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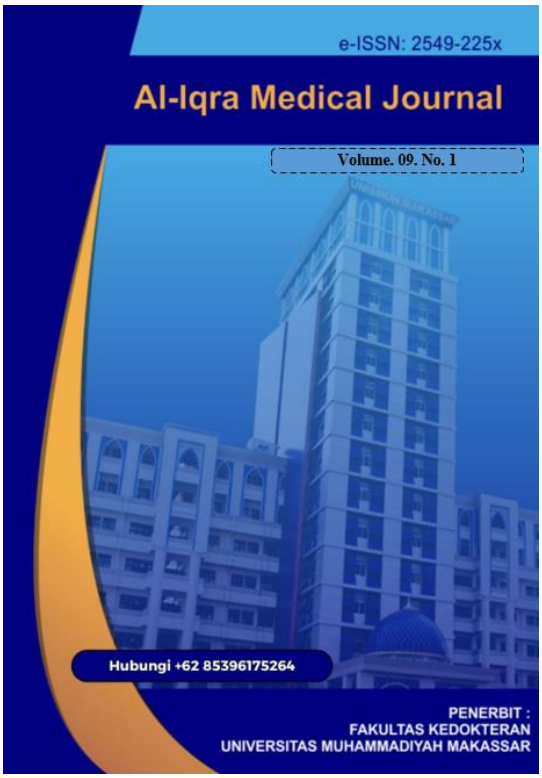

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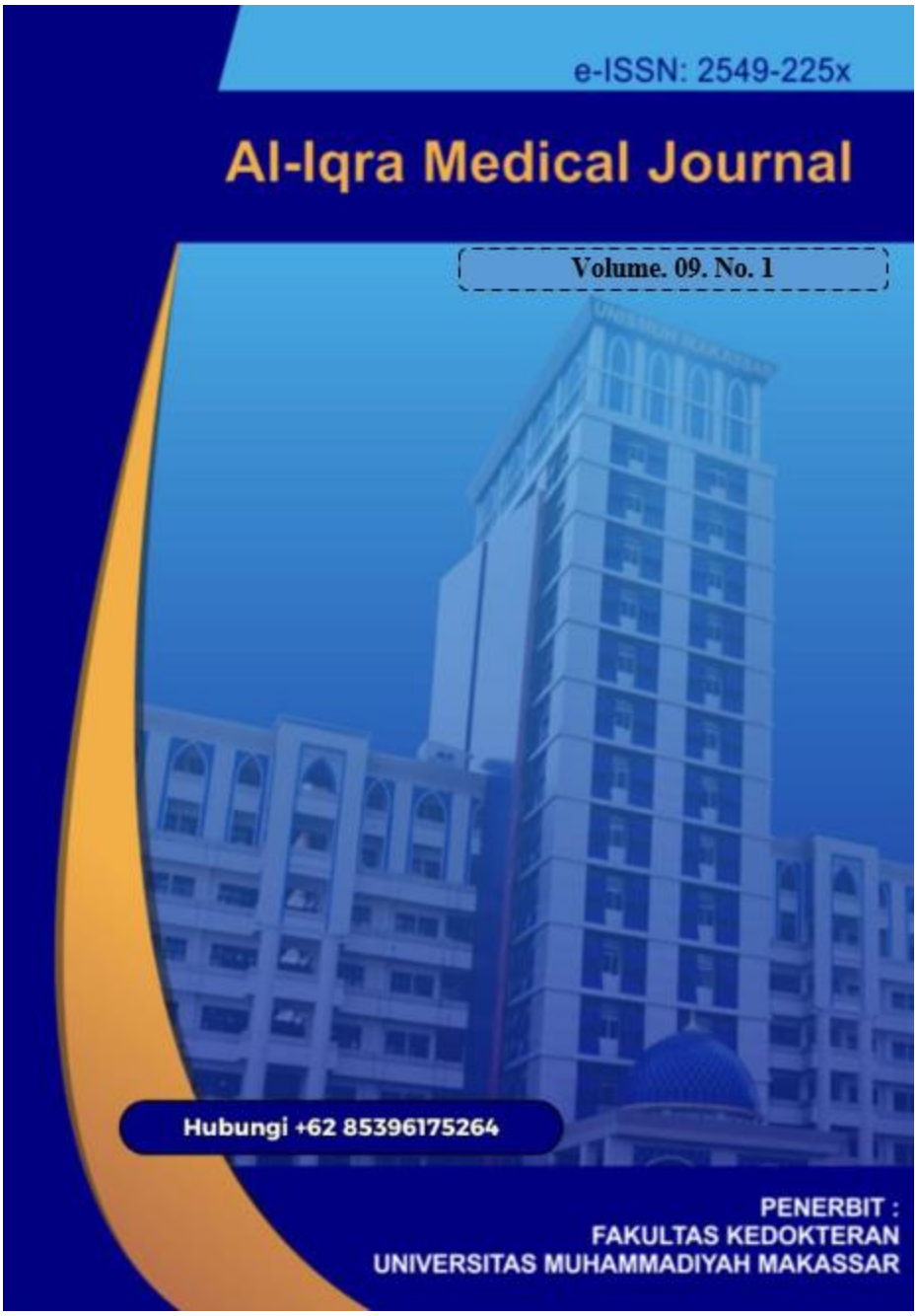

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EFFECT OF INTRAMUSCULAR SECRETOME ON TREATMENT RESPONSE IN TYPE 2 DIABETES MELLITUS PATIENTS

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Abstract

Introduction: This study meant to evaluate the efficacy of intramuscular mesenchymal stem cell derived secretome therapy to improve the glycemic control among diabetic patients with Type 2 Diabetes Mellitus (T2DM) on stable insulin or oral hypoglycemic agents (OHO). n=30 per group (Insulin + Secretome; OHO + Secretome). Methods: Pre–post controlled design; biweekly 2 mL intramuscular secretome for 12 weeks; primary outcomes HbA1c, FBG, 2hPP; standard tests per normality. Participants were divided into two groups: Insulin + Secretome and OHO + Secretome. All subjects received intramuscular injections of mesenchymal stem cell (MSC)-derived secretome (2 mL) every two weeks over a 12-week period (six injections total). Primary outcomes included changes in HbA1c, fasting blood glucose (FBG), and two-hour postprandial glucose (2hPPBG). Statistical analyses used paired t-tests or Wilcoxon tests for within-group comparisons and independent t-tests or Mann-Whitney U tests for between-group comparisons. Results: At baseline, both groups had comparable HbA1c and glucose profiles. After 12 weeks, significant reductions were observed in both treatment arms. HbA1c decreased by -1.10 ± 0.45 (Insulin) and -1.33 ± 0.36 (OHO); between-group ΔHbA1c ($p < 0.05$). Both groups also showed clinically relevant reductions in FBG and 2hPPBG levels. No major adverse effects were reported. Conclusion: Intramuscular MSC-secretome improved glycemic control across background therapies; benefit modestly greater with OHO. No major adverse events were observed.

Keywords: Secretome, Type 2 Diabetes Mellitus, HbA1c, Insulin, Oral Hypoglycemic Agents.

Abstrak

Pendahuluan: Penelitian ini adalah untuk mengevaluasi efikasi terapi sekretom yang berasal dari sel punca mesenkimal secara intramuskular dalam meningkatkan kendali glikemik pada pasien diabetes melitus tipe 2 yang berada pada terapi insulin stabil atau obat hipoglikemik oral. n = 30 per kelompok (Insulin + Secretome; OHO + Secretome). Metode: Desain terkontrol pre–post; pemberian sekretom intramuskular 2 mL setiap dua minggu selama 12 minggu; luaran primer HbA1c, glukosa darah puasa (FBG), dan glukosa dua jam postprandial. Peserta dibagi menjadi dua kelompok: Insulin + Secretome dan OHO + Secretome. Semua subjek menerima injeksi intramuskular sekretom turunan MSC (2 mL) setiap dua minggu selama 12 minggu (total enam injeksi). Luaran primer mencakup perubahan HbA1c, FBG, dan 2hPPBG. Analisis statistik menggunakan uji t berpasangan atau uji Wilcoxon untuk perbandingan dalam-kelompok dan uji t independen atau Mann–Whitney U untuk perbandingan antar-kelompok. Hasil: Pada baseline, kedua kelompok memiliki profil HbA1c dan glukosa yang sebanding. Setelah 12 minggu, penurunan bermakna terlihat pada kedua lengan terapi. HbA1c menurun sebesar −1.10 ± 0.45 (Insulin) dan −1.33 ± 0.36 (OHO); ΔHbA1c antar-kelompok bermakna ($p < 0.05$). Kedua kelompok juga menunjukkan penurunan yang bermakna secara klinis pada FBG dan 2hPPBG. Tidak ada efek samping signifikan yang dilaporkan. Kesimpulan: Sekretom MSC intramuskular memperbaiki kendali glikemik pada berbagai terapi; manfaatnya sedikit lebih besar pada kelompok OHO. Tidak ditemukan kejadian merugikan yang signifikan.

Kata Kunci : Secretome, Diabetes Melitus Tipe 2, HbA1c, Insulin, Obat Hipoglikemik Oral

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disease characterized primarily by persistent hyperglycemia resulted from compromised the secretion of insulin, insulin insensitivity, or a combination of both conditions. [1] The global prevalence of T2DM continues to rise sharply, making it a significant public health challenge. Chronic hyperglycemia in T2DM is associated with various macrovascular and microvascular complications, substantially reducing patients' quality of life and increasing morbidity and mortality risks. [2]

Effective management of T2DM commonly involves oral hypoglycemic agents and insulin therapy. However, despite current pharmacological treatments, many patients still struggle to achieve optimal glycemic control and experience disease progression, suggesting the necessity of adjunctive therapies aimed at improving metabolic outcomes and limiting complications.[3] Persistent hyperglycemia exacerbates oxidative stress and systemic inflammation, negatively impacting insulin sensitivity, pancreatic beta-cell function, and vascular integrity, thereby increasing the risk of cardiovascular events, nephropathy, retinopathy, and neuropathy.[4]

One promising novel therapeutic strategy that has emerged recently involves utilizing the mesenchymal stem cell (MSC)-secretome, a bioactive product containing growth factors, cytokines, extracellular vesicles, and other soluble molecules secreted by mesenchymal stem cells. [5] The MSC-secretome has demonstrated significant therapeutic potential, including anti-inflammatory, antioxidative, pro-angiogenic, and immunomodulatory effects, and has been considered an effective approach for treating degenerative and chronic inflammatory conditions, including diabetes mellitus. [6,7]

Previous research indicates that MSC-secretome can improve glucose metabolism, increase insulin sensitivity, and lower systemic inflammatory response in diabetic animal models. [8,9] Studies by Sari et al. (2024) and Trigo et al. (2024) reported that MSC-secretome administration effectively alleviated oxidative stress, preserved pancreatic beta-cell function, and improved vascular endothelial integrity, suggesting its therapeutic potential in managing T2DM complications.[10–12] However, limited previous studies have evaluated the effects of MSC-secretome administration on glycemic control, insulin requirements, and treatment response in T2DM patients undergoing different therapeutic regimens, such as insulin or oral hypoglycemic agents.

The present research aims to evaluate the effects of intramuscular injection of MSC-secretome on glucose status and metabolic responses in T2DM patients managed with insulin or oral antidiabetic drugs. Specifically, this research aims to: (to evaluate the efficacy of MSC-secretome in enhancing glycemic control indicators, particularly HbA1c, fasting blood glucose (FBG) and 2-hour postprandial blood glucose (2hPPBG) (2hPPBG) in T2DM patients; (b) compare the response differences between insulin-treated and oral hypoglycemic agent-treated patient groups following MSC-secretome treatment; and (c) explore the potential of MSC-secretome as an adjunctive therapy for enhancing diabetes treatment outcomes and mitigating diabetes-related metabolic complications.

METHODS

This study employed a clinical experimental design using a pre-post control group approach to evaluate the effect of intramuscular secretome administration on treatment response in patients with Type 2 Diabetes Mellitus (T2DM). Participants were

stratified into two groups based on their current diabetes treatment regimen. The first group consisted of patients who had been receiving insulin therapy, while the second group included patients who had been treated with oral hypoglycemic agents (OHO). All participants received intramuscular injections of mesenchymal stem cell-derived secretome every two weeks for a total period of twelve weeks, resulting in six injections per subject. The type and dosage of their ongoing antidiabetic medication (either insulin or OHO) remained unchanged throughout the intervention period unless clinically indicated otherwise. Participants were instructed to maintain their usual diet and physical activity throughout the 12-week intervention; these behaviors were not prospectively quantified and are acknowledged as potential confounders.

The study population comprised patients with confirmed T2DM diagnoses who were undergoing routine follow-up at Naura Medika Clinic, SMC clinic and Hopkins Clinic in Jakarta. Participants were selected using purposive sampling techniques. The inclusion criteria were as follows: adult patients between 30 and 65 years old, with a confirmed diagnosis of T2DM for at least one year, a baseline HbA1c level of 7% or higher, and stable diabetes treatment (either insulin or OHO) for a minimum of three months prior to the study. Only patients who willingly provided written informed consent were enrolled in the study. Exclusion criteria involved patients diagnosed with type 1 diabetes mellitus (T1DM), those with serious chronic conditions such as stage 4–5 chronic kidney disease, congestive heart failure, chronic liver disease, or a history of stroke. Additional exclusions included pregnant or breastfeeding women, individuals with acute or chronic infections, and those with a known allergy to biological products such as stem cell derivatives.

To ensure adequate statistical power, a minimum of 30 participants were enrolled in each group, making a total of at least 60 subjects. This sample size was based on prior estimations of effect size and variability from existing literature on similar interventions. Normality was evaluated using the Shapiro–Wilk test per variable and per group at each time point and for Δ values (post–pre).

The intervention consisted of intramuscular delivery of mesenchymal stem cell–derived secretome (MSC-secretome), which was produced in a standardized and sterile process following Good Manufacturing Practice (GMP) protocols. Each injection contained 2 milliliters of MSC-secretome, and the injections were administered alternately in the gluteal or deltoid muscles. All injections were performed by trained medical professionals under sterile conditions. Participants continued their baseline diabetes therapy (insulin or oral agents) throughout the study period without modifications, unless clinical evaluation necessitated adjustment.

Subjects were divided into two parallel intervention groups based on their previous treatment. The first was the "Insulin + Secretome" group, in which patients continued their standard insulin regimen along with the addition of secretome injections. The second was the "OHO + Secretome" group, in which patients receiving oral antidiabetic drugs were administered the same secretome protocol.

The study's primary outcomes included changes in Hemoglobin A1c (HbA1c) percentage, fasting blood glucose (FBG) levels, and two-hour postprandial blood glucose (2hPPBG) levels. These parameters were measured at baseline, mid-intervention (week 6), and post-intervention (week 12). Secondary outcomes included changes in

insulin sensitivity index measured via HOMA-IR, daily insulin or OHO dosage requirements, body mass index (BMI), lipid profile (total cholesterol, HDL, LDL, and triglycerides), renal function markers (urea and serum creatinine), and the presence of any adverse effects or allergic reactions during the study period. All laboratory assessments were conducted after an overnight fast of 8 to 10 hours.

Data collection occurred in three stages: prior to the first injection (baseline), after the third injection at week 6 (midpoint), and after the sixth injection at week 12 (post-intervention). During each assessment, all clinical and biochemical parameters were measured using standardized laboratory protocols.

All statistical analyses were performed using SPSS version 26.0. Descriptive statistics were used to summarize participants' demographic and clinical characteristics. The Shapiro–Wilk test was applied to assess the normality of each continuous variable. Comparative analyses within groups (pre- and post-intervention) were Within-group comparisons were conducted using paired t-tests for normally distributed variables or the Wilcoxon signed-rank test for non-parametric data. Between-group comparisons were performed using independent t-tests for normally distributed data or the Mann–Whitney U test for non-normally distributed data. Additionally, repeated-measures ANOVA or the Friedman test was applied to assess changes in outcomes across the three time points (baseline, mid, and post-intervention). A p-value < 0.05 was considered statistically significant.

This research study was approved by SMC ethics committee and adhered to the ethical principles outlined in the Declaration of Helsinki with Number : SMC/XI/12/23. Before enrollment, all subjects were fully informed about the study's nature, objectives, potential risks, and anticipated benefits, and then provided written informed consent. Participants were also assured that they could withdraw from the study at any time without penalty or loss of entitled benefits.

The overall research process followed a structured flow beginning with the recruitment and eligibility screening of participants, followed by informed consent and group stratification based on therapy type. Baseline data including HbA1c, FBG, 2hPPBG, lipid profile, BMI, and other relevant parameters were then collected. Secretome therapy was administered intramuscularly every two weeks for 12 weeks. Midpoint evaluation was conducted at week 6 after the third injection, and the final evaluation was carried out at week 12 following the sixth and last injection. After data collection was completed, statistical analysis and interpretation were performed to evaluate the treatment response and overall effect of secretome administration in each treatment group.

This case report is intended to report the care outcomes of a DM patient who received treatment at the Toari Community Health Center in Kolaka Regency. Through regular monitoring of the patient's condition, blood glucose control, medication adherence, and wound care, the Toari Community Health Center implemented optimal treatment. Documentation and recording of the patient's condition were then conducted.

RESULTS

Participant Characteristics

A total of 60 patients with Type 2 Diabetes Mellitus (T2DM) participated in this study, divided equally into two groups based on their ongoing diabetes treatment regimen: 30 patients in the Insulin + Secretome group and

30 in the Oral Hypoglycemic Agents (OHO) + Secretome group. The mean age of participants in the Insulin + Secretome group was slightly greater than that observed in the OHO + Secretome group, although both groups were comparable in terms of age distribution and gender ratio. Baseline glycemic profiles were comparable between groups. Mean (±SD) baseline values were: HbA1c 8.73 ± 0.75% (Insulin) vs 8.93 ± 0.67% (OHO); FBG 164.34 ± 21.20 vs 156.21 ± 17.65 mg/dL; 2hPP 233.32 ± 34.70 vs 238.89 ± 37.11 mg/dL (see Table 1).

Table 1. Baseline Clinical Parameters in Both Groups

Parameter	Insulin + Secretome (Mean ± SD)	OHO + Secretome (Mean ± SD)
HbA1c (%)	8.73 ± 0.75	8.93 ± 0.67
Fasting Blood Glucose (mg/dL)	164.34 ± 21.20	156.21 ± 17.65
2h Postprandial Glucose (mg/dL)	233.32 ± 34.70	238.89 ± 37.11

Source : Digambiro RA et al, 2025

Table 1 shows that prior to the intervention, the mean baseline HbA1c level in the Insulin group was 8.65% (SD = 0.82), while in the OHO group it was slightly higher at 8.82% (SD = 0.65). Baseline fasting glucose levels were also comparable between the two groups, with means of 162.21 mg/dL (SD = 16.37) in the Insulin group and 167.64 mg/dL (SD = 17.84) in the OHO group. Postprandial glucose levels averaged 241.53 mg/dL (SD = 31.76) in the Insulin group and 231.60 mg/dL (SD = 33.87) in the OHO group before treatment began.

Table 2. Change in HbA1c Levels Following Secretome Intervention

Parameter	Insulin + Secretome (Mean ± SD)	OHO + Secretome (Mean ± SD)
Δ HbA1c (%)	1.10 ± 0.45	1.33 ± 0.36

Source : Digambiro RA et al, 2025

After 12 weeks, ΔHbA1c was −1.10 ± 0.45% (Insulin) and −1.33 ± 0.36% (OHO); ΔFBG and Δ2hPP were both significant within-group but not different between groups (FBG p≈0.5298, 2hPP p≈0.2912). As shown in Table 2, the mean reduction in HbA1c was 1.10% (SD = 0.45) in the Insulin group and 1.33% (SD = 0.36) in the OHO group. This indicates a substantial improvement in long-term glycemic control following secretome administration in both treatment arms.

The decrease in fasting blood glucose (GDP) was also notable, with a mean reduction of 27.70 mg/dL (SD = 8.55) in the Insulin group and 25.80 mg/dL (SD = 9.34) in the OHO group. Although both groups demonstrated significant reductions in fasting glucose levels, the changes were relatively similar in magnitude.

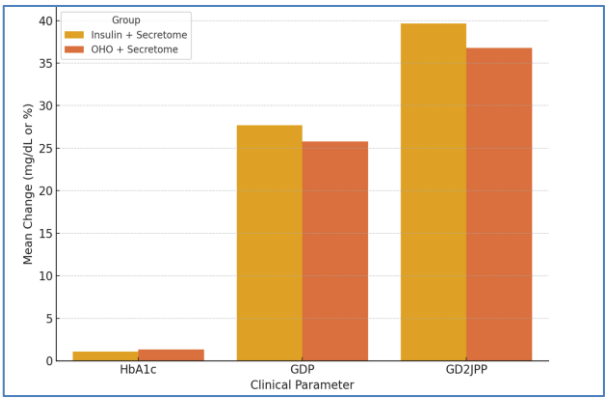

Figure 1. Mean Reduction In HbA1c, Fasting Glucose, And Postprandial Glucose. *Source : Digambiro RA et al, 2025*

In terms of two-hour postprandial glucose levels, the Insulin group exhibited a mean reduction of 39.63 mg/dL (SD = 9.83),

while the OHO group showed a reduction of 36.78 mg/dL (SD = 10.87). These findings confirm that secretome therapy produced clinically relevant improvements in glycemic profiles among patients treated with either insulin or oral agents.

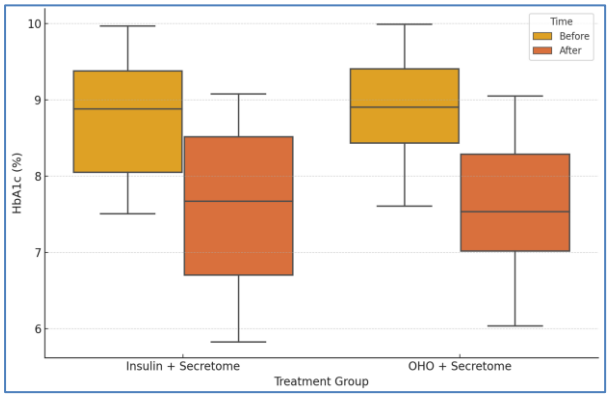

Figure 2. Distribution of HbA1c Levels Before and After Secretome Therapy. *Source : Digambiro RA et al, 2025*

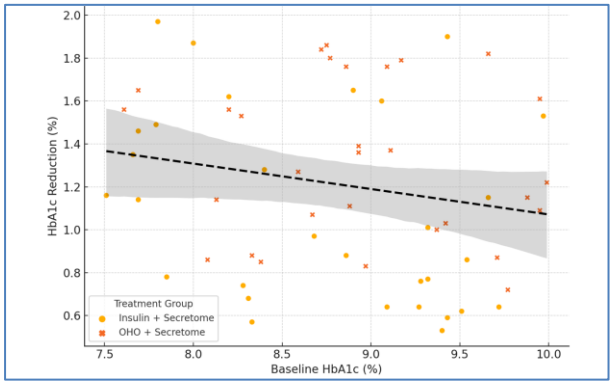

Figure 3. Correlation Between Baseline HbA1c and Reduction After Secretome Therapy. *Source : Digambiro RA et al, 2025*

Statistical Analysis of Group Differences

Normality testing using the Shapiro-Wilk test indicated that the HbA1c data for the Insulin group did not follow a normal distribution ($p = 0.028$ at baseline and $p = 0.036$ post-intervention), while the OHO group data was normally distributed ($p = 0.382$ and $p = 0.430$, respectively). Based on this, the Wilcoxon Signed-Rank Test was used for within-group comparison in the Insulin group, and the Paired T-Test was applied in the OHO group.

In both groups, a statistically significant improvement was found in HbA1c values post-intervention ($p < 0.05$), indicating that secretome therapy significantly improved glycemic control over the 12-week treatment period regardless of the background therapy.

For between-group comparisons of HbA1c changes, the Mann-Whitney U Test was employed due to non-normal distribution in one group. The test revealed a statistically significant difference ($p < 0.05$) in the magnitude of HbA1c reduction between the Insulin and OHO groups, with the OHO group demonstrating a slightly greater mean change.

Intramuscular administration of mesenchymal secretome every two weeks for twelve weeks resulted in significant and clinically meaningful improvements in HbA1c, fasting glucose, and postprandial glucose levels in both patient groups. The changes were more pronounced in the OHO group compared to the Insulin group, particularly in terms of HbA1c reduction, although both groups experienced substantial metabolic benefits. No severe adverse effects were reported during the intervention period, and treatment adherence was high across all participants.

DISCUSSION

The primary objective of this study was to assess the efficacy of intramuscular secretome therapy in enhancing glycemic control among patients with type 2 diabetes mellitus (T2DM) who were receiving either insulin therapy or oral hypoglycemic agents (OHO). T2DM is a chronic metabolic disorder characterized by insulin resistance, progressive β-cell dysfunction, and low-grade systemic inflammation.(13,14) Despite the availability of various pharmacological interventions, a significant number of patients fail to achieve optimal glycemic targets, thus prompting the exploration of adjunctive biological therapies such as mesenchymal stem cell (MSC)-derived

secretome.(15,16)

The findings of this study demonstrated that intramuscular administration of MSC-secretome every two weeks over a 12-week period markedly decreased HbA1c levels in both treatment groups. The mean reduction in HbA1c was 1.10% in the Insulin + Secretome group and 1.33% in the OHO + Secretome group, indicating substantial improvement in long-term glycemic control regardless of baseline therapy. These results suggest that secretome therapy may exert its therapeutic effects independently of the existing treatment modality, possibly through mechanisms such as enhanced insulin sensitivity, anti-inflammatory modulation, and improvement of endothelial function.(16–18)

The observed reductions in fasting blood glucose (GDP) and two-hour postprandial glucose (GD2JPP) levels further support the glycometabolic benefits of secretome therapy. Both groups experienced similar magnitudes of reduction in glucose levels, highlighting the consistency and reproducibility of the intervention's effects. These outcomes align with previous preclinical studies that have shown MSC-secretome to promote glucose uptake in peripheral tissues, improve β-cell survival, and regulate cytokine production involved in glucose metabolism.(17,18)

The slight superiority in HbA1c reduction observed in the OHO group may be attributed to a relatively intact endogenous insulin response in these patients, allowing the bioactive factors in the secretome—such as IGF-1, VEGF, TGF-β, and anti-inflammatory cytokines—to exert synergistic effects with existing oral agents. On the other hand, patients already on insulin may have had more advanced disease or greater β-cell exhaustion, potentially limiting the extent of secretome response.(1,19,20)

Notably, statistical analysis confirmed that the reductions in HbA1c were significant within each group and between the two groups. While both treatment arms benefited from secretome, the between-group comparison showed a statistically significant greater reduction in HbA1c in favor of the OHO group. This highlights the importance of baseline treatment context in modulating biological therapy outcomes.

From a clinical standpoint, these findings support MSC-secretome as a promising adjunctive therapy in the management of T2DM. Its pleiotropic mechanisms, including anti-inflammatory, angiogenic, and regenerative actions—may offer additional metabolic stability without the risk of hypoglycemia commonly associated with escalating doses of pharmacologic agents.(17)

However, this study is not without limitations. The sample size, while sufficient for statistical analysis, was relatively modest and restricted to a single study setting. Additionally, the duration of follow-up was limited to 12 weeks; therefore, long-term sustainability of the observed improvements remains to be investigated. Future research should include multicenter trials with extended follow-up and explore molecular biomarkers to better understand the mechanistic pathways involved.

CONCLUSION

Intramuscular secretome therapy significantly improved glycemic control in T2DM patients on both insulin and oral antidiabetic therapy, with greater benefit observed in the OHO-treated group. These findings open new avenues for integrating regenerative biologics into mainstream diabetes care and warrant further investigation into the optimal use and long-term benefits of

MSC-secretome in metabolic diseases.

High blood sugar levels are associated with the development of atherosclerosis, which in turn inhibits the delivery of essential nutrients to the wound, thus impeding the healing process. Therefore, blood sugar levels are monitored to ensure they remain within normal limits, controlled by administering medications. Wound cleaning and debridement are also performed to thoroughly remove necrotic tissue and toxic exudate, allowing for normal healthy tissue growth.

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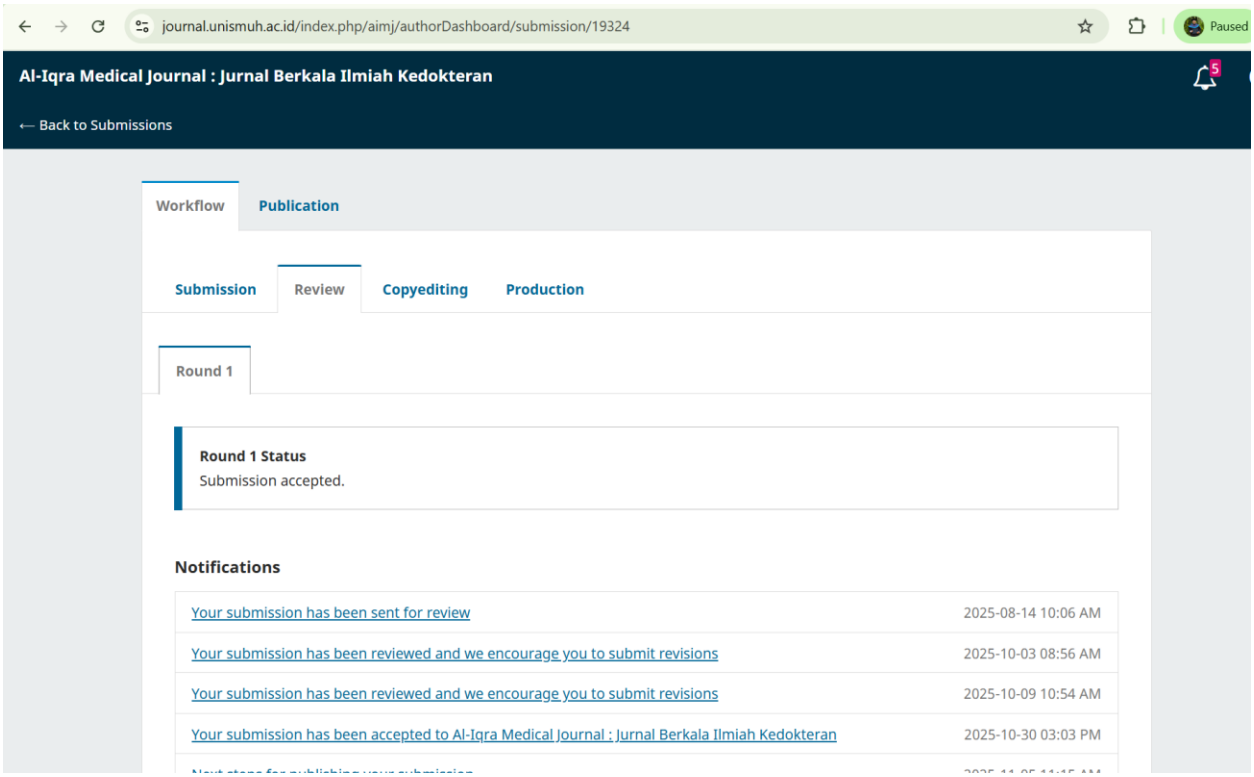
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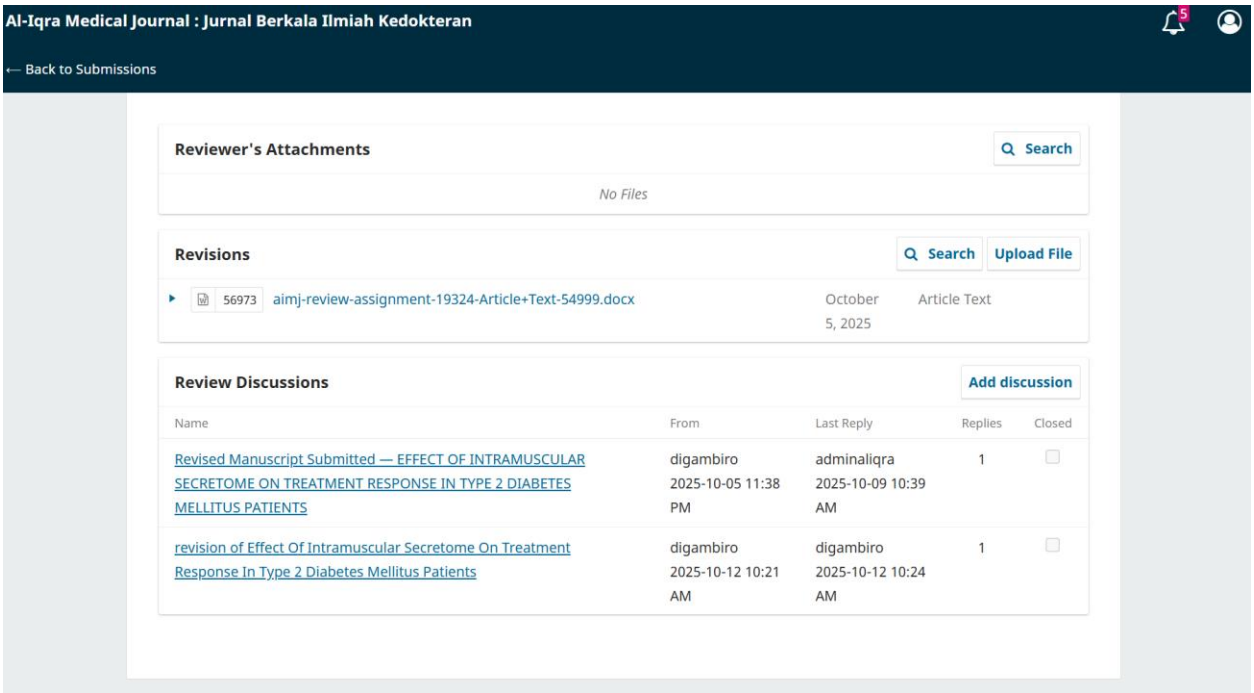
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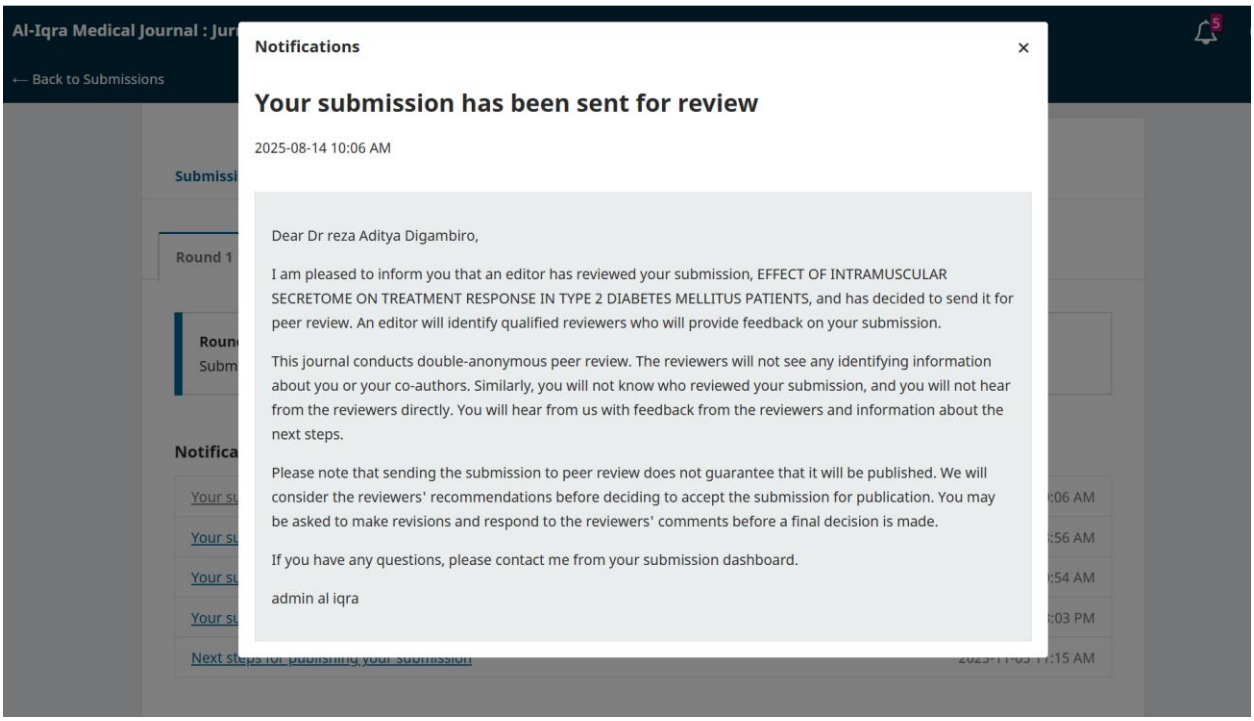
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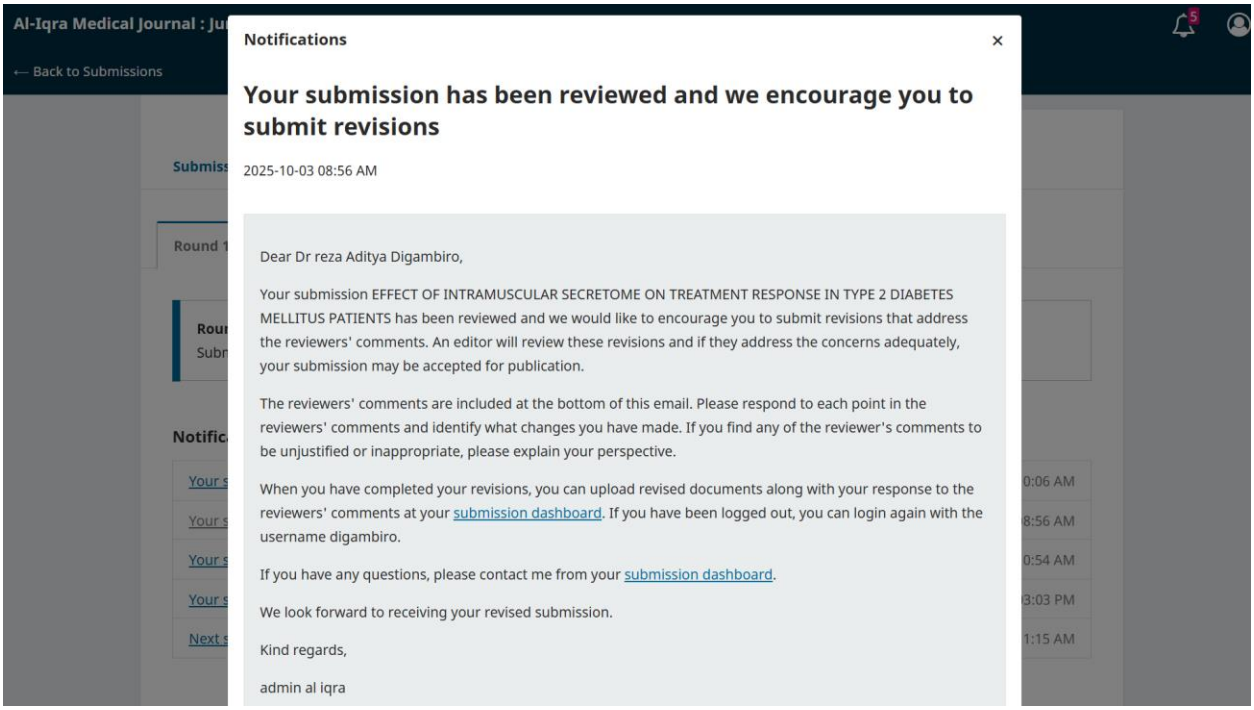
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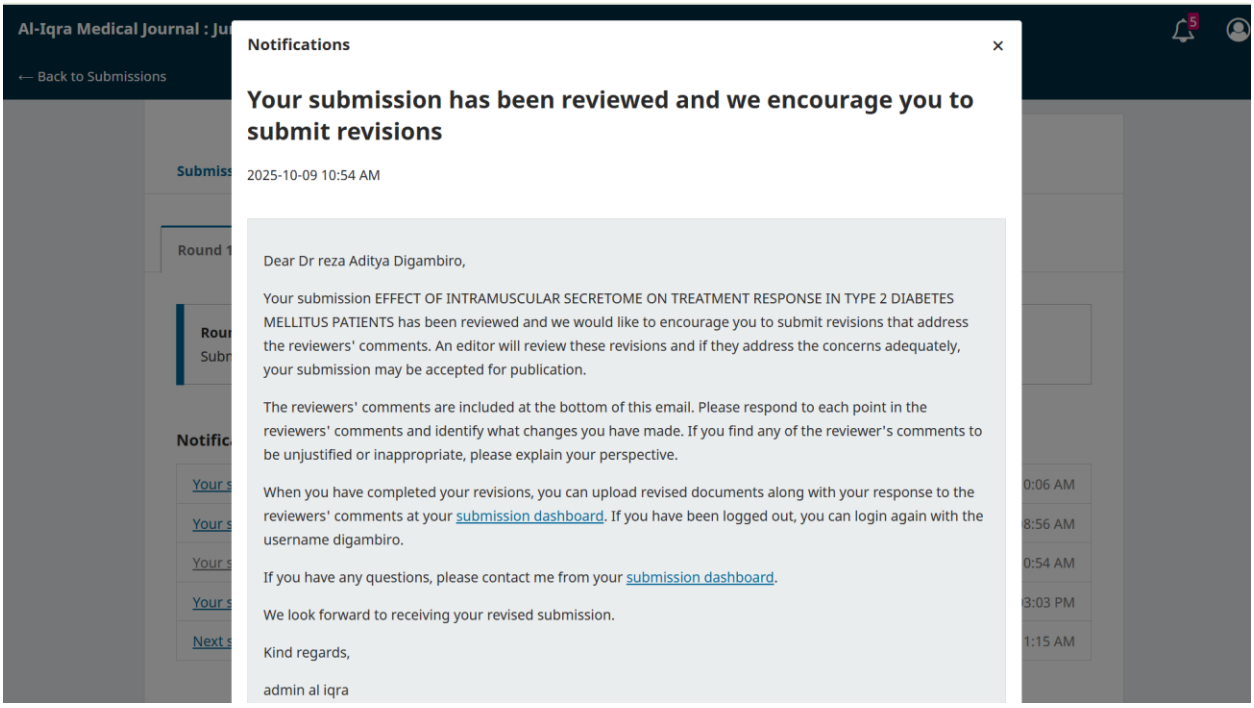

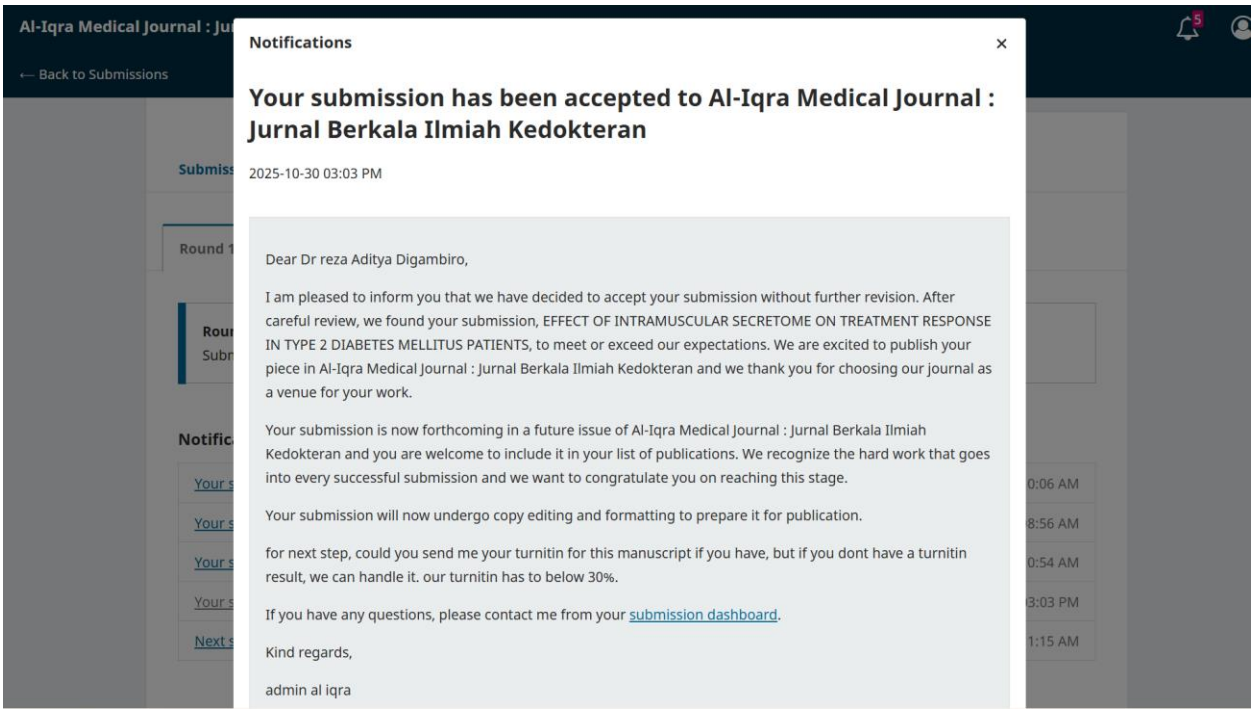

Reviewer 1:

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Reviewer 2:
Recommendation: Revisions Required

This is an interesting study on the addition of secretome to conventional therapy for type 2 diabetes mellitus. The manuscript would be strengthened if comparisons were made between the insulin-only group and the insulin + secretome group, as well as between the OHO-only group and the OHO + secretome group. In addition, important study characteristics such as patients' diet, physical activity, age, and gender, which may have influenced the outcome, were not reported.

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Reviewer 1:
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Reviewer 2:
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Secretome diabetes

by Reza Aditya Digambiro FK

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EFFECT OF INTRAMUSCULAR SECRETOME ON TREATMENT RESPONSE IN TYPE 2 DIABETES MELLITUS PATIENTS

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Abstract

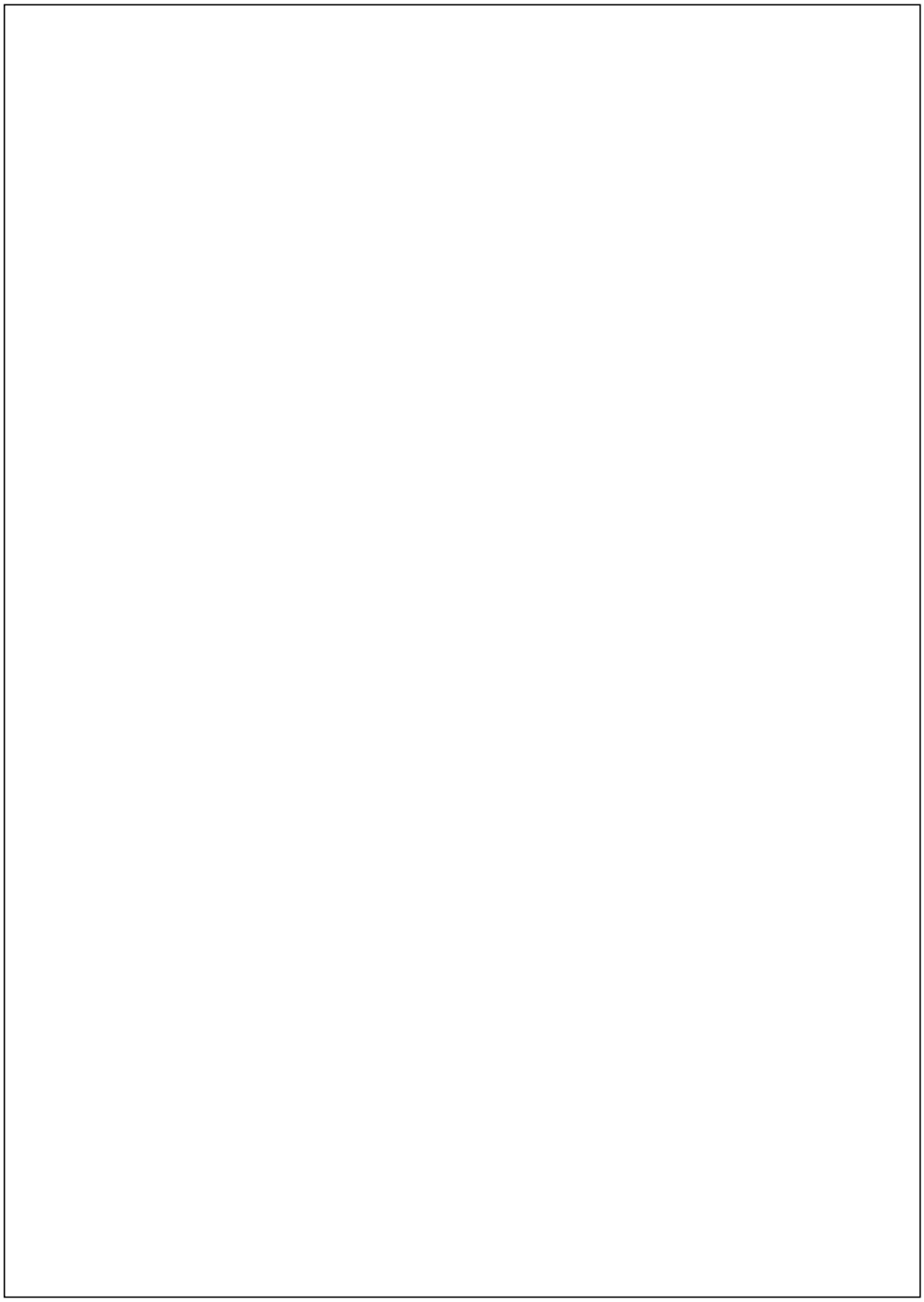
Introduction: This study meant to evaluate the efficacy of intramuscular mesenchymal stem cell derived secretome therapy to improve the glycemic control among diabetic patients with Type 2 Diabetes Mellitus (T2DM) on stable insulin or oral hypoglycemic agents (OHO). n=30 per group (Insulin + Secretome; OHO + Secretome). Methods: Pre–post controlled design; biweekly 2 mL intramuscular secretome for 12 weeks; primary outcomes HbA1c, FBG, 2hPP; standard tests per normality. Participants were divided into two groups: Insulin + Secretome and OHO + Secretome. All subjects received intramuscular injections of mesenchymal stem cell (MSC)-derived secretome (2 mL) every two weeks over a 12-week period (six injections total). Primary outcomes included changes in HbA1c, fasting blood glucose (FBG), and two-hour postprandial glucose (2hPPBG). Statistical analyses used paired t-tests or Wilcoxon tests for within-group comparisons and independent t-tests or Mann-Whitney U tests for between-group comparisons. Results: At baseline, both groups had comparable HbA1c and glucose profiles. After 12 weeks, significant reductions were observed in both treatment arms. HbA1c decreased by -1.10 ± 0.45 (Insulin) and -1.33 ± 0.36 (OHO); between-group ΔHbA1c ($p < 0.05$). Both groups also showed clinically relevant reductions in FBG and 2hPPBG levels. No major adverse effects were reported. Conclusion: Intramuscular MSC-secretome improved glycemic control across background therapies; benefit modestly greater with OHO. No major adverse events were observed.

Keywords: Secretome, Type 2 Diabetes Mellitus, HbA1c, Insulin, Oral Hypoglycemic Agents.

Abstrak

Pendahuluan: Penelitian ini adalah untuk mengevaluasi efikasi terapi sekretom yang berasal dari sel punca mesenkimal secara intramuskular dalam meningkatkan kendali glikemik pada pasien diabetes melitus tipe 2 yang berada pada terapi insulin stabil atau obat hipoglikemik oral. n = 30 per kelompok (Insulin + Secretome; OHO + Secretome). Metode: Desain terkontrol pre–post; pemberian sekretom intramuskular 2 mL setiap dua minggu selama 12 minggu; luaran primer HbA1c, glukosa darah puasa (FBG), dan glukosa dua jam postprandial. Peserta dibagi menjadi dua kelompok: Insulin + Secretome dan OHO + Secretome. Semua subjek menerima injeksi intramuskular sekretom turunan MSC (2 mL) setiap dua minggu selama 12 minggu (total enam injeksi). Luaran primer mencakup perubahan HbA1c, FBG, dan 2hPPBG. Analisis statistik menggunakan uji t berpasangan atau uji Wilcoxon untuk perbandingan dalam-kelompok dan uji t independen atau Mann–Whitney U untuk perbandingan antar-kelompok. Hasil: Pada baseline, kedua kelompok memiliki profil HbA1c dan glukosa yang sebanding. Setelah 12 minggu, penurunan bermakna terlihat pada kedua lengan terapi. HbA1c menurun sebesar −1.10 ± 0.45 (Insulin) dan −1.33 ± 0.36 (OHO); ΔHbA1c antar-kelompok bermakna ($p < 0.05$). Kedua kelompok juga menunjukkan penurunan yang bermakna secara klinis pada FBG dan 2hPPBG. Tidak ada efek samping signifikan yang dilaporkan. Kesimpulan: Sekretom MSC intramuskular memperbaiki kendali glikemik pada berbagai terapi; manfaatnya sedikit lebih besar pada kelompok OHO. Tidak ditemukan kejadian merugikan yang signifikan.

Kata Kunci : Secretome, Diabetes Melitus Tipe 2, HbA1c, Insulin, Obat Hipoglikemik Oral



INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disease characterized primarily by persistent hyperglycemia resulted from compromised the secretion of insulin, insulin insensitivity, or a combination of both conditions. [1] The global prevalence of T2DM continues to rise sharply, making it a significant public health challenge. Chronic hyperglycemia in T2DM is associated with various macrovascular and microvascular complications, substantially reducing patients' quality of life and increasing morbidity and mortality risks. [2]

Effective management of T2DM commonly involves oral hypoglycemic agents and insulin therapy. However, despite current pharmacological treatments, many patients still struggle to achieve optimal glycemic control and experience disease progression, suggesting the necessity of adjunctive therapies aimed at improving metabolic outcomes and limiting complications.[3] Persistent hyperglycemia exacerbates oxidative stress and systemic inflammation, negatively impacting insulin sensitivity, pancreatic beta-cell function, and vascular integrity, thereby increasing the risk of cardiovascular events, nephropathy, retinopathy, and neuropathy.[4]

One promising novel therapeutic strategy that has emerged recently involves utilizing the mesenchymal stem cell (MSC)-secretome, a bioactive product containing growth factors, cytokines, extracellular vesicles, and other soluble molecules secreted by mesenchymal stem cells. [5] The MSC-secretome has demonstrated significant therapeutic potential, including anti-inflammatory, antioxidative, pro-angiogenic, and immunomodulatory effects, and has been considered an effective approach for treating degenerative and chronic inflammatory conditions, including diabetes mellitus. [6,7]

Previous research indicates that MSC-secretome can improve glucose metabolism, increase insulin sensitivity, and lower systemic inflammatory response in diabetic animal models. [8,9] Studies by Sari et al. (2024) and Trigo et al. (2024) reported that MSC-secretome administration effectively alleviated oxidative stress, preserved pancreatic beta-cell function, and improved vascular endothelial integrity, suggesting its therapeutic potential in managing T2DM complications.[10–12] However, limited previous studies have evaluated the effects of MSC-secretome administration on glycemic control, insulin requirements, and treatment response in T2DM patients undergoing different therapeutic regimens, such as insulin or oral hypoglycemic agents.

The present research aims to evaluate the effects of intramuscular injection of MSC-secretome on glucose status and metabolic responses in T2DM patients managed with insulin or oral antidiabetic drugs. Specifically, this research aims to: (to evaluate the efficacy of MSC-secretome in enhancing glycemic control indicators, particularly HbA1c, fasting blood glucose (FBG) and 2-hour postprandial blood glucose (2hPPBG) (2hPPBG) in T2DM patients; (b) compare the response differences between insulin-treated and oral hypoglycemic agent-treated patient groups following MSC-secretome treatment; and (c) explore the potential of MSC-secretome as an adjunctive therapy for enhancing diabetes treatment outcomes and mitigating diabetes-related metabolic complications.

METHODS

This study employed a clinical experimental design using a pre-post control group approach to evaluate the effect of intramuscular secretome administration on treatment response in patients with Type 2 Diabetes Mellitus (T2DM). Participants were

stratified into two groups based on their current diabetes treatment regimen. The first group consisted of patients who had been receiving insulin therapy, while the second group included patients who had been treated with oral hypoglycemic agents (OHO). All participants received intramuscular injections of mesenchymal stem cell-derived secretome every two weeks for a total period of twelve weeks, resulting in six injections per subject. The type and dosage of their ongoing antidiabetic medication (either insulin or OHO) remained unchanged throughout the intervention period unless clinically indicated otherwise. Participants were instructed to maintain their usual diet and physical activity throughout the 12-week intervention; these behaviors were not prospectively quantified and are acknowledged as potential confounders.

The study population comprised patients with confirmed T2DM diagnoses who were undergoing routine follow-up at Naura Medika Clinic, SMC clinic and Hopkins Clinic in Jakarta. Participants were selected using purposive sampling techniques. The inclusion criteria were as follows: adult patients between 30 and 65 years old, with a confirmed diagnosis of T2DM for at least one year, a baseline HbA1c level of 7% or higher, and stable diabetes treatment (either insulin or OHO) for a minimum of three months prior to the study. Only patients who willingly provided written informed consent were enrolled in the study. Exclusion criteria involved patients diagnosed with type 1 diabetes mellitus (T1DM), those with serious chronic conditions such as stage 4–5 chronic kidney disease, congestive heart failure, chronic liver disease, or a history of stroke. Additional exclusions included pregnant or breastfeeding women, individuals with acute or chronic infections, and those with a known allergy to biological products such as stem cell derivatives.

To ensure adequate statistical power, a minimum of 30 participants were enrolled in each group, making a total of at least 60 subjects. This sample size was based on prior estimations of effect size and variability from existing literature on similar interventions. Normality was evaluated using the Shapiro–Wilk test per variable and per group at each time point and for Δ values (post–pre).

The intervention consisted of intramuscular delivery of mesenchymal stem cell–derived secretome (MSC-secretome), which was produced in a standardized and sterile process following Good Manufacturing Practice (GMP) protocols. Each injection contained 2 milliliters of MSC-secretome, and the injections were administered alternately in the gluteal or deltoid muscles. All injections were performed by trained medical professionals under sterile conditions. Participants continued their baseline diabetes therapy (insulin or oral agents) throughout the study period without modifications, unless clinical evaluation necessitated adjustment.

Subjects were divided into two parallel intervention groups based on their previous treatment. The first was the "Insulin + Secretome" group, in which patients continued their standard insulin regimen along with the addition of secretome injections. The second was the "OHO + Secretome" group, in which patients receiving oral antidiabetic drugs were administered the same secretome protocol.

The study's primary outcomes included changes in Hemoglobin A1c (HbA1c) percentage, fasting blood glucose (FBG) levels, and two-hour postprandial blood glucose (2hPPBG) levels. These parameters were measured at baseline, mid-intervention (week 6), and post-intervention (week 12). Secondary outcomes included changes in

insulin sensitivity index measured via HOMA-IR, daily insulin or OHO dosage requirements, body mass index (BMI), lipid profile (total cholesterol, HDL, LDL, and triglycerides), renal function markers (urea and serum creatinine), and the presence of any adverse effects or allergic reactions during the study period. All laboratory assessments were conducted after an overnight fast of 8 to 10 hours.

Data collection occurred in three stages: prior to the first injection (baseline), after the third injection at week 6 (midpoint), and after the sixth injection at week 12 (post-intervention). During each assessment, all clinical and biochemical parameters were measured using standardized laboratory protocols.

All statistical analyses were performed using SPSS version 26.0. Descriptive statistics were used to summarize participants' demographic and clinical characteristics. The Shapiro–Wilk test was applied to assess the normality of each continuous variable. Comparative analyses within groups (pre- and post-intervention) were Within-group comparisons were conducted using paired t-tests for normally distributed variables or the Wilcoxon signed-rank test for non-parametric data. Between-group comparisons were performed using independent t-tests for normally distributed data or the Mann–Whitney U test for non-normally distributed data. Additionally, repeated-measures ANOVA or the Friedman test was applied to assess changes in outcomes across the three time points (baseline, mid, and post-intervention). A p-value < 0.05 was considered statistically significant.

This research study was approved by SMC ethics committee and adhered to the ethical principles outlined in the Declaration of Helsinki with Number : SMC/XI/12/23. Before enrollment, all subjects were fully informed about the study's nature, objectives, potential risks, and anticipated benefits, and then provided written informed consent. Participants were also assured that they could withdraw from the study at any time without penalty or loss of entitled benefits.

The overall research process followed a structured flow beginning with the recruitment and eligibility screening of participants, followed by informed consent and group stratification based on therapy type. Baseline data including HbA1c, FBG, 2hPPBG, lipid profile, BMI, and other relevant parameters were then collected. Secretome therapy was administered intramuscularly every two weeks for 12 weeks. Midpoint evaluation was conducted at week 6 after the third injection, and the final evaluation was carried out at week 12 following the sixth and last injection. After data collection was completed, statistical analysis and interpretation were performed to evaluate the treatment response and overall effect of secretome administration in each treatment group.

This case report is intended to report the care outcomes of a DM patient who received treatment at the Toari Community Health Center in Kolaka Regency. Through regular monitoring of the patient's condition, blood glucose control, medication adherence, and wound care, the Toari Community Health Center implemented optimal treatment. Documentation and recording of the patient's condition were then conducted.

RESULTS

Participant Characteristics

A total of 60 patients with Type 2 Diabetes Mellitus (T2DM) participated in this study, divided equally into two groups based on their ongoing diabetes treatment regimen: 30 patients in the Insulin + Secretome group and

30 in the Oral Hypoglycemic Agents (OHO) + Secretome group. The mean age of participants in the Insulin + Secretome group was slightly greater than that observed in the OHO + Secretome group, although both groups were comparable in terms of age distribution and gender ratio. Baseline glycemic profiles were comparable between groups. Mean (±SD) baseline values were: HbA1c 8.73 ± 0.75% (Insulin) vs 8.93 ± 0.67% (OHO); FBG 164.34 ± 21.20 vs 156.21 ± 17.65 mg/dL; 2hPP 233.32 ± 34.70 vs 238.89 ± 37.11 mg/dL (see Table 1).

Table 1. Baseline Clinical Parameters in Both Groups

Parameter	Insulin + Secretome (Mean ± SD)	OHO + Secretome (Mean ± SD)
HbA1c (%)	8.73 ± 0.75	8.93 ± 0.67
Fasting Blood Glucose (mg/dL)	164.34 ± 21.20	156.21 ± 17.65
2h Postprandial Glucose (mg/dL)	233.32 ± 34.70	238.89 ± 37.11

Source : Digambiro RA et al, 2025

Table 1 shows that prior to the intervention, the mean baseline HbA1c level in the Insulin group was 8.65% (SD = 0.82), while in the OHO group it was slightly higher at 8.82% (SD = 0.65). Baseline fasting glucose levels were also comparable between the two groups, with means of 162.21 mg/dL (SD = 16.37) in the Insulin group and 167.64 mg/dL (SD = 17.84) in the OHO group. Postprandial glucose levels averaged 241.53 mg/dL (SD = 31.76) in the Insulin group and 231.60 mg/dL (SD = 33.87) in the OHO group before treatment began.

Table 2. Change in HbA1c Levels Following Secretome Intervention

Parameter	Insulin + Secretome (Mean ± SD)	OHO + Secretome (Mean ± SD)
Δ HbA1c (%)	1.10 ± 0.45	1.33 ± 0.36

Source : Digambiro RA et al, 2025

After 12 weeks, ΔHbA1c was −1.10 ± 0.45% (Insulin) and −1.33 ± 0.36% (OHO); ΔFBG and Δ2hPP were both significant within-group but not different between groups (FBG p≈0.5298, 2hPP p≈0.2912). As shown in Table 2, the mean reduction in HbA1c was 1.10% (SD = 0.45) in the Insulin group and 1.33% (SD = 0.36) in the OHO group. This indicates a substantial improvement in long-term glycemic control following secretome administration in both treatment arms.

The decrease in fasting blood glucose (GDP) was also notable, with a mean reduction of 27.70 mg/dL (SD = 8.55) in the Insulin group and 25.80 mg/dL (SD = 9.34) in the OHO group. Although both groups demonstrated significant reductions in fasting glucose levels, the changes were relatively similar in magnitude.

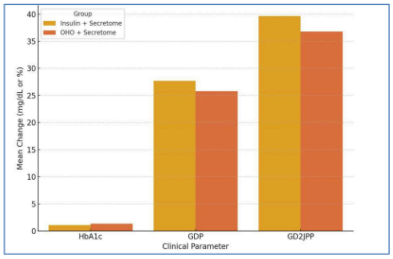


Figure 1. Mean Reduction In HbA1c, Fasting Glucose, And Postprandial Glucose. *Source : Digambiro RA et al, 2025*

In terms of two-hour postprandial glucose levels, the Insulin group exhibited a mean reduction of 39.63 mg/dL (SD = 9.83),

while the OHO group showed a reduction of 36.78 mg/dL (SD = 10.87). These findings confirm that secretome therapy produced clinically relevant improvements in glycemic profiles among patients treated with either insulin or oral agents.

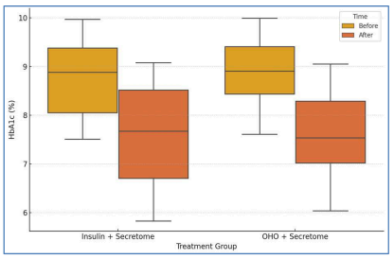


Figure 2. Distribution of HbA1c Levels Before and After Secretome Therapy. *Source : Digambiro RA et al, 2025*

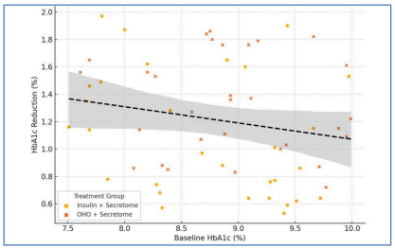


Figure 3. Correlation Between Baseline HbA1c and Reduction After Secretome Therapy. *Source : Digambiro RA et al, 2025*

Statistical Analysis of Group Differences

Normality testing using the Shapiro-Wilk test indicated that the HbA1c data for the Insulin group did not follow a normal distribution ($p = 0.028$ at baseline and $p = 0.036$ post-intervention), while the OHO group data was normally distributed ($p = 0.382$ and $p = 0.430$, respectively). Based on this, the Wilcoxon Signed-Rank Test was used for within-group comparison in the Insulin group, and the Paired T-Test was applied in the OHO group.

In both groups, a statistically significant improvement was found in HbA1c values post-intervention ($p < 0.05$), indicating that secretome therapy significantly improved glycemic control over the 12-week treatment period regardless of the background therapy.

For between-group comparisons of HbA1c changes, the Mann-Whitney U Test was employed due to non-normal distribution in one group. The test revealed a statistically significant difference ($p < 0.05$) in the magnitude of HbA1c reduction between the Insulin and OHO groups, with the OHO group demonstrating a slightly greater mean change.

Intramuscular administration of mesenchymal secretome every two weeks for twelve weeks resulted in significant and clinically meaningful improvements in HbA1c, fasting glucose, and postprandial glucose levels in both patient groups. The changes were more pronounced in the OHO group compared to the Insulin group, particularly in terms of HbA1c reduction, although both groups experienced substantial metabolic benefits. No severe adverse effects were reported during the intervention period, and treatment adherence was high across all participants.

DISCUSSION

The primary objective of this study was to assess the efficacy of intramuscular secretome therapy in enhancing glycemic control among patients with type 2 diabetes mellitus (T2DM) who were receiving either insulin therapy or oral hypoglycemic agents (OHO). T2DM is a chronic metabolic disorder characterized by insulin resistance, progressive β-cell dysfunction, and low-grade systemic inflammation.(13,14) Despite the availability of various pharmacological interventions, a significant number of patients fail to achieve optimal glycemic targets, thus prompting the exploration of adjunctive biological therapies such as mesenchymal stem cell (MSC)-derived

secretome.(15,16)

The findings of this study demonstrated that intramuscular administration of MSC-secretome every two weeks over a 12-week period markedly decreased HbA1c levels in both treatment groups. The mean reduction in HbA1c was 1.10% in the Insulin + Secretome group and 1.33% in the OHO + Secretome group, indicating substantial improvement in long-term glycemic control regardless of baseline therapy. These results suggest that secretome therapy may exert its therapeutic effects independently of the existing treatment modality, possibly through mechanisms such as enhanced insulin sensitivity, anti-inflammatory modulation, and improvement of endothelial function.(16–18)

The observed reductions in fasting blood glucose (GDP) and two-hour postprandial glucose (GD2JPP) levels further support the glycometabolic benefits of secretome therapy. Both groups experienced similar magnitudes of reduction in glucose levels, highlighting the consistency and reproducibility of the intervention's effects. These outcomes align with previous preclinical studies that have shown MSC-secretome to promote glucose uptake in peripheral tissues, improve β-cell survival, and regulate cytokine production involved in glucose metabolism.(17,18)

The slight superiority in HbA1c reduction observed in the OHO group may be attributed to a relatively intact endogenous insulin response in these patients, allowing the bioactive factors in the secretome—such as IGF-1, VEGF, TGF-β, and anti-inflammatory cytokines—to exert synergistic effects with existing oral agents. On the other hand, patients already on insulin may have had more advanced disease or greater β-cell exhaustion, potentially limiting the extent of secretome response.(1,19,20)

Notably, statistical analysis confirmed that the reductions in HbA1c were significant within each group and between the two groups. While both treatment arms benefited from secretome, the between-group comparison showed a statistically significant greater reduction in HbA1c in favor of the OHO group. This highlights the importance of baseline treatment context in modulating biological therapy outcomes.

From a clinical standpoint, these findings support MSC-secretome as a promising adjunctive therapy in the management of T2DM. Its pleiotropic mechanisms, including anti-inflammatory, angiogenic, and regenerative actions—may offer additional metabolic stability without the risk of hypoglycemia commonly associated with escalating doses of pharmacologic agents.(17)

However, this study is not without limitations. The sample size, while sufficient for statistical analysis, was relatively modest and restricted to a single study setting. Additionally, the duration of follow-up was limited to 12 weeks; therefore, long-term sustainability of the observed improvements remains to be investigated. Future research should include multicenter trials with extended follow-up and explore molecular biomarkers to better understand the mechanistic pathways involved.

CONCLUSION

Intramuscular secretome therapy significantly improved glycemic control in T2DM patients on both insulin and oral antidiabetic therapy, with greater benefit observed in the OHO-treated group. These findings open new avenues for integrating regenerative biologics into mainstream diabetes care and warrant further investigation into the optimal use and long-term benefits of

MSC-secretome in metabolic diseases.

High blood sugar levels are associated with the development of atherosclerosis, which in turn inhibits the delivery of essential nutrients to the wound, thus impeding the healing process. Therefore, blood sugar levels are monitored to ensure they remain within normal limits, controlled by administering medications. Wound cleaning and debridement are also performed to thoroughly remove necrotic tissue and toxic exudate, allowing for normal healthy tissue growth.

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