secretome injection groups in sheep, also showed significantly better microscopic and macroscopic OARSI scores compared to the hyaluronic acid group [10]. Conversely, the higher COMP levels in the HA group in this study are in line with the findings of Gonzalez-Fuentes et al., who reported that intra-articular HA injections significantly and continuously increased levels of cartilage breakdown biomarkers during follow-up [11], thus highlighting the differences in effectiveness between viscogenic and biologic therapies in treating cartilage degeneration in knee OA.

The WOMAC score analysis showed a significant difference between the two groups, with either lower or better scores in the MSC secretome group ($p<0.001$). The WOMAC score is used to assess pain, stiffness, and physical function in knee OA patients, making it an important indicator in assessing the effectiveness of therapy. A study by Partan et al. showed that patients who received MSC secretome injections earlier had better long-term clinical outcomes, although knee function improvement at three months between the two groups was not significantly different [8,12]. A similar pattern was also shown by Kim et al., who found superior clinical improvement in the HA group in the first three months, but functional scores of MSC patients were significantly better than HA at one-year follow-up [13]. However, some meta-analyses of MSC therapy in OA also reported that the superiority of MSCs over controls was not always consistent and was influenced by heterogeneity in cell source, dose, and OA severity in the studied population [14]. The findings of this study showed a significant difference in pain and functional symptom improvement within three months of therapy, which supports the importance of selecting the right therapy according to the patient's condition.

The main strength of this study lies in the equivalence of baseline characteristics between the two comparison groups, achieved through strict inclusion and exclusion criteria, thus minimizing potential bias due to confounding variables such as age, gender, and OA severity. This study has two main limitations: the relatively small sample size in each group and the limited follow-up duration of three months, which makes it impossible to describe the long-term course of clinical outcomes and cartilage biomarkers.

CONCLUSION

This study showed a statistically significant difference in knee synovial fluid COMP levels and WOMAC scores between grade 2 and 3 knee OA patients who received intra-articular injection of MSC secretome compared to HA injection at the third month, with the MSC secretome group showing lower COMP levels and WOMAC scores; therefore, examination of joint fluid COMP levels can be considered as a parameter for assessing the condition of the knee OA joint in addition to functional scores such as WOMAC, and further studies with a larger sample size and longer follow-up duration are needed to confirm the relationship between COMP levels and WOMAC scores and strengthen the understanding of this biomarker as an indicator of prognosis and functional recovery of knee OA patients.

Declaration by Authors

Ethical Approval: Approved

Acknowledgement: We express our deepest gratitude to all parties for their support of this study.

Source of Funding: All funding was provided by the authors without external sources.

Conflict of Interest: No conflicts of interest declared.

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How to cite this article: Andrew Sutheno, I Gusti Ngurah Wien Aryana, Made Bramantya Karna. The differences in cartilaginous oligomeric matrix protein levels and Womac scores in knee OA patients 3 months after mesenchymal stem cell secretome injection compared with hyaluronic acid injection. *International Journal of Research and Review*. 2026; 13(6): 542-548. DOI: *https://doi.org/10.52403/ijrr.20260652*

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