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Hypoxia-Conditioned Mesenchymal Stem Cells (HC-MSC)-Derived Secretome Gel Induce IL-10 to Improve Diabetic Foot Ulcers via Reduced NF-κB p65 Gene Expression: A Randomized Controlled Trial

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Abstract

Background: Diabetic foot ulcers (DFUs) are a serious complication of diabetes mellitus, often leading to severe outcomes. Given the limitations of current treatments, other strategies are needed to address this gap. Recently, the administration of hypoxia-conditioned mesenchymal stem cells (HC-MSC) secretome has shown promise in treating DFUs, particularly in improving wound healing. This study aims to evaluate the efficacy of HC-MSC-derived secretome gel in treating DFUs by assessing its impact on inflammatory biomarkers, specifically IL-10 and NF-κB p65 gene expression.

Methods and Results: This randomized, prospective, controlled clinical trial included 16 patients with type 2 diabetes mellitus (T2DM) and Grade 2–3 DFUs. A control group (n=8) was treated with a placebo/base gel, and an intervention group was treated with HC-MSC-derived secretome gel produced by the Stem Cell and Cancer Research Center, Indonesia. The clinical wound volume, IL-10, and NF-κB p65 were assessed pre- and post-treatment.

The relative quantification (RQ) of IL-10 showed a significant increase in the intervention group on Day 7 after treatment compared to the placebo group (mean difference of 1.12, $P<0.001$), indicating an enhanced anti-inflammatory response. The RQ of NF-κB p65 gene expression significantly decreased in the intervention group (mean difference of 0.488, $P=0.001$), suggesting reduced inflammatory signaling. These results correlate with improved wound healing in the intervention group, evidenced by reductions in wound volume (mean difference of 0.826 cm^3, $P=0.002$) on Day 7 after treatment.

Conclusion: HC-MSC-derived secretome gel significantly enhanced IL-10 expression and reduced NF-κB p65 gene expression in DFUs, improving wound healing outcomes. This approach shows promise as an alternative to conventional treatments. Further research is needed to understand the mechanisms involved.(**International Journal of Biomedicine. 2025;15(1):78-83.**)

Keywords: diabetes mellitus • mesenchymal stem cell • IL-10 • p65 • wound healing

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Introduction

Diabetic foot ulcers (DFUs) are a major associated condition of diabetes mellitus that impairs the quality of life and increases health care costs.[1] Globally, the incidence of DFUs is approximately 6.3%,[2] with higher rates observed in patients with longer diabetes duration and poor glycemic control. Therefore, new healing methods and approaches that would improve the healing process in DFU patients are critical and scarce.

Recent literature has highlighted the angiogenic and immunomodulatory capacity of mesenchymal stem cells (MSCs) as a promising avenue for enhancing wound healing in DFUs.[3] Therefore, new healing methods and approaches that would improve the healing process in DFU patients are critical. MSCs, with their immunoregulatory properties, can modulate inflammation and aid tissue repair, including in DFUs.[4] Characterized by spindle-shaped morphology, surface markers (CD73, CD90, CD105), and differentiation potential, MSCs, especially when hypoxia-preconditioned (H-MSCs), show enhanced therapeutic effectiveness due to increased secretion of paracrine factors like IL-10, VEGF, PDGF, and TGF-β.[5,6] IL-10 reduces inflammation by inhibiting pro-inflammatory cytokines, which is crucial for managing chronic wounds like DFUs.[7] NF-κB p65, overexpressed in chronic wounds, regulates inflammation-related genes.[8] While MSCs have improved wound healing in diabetic models, results vary. This study focuses on hypoxic MSCs for greater consistency and efficacy in DFU treatment.

This study aimed to evaluate the efficacy of HC-MSC-derived secretome gel in treating DFUs by assessing its impact on inflammatory biomarkers, specifically IL-10 and NF-κB p65 gene expression.

Methods

Study Design

This randomized, prospective, controlled clinical trial included 16 patients with type 2 diabetes mellitus (T2DM) and Grade 2–3 DFUs. Table 1 summarizes the inclusion and exclusion criteria used to select participants for the study. A control group was treated with a placebo/base gel and an intervention group was treated with HC-MSC-derived secretome gel produced by the Stem Cell and Cancer Research Center, Indonesia.

Table 1.

Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Patients over 40	Liver cirrhosis
Albumin levels >3 mg/dL	Critical illnesses (acute stroke, acute myocardial infarction)
HbA1c levels > 8%	Critical limb ischemia
Hemoglobin levels >10 mg%	Acute complications (diabetic ketoacidosis, hyperosmolar hyperglycemic state, hypoglycemia)
	Pregnancy or breastfeeding

The study was carried out from November 2023 to May 2024. MSCs were isolated from human umbilical cord-derived MSCs (hUC-MSCs) and obtained with informed consent from donors post-childbirth. The umbilical cords were processed to isolate MSCs, which were then cultured under hypoxic conditions (1-5% oxygen) to enhance their therapeutic potential.

The MSCs were characterized using flow cytometry to confirm the presence of markers like CD73, CD90, and CD105 and the absence of hematopoietic markers such as CD34 and CD45. The MSC's differentiation potential was also assessed. For secretome production, MSCs were cultured to confluence, then incubated in serum-free medium under hypoxia for 24–48 hours to produce a secretome rich in bioactive molecules.

The trial was conducted at Sultan Agung Islamic Hospital, Semarang, Indonesia. HC-MSC-derived secretome gel, containing 200 µL of secretome at a 20% concentration, was applied topically to wounds daily before sleep for 2 weeks. The dosage was based on preclinical studies showing optimal wound healing at this concentration. The nighttime application was chosen to reduce gel displacement and take advantage of the body's natural repair processes during sleep.

Study Procedure

The study initially included 20 T2DM patients with Grade 2-3 DFUs, as classified by the Wagner scale. However, four subjects were excluded before the study began due to ineligibility based on the criteria. Ultimately, 16 patients were included in the study, with 10 having Grade 2 DFUs and 6 having Grade 3 DFUs (Figure 1). The patients were evenly divided into two groups. Both groups received standard antidiabetic therapy. In addition, the intervention group (n=8) received 30 mL of the HC-MSC-derived secretome gel, with confirmed positive markers CD73+, CD90+, and CD105+, and negative markers CD45-, CD34-, CD11b-, and HLA-DR-. The placebo-based group (n=8) received the placebo/base gel. Both gels were produced by Stem Cell and Cancer Research, Semarang, Indonesia.

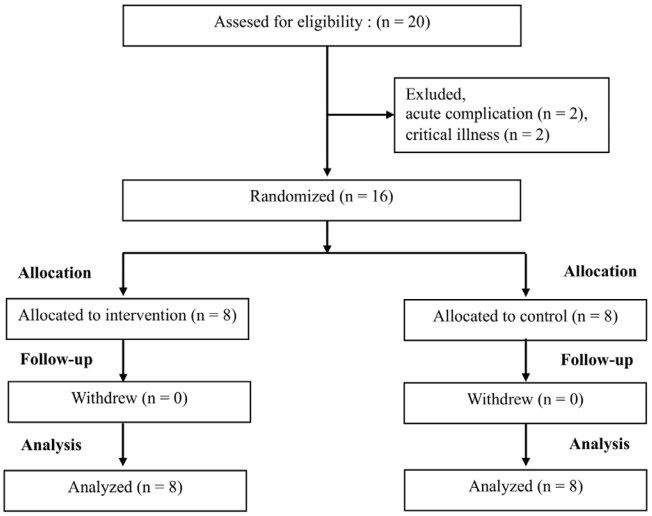

Fig. 1*. Flow diagram for study participants.*

IL-10 and NF-κB p65 expression were measured before and after 7 days of treatment, and wound healing parameters were evaluated after 7 and 14 days. Inflammatory and growth parameters were assessed using 50 mg tissue samples. The analysis was employed using ELISA assay.

Statistical analysis was performed using GraphPad Prism 10. Baseline characteristics were summarized as frequencies and percentages for categorical variables and mean±standard deviation (SD) for continuous variables. Group comparisons

concerning categorical variables were performed using chi-square or Fisher's exact tests. Student's unpaired and paired t-tests were used to compare two groups for data with normal distribution. The Kruskal-Wallis H test/one-way ANOVA was used to compare three or more groups. The LSD test was used to make direct comparisons between two means from two individual groups. A *P*-value of <0.05 was considered statistically significant.

Ethical Consideration

This study was approved by the Ethical Committee of Sultan Agung Islamic Hospital, Semarang, Indonesia (No. 2/KEPK-RSISA/I/2024). Informed consent was obtained from all participants before their enrollment. All data were handled in accordance with the principles of confidentiality and participant rights. All participants provided informed consent after being fully informed about the purpose and procedures of the study.

Results

The study comprised a sample of 16 participants: 7 females (43.8%) and 9 males (56.3%). Participants were evenly allocated into the control group (n=8) and the intervention group (n=8). Baseline characteristics, including age, HbA1c levels, and other clinical parameters, were similar across both groups, with no significant differences observed. The distribution of DFUs showed that most ulcers were located on the lower parts of the right or left foot, with percentages detailed in Table 2.

Table 2

Baseline demographic and clinical features of participants

Clinical features	Placebo/base gel	HC-MSC secretome gel	*P*-value
n	8	8	
Gender			
Male, n (%)	6 (75)	3 (37.5)	0.313
Female, n (%)	2 (25)	5 (62.5)	
Age, y	61.13 ± 3.80	58.63 ± 3.21	0.177
Hemoglobin, g/dL	11.8 ± 0.34	12.1 ± 0.52	0.194
Leucocytes, 10^3/µL	9.64 ± 0.40	9.20 ± 0.52	0.079
Albumin, g/dL	4.12 ± 0.26	3.92 ± 0.14	0.076
HbA1c, %	7.84 ± 0.69	8.38 ± 0.45	0.085
Random blood glucose, g/dL	193 ± 28	177 ± 19	0.202

ANOVA and Fisher's LSD analysis demonstrated significant reductions in wound volume over 14 days (Figure 2). At Day 0, there was no significant difference between the placebo/base gel and HC-MSC-derived secretome gel groups (mean difference of 0.075, *P*=0.734). By Day 7, the placebo/base gel showed a significant reduction in wound volume by 0.524 cm^3 (mean difference of 0.377, *P*=0.030), while the secretome gel group had a more pronounced reduction by 0.826 cm^3 (mean difference of 0.826, *P*=0.002). The percentage reduction was significantly greater with the secretome gel, particularly in DFU Grade 3 compared to Grade 2. These findings, supported by graphical data, indicate that while both treatments reduced wound volume, the secretome gel was more effective. Figure 3 shows that significant healing occurred in the wound treated with the HC-MSC-derived secretome gel compared to the placebo/base gel, as reflected by the almost halving of size, depth, and inflammation of the wound.

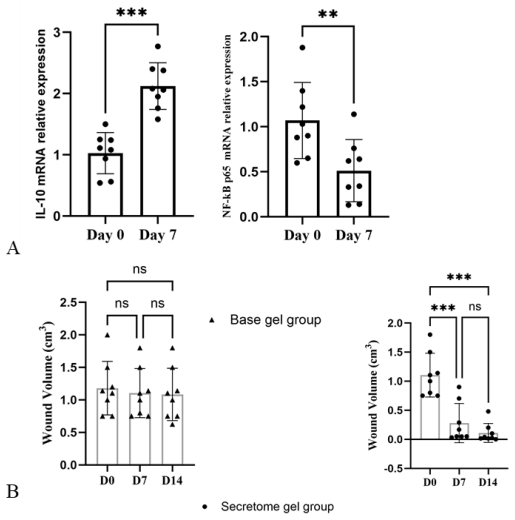

Fig. 2. *Assessment of efficacy. A. Before vs. Post-treatment in the HC-MSC secretome gel group. B. The placebo/base gel group vs. the HC-MSC secretome gel group.*

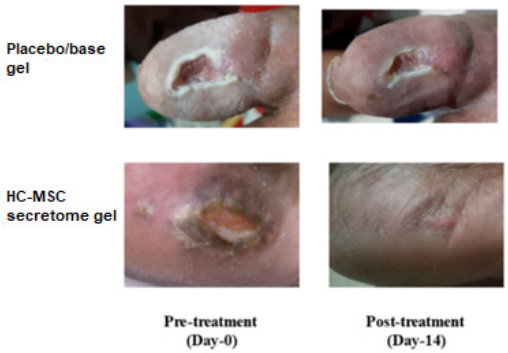

Fig. 3. *Wound volume in DFU patients before and after intervention.*

The study assessed IL-10 and NF-κB p65 mRNA expression in two groups. For IL-10, there was no significant difference between groups on Day 0 (mean difference of 0.0275, *P*=0.831). On Day 7, the HC-MSC-derived secretome gel group showed a significant increase in IL-10 expression compared to the placebo/base gel group (mean difference of

1.12, $P<0.001$). The placebo/base gel group did not show significant changes in IL-10 expression from Day 0 to Day 7 (mean difference 0.0, $P>0.999$) (Figure 2).

For NF-κB p65, no significant difference was observed between groups on Day 0 (mean difference of 0.07, $P=0.612$). On Day 7, the HC-MSC-derived secretome gel group had significantly lower NF-κB p65 mRNA expression than the placebo/base gel group (mean difference 0.488, $P=0.001$). The placebo/base gel group showed no significant change in NF-κB p65 expression from Day 0 to Day 7 (mean difference 0.0, $P>0.999$), while the HC-MSC-derived secretome gel group exhibited a significant reduction (mean difference 0.558, $P=0.003$) (Figure 2).

The correlation analysis between changes in wound volume, IL-10, and p65 after secretome administration showed varying levels of association. The correlation between the change in wound volume and IL-10 revealed a moderate negative correlation (r=-0.4), suggesting that a decrease in wound volume is weakly associated with an increase in IL-10 levels. However, this correlation was not statistically significant ($P=0.128$). Similarly, the correlation between wound volume and p65 expression demonstrated a negligible positive relationship (r=0.08, $P=0.775$), indicating little to no connection between these variables. Lastly, the correlation between IL-10 and p65 showed a weak negative correlation (r=-0.37), implying a tendency for increased IL-10 to be associated with decreased p65 expression; however, this relationship also failed to reach statistical significance ($P=0.148$). Overall, none of the correlations observed were statistically significant, suggesting that the changes in wound volume, IL-10 and p65 are not strongly associated with the context of this study.

Discussion

Several key points emerge when discussing the effects of HC-MSC-derived secretome gel on DFUs compared to previous research.[9] Previous studies have extensively explored the potential of MSCs in promoting wound healing, particularly in the context of chronic wounds such as DFUs. [10-12] MSCs promote tissue repair and modulate immune responses through differentiation and secretion of bioactive molecules.[13] In a study by Ding et al.,[14] mesenchymal stem cell (MSC)-derived extracellular vesicles aided in cell communication and tissue regeneration. Hypoxic MSCs, exposed to low oxygen, show enhanced therapeutic effects due to increased growth factors, cytokines, and anti-inflammatory molecules. Hypoxic preconditioning improves the secretome's ability to promote angiogenesis, reduce inflammation, and accelerate wound closure in diabetic wounds through elevated vascular endothelial growth factor.[15]

The current study confirms that the hypoxic MSC secretome enhances IL-10 expression and reduces NF-κB p65 gene expression, reflecting its strong anti-inflammatory effects.[16,17] These results align with existing research on MSC-derived therapies, which mitigate the prolonged inflammation in DFUs and foster a more favorable healing environment.[18] Using MSC secretome, particularly under hypoxic conditions, overcomes direct stem cell transplantation limitations, including safety concerns and immune rejection.[19] It offers a standardized, safer, and more controlled therapeutic option for managing chronic wounds.[20]

The current study highlights the effectiveness of HC-MSC secretome in treating diabetic foot ulcers, supporting previous research on MSC-derived exosomes and secretomes in enhancing wound healing through improved angiogenesis, anti-inflammatory effects, and cellular function.[21] The study assessed the impact of base gel versus secretome gel on wound volume, IL-10, and NF-κB p65 mRNA expression over 7 days. Results showed a significant reduction in wound volume with secretome gel compared to base gel, indicating superior efficacy in promoting wound closure. This suggests that secretome gel accelerates wound healing by enhancing angiogenesis and cellular proliferation, marking it a promising treatment for diabetic ulcers.[22-24] The significant decrease in wound volume in the secretome gel group underscores its potential as a promising treatment for diabetic ulcers.

IL-10 is an anti-inflammatory cytokine crucial in regulating the immune response during the wound healing process.[25] The analysis revealed a significant increase in IL-10 expression in the HC-MSC-derived secretome gel group compared to the placebo/base gel group over the 7-day period. This upregulation of IL-10 in the HC-MSC-derived secretome gel group indicates its potent anti-inflammatory properties. Elevated IL-10 levels can help modulate the inflammatory response, reducing excessive inflammation that can impede wound healing.[26,27] The ability of the secretome gel to enhance IL-10 expression highlights its potential to create a conducive environment for efficient wound repair and tissue regeneration.[28-30]

This study highlights the significant potential of hypoxic MSC secretome for treating DFUs. The use of HC-MSC-derived secretome gel markedly increased IL-10 levels and decreased NF-κB p65 gene expression, demonstrating enhanced anti-inflammatory effects and improved wound healing compared to placebo. Future research should aim to refine MSC secretome's dosing and delivery methods, optimize its clinical application, and investigate its detailed mechanisms in chronic wound healing.

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Competing Interests

The authors declare that they have no competing interests.

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