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Original Article

Safety and efficacy of allogeneic umbilical cord-derived mesenchymal stem cell transplantation in type 2 diabetes: a pilot clinical trial

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Abstract: Background: Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance and β-cell dysfunction, with chronic inflammation playing a central pathogenic role. Mesenchymal stem cells (MSCs) possess therapeutic potential through immunomodulatory and tissue-reparative properties. This study aimed to evaluate the safety and efficacy of intravenous allogeneic umbilical cord-derived MSCs (UC-MSCs) in patients with T2DM. Methods: Eleven adults with T2DM (disease duration ≥ 10 years; HbA1c ≤ 8%) received a single intravenous infusion of 1×10^8 UC-MSCs. This open-label pilot trial assessed safety (adverse events, hematologic and metabolic parameters) and efficacy (glycemic control and inflammatory gene expression) over a 2-month follow-up period. UC-MSCs were isolated under standardized conditions. Results: UC-MSC transplantation in patients with T2DM was well tolerated, with only transient fever (36.3%) and mild muscle pain (18.2%) reported. The intervention resulted in significant metabolic improvements, including a 2.1% reduction in HbA1c (P = 0.00095) and a decrease in fasting glucose by 93.7 mg/dL (P = 0.00097). Treatment also modulated inflammatory pathways, as evidenced by upregulating of IKBα (1.76-fold, P = 0.0067) and downregulating of TNFα (0.62-fold) and IL-6 (0.65-fold). Variability in IKBα expression accounted for 48% of the variance in HbA1c (r = -0.69). Two distinct response patterns were observed: improvement in insulin sensitivity (7/11) via NF-κB suppression, and enhancement of β-cell function (3/11). Conclusion: Allogeneic UC-MSC transplantation appears safe and significantly improves glycemic control in patients with T2DM. The heterogeneity in patient responses underscores the importance of stratification based on inflammatory status. These findings support UC-MSC therapy as a promising disease-modifying strategy and highlight the need for larger, controlled clinical trials.

Keywords: Type 2 diabetes, mesenchymal stem cells, umbilical cord, cell therapy, inflammation, NF-κB pathway, insulin resistance, gene expression, clinical trial

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease and a global pandemic, currently affecting approximately 537 million adults worldwide about one in ten individuals aged 20-79 years. The vast majority of these cases are type 2 diabetes mellitus (T2DM). DM ranks among the leading causes of premature mortality, with its global incidence and prevalence steadily increasing. The number of affected individuals is projected to rise to 643 million by 2030 and 783 million by 2045 [1, 2]. T2DM develops from insulin resistance (IR) and β-cell dysfunction, often preceded by metabolic dysfunction syndrome (MDS), which includes conditions such as pre-obesity and dyslipidemia. Key signaling pathways involved in T2DM include defects in

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insulin signaling and inflammation mediated by Nuclear Factor kappa B (NF-κB), Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT), and c-Jun N-terminal Kinase (JNK) pathways, as well as endoplasmic reticulum stress (ERS). These factors collectively impair insulin sensitivity and β-cell function. Genetic factors also contribute, with genes such as Transcription Factor 7 Like 2 (TCF7L2), Glucokinase (GCK), and Peroxisome Proliferator-Activated Receptor Gamma (PPARG) influencing insulin secretion and resistance. Altered expression of these genes, along with upregulated inflammatory markers, further exacerbates the disease by impairing glucose uptake and promoting chronic inflammation [3]. Chronic inflammation is a central mechanism in T2DM pathogenesis. Key inflammatory mediators, including Tumor Necrosis Factor alpha (TNF-α), Interleukin-6 (IL-6), and Inhibitor of Nuclear Factor Kappa B alpha (IKB-α), play pivotal roles in the development of IR and β-cell dysfunction [4-6]. TNF-α impairs insulin signaling by promoting serine phosphorylation of insulin receptor substrates. This process reduces glucose uptake and increased lipolysis, worsening ectopic fat deposition and IR [7, 8]. IL-6 contributes to IR by activating the JAK/STAT pathway. This activation upregulates suppressor of cytokine signaling 3 (SOCS3), which inhibits insulin receptor substrate-1 (IRS-1) and reduces insulin sensitivity [9, 10]. Additionally, IL-6 stimulates hepatic gluconeogenesis, leading to hyperglycemia. IKB-α regulates the NF-κB pathway; Its phosphorylation and subsequent degradation activate NF-κB, which moves to the nucleus and promotes transcription of pro-inflammatory genes. This process perpetuates systemic inflammation and IR. Together, these inflammatory mediators disrupt insulin signaling, impair glucose homeostasis, and contribute to the metabolic disturbances seen in T2DM [5, 9]. Targeting these inflammatory pathways offers promising therapeutic strategies to improve insulin sensitivity and β-cell function in T2DM management. Recently, stem cells have emerged as a novel treatment for various diseases. Their unique abilities include regenerating damaged tissues, differentiating into specialized cell types, and modulating the immune system [11-16]. Mesenchymal stem cells (MSCs) are a versatile population of multipotent progenitor cells. They can differentiate into various cell types, including osteoblasts, adipocytes, and chondrocytes. MSCs are typically sourced from bone marrow, adipose tissue, and umbilical cord. These cells play a crucial role in regenerative medicine because of their self-renewal capacity and ability to repair damaged tissues [17-20].

MSCs are also known for their immunomodulatory and anti-inflammatory properties. These features make them particularly effective in treating diseases with an inflammatory component, such as T2DM [14]. Upon transplantation, MSCs secrete various bioactive molecules, including growth factors, cytokines, and extracellular vesicles. Together, these factors promote tissue repair, reduce inflammation, and enhance cellular regeneration [21-23]. Furthermore, MSCs exhibit low immunogenicity, which reduces the risk of immune rejection and improves their safety in clinical applications [24]. In T2DM, MSCs offer a promising therapeutic approach due to their ability to improve IR, enhance glucose metabolism, and restore pancreatic β-cell function [25, 26]. The therapeutic effects of MSCs in T2DM are mainly mediated by paracrine signaling. This includes the secretion of insulin-like growth factors, vascular endothelial growth factor (VEGF), and other cytokines that increase insulin sensitivity and reduce hyperglycemia [27, 28].

Moreover, MSC-derived exosomes have been identified as key mediators of these effects. They facilitate intercellular communication and promote tissue repair. These findings highlight the promising potential of MSC therapy as a treatment option for T2DM and justify further research to optimize clinical use [29]. Several clinical studies have demonstrated the therapeutic potential of bone marrow-derived mesenchymal stem cells (BM-MSCs) in treating T2DM [30-34]. Similarly, mesenchymal stem cells derived from umbilical cord tissue (UC-MSCs) show immunomodulatory effects comparable to of BM-MSCs. UC-MSCs also offer advantages such as easier procurement, higher cell yield, minimal donor discomfort, lower costs, rapid collection, and reduced immunogenicity [35]. However, clinical investigations specifically evaluating UC-MSCs in T2DM are limited. The main objectives of this study were to assess the safety and efficacy of intravenous (IV) administration of allogeneic UC-MSCs in T2DM patients.

Materials and methods

Study design and ethical statement

This open-label, single-arm, pilot clinical trial evaluated the safety and preliminary efficacy of IV allogeneic UC-MSCs in patients with T2DM. The study followed the Declaration of Helsinki Ethical Principles and Good Clinical Practices. It was approved by the Ethics Committee of Mashhad University of Medical Sciences, Iran (Reg. No: IR.MUMS.REC.1403.065). The trial was registered with the Iranian Registry of Clinical Trials (ID: IRCT20130811014330N10). Informed consent was obtained from all participants, who were permanent residents or citizens of Iran.

Participants

Participants in this trial were aged 20 to 65 years and had a T2DM history of at least 10 years. Eleven patients meeting the World Health Organization (WHO) criteria for definite T2DM were enrolled. Inclusion criteria were: (1) Body Mass Index (BMI) between 24 and 35 kg/m^2; (2) HbA1c > 8; (3) stable exogenous insulin dose of 0.5 to 1.5 U/kg/day for at least 3 months before treatment; (4) no use of biologic drugs; and (5) use of insulin analogs without pioglitazone treatment in the previous 3 months. Exclusion criteria included: (1) other chronic underlying diseases; (2) diabetic coma; (3) hyperosmolar syndrome; (4) renal insufficiency (glomerular filtration rate < 60 ml/min); (5) myocardial infarction or stroke within 3 months before treatment; and (6) participation in concurrent clinical trials.

Cell preparation and culture

The UC-MSCs were isolated, expanded, and characterized according to Good Manufacturing Practice (GMP) standards. Umbilical cords were obtained from healthy mothers after elective cesarean delivery. This was done following International Society for Cellular Therapy (ISCT) guidelines and with prior written informed consent. Obstetric exclusion criteria for cord collection included clinical chorioamnionitis, intrapartum fever, prolonged rupture of membranes (> 24 h), pre-eclampsia, and perinatal sepsis. Donors were between 20-35 years of age, had normal pregnancies, and were free from metabolic or autoimmune disorders. To ensure biosafety, maternal peripheral blood samples were screened for major infectious diseases, including HIV, HBV, HCV, and HTLV-I/II. Only cords from seronegative donors were used for UC-MSC isolation. All procedures were performed under the supervision of the institutional ethics committee (Approval No: IR.MUMS.REC.1403.065). Immediately after collection, cords were placed in sterile phosphate-buffered saline (PBS) supplemented with antibiotics and transported under controlled conditions (2-8°C) to our GMP-certified laboratory for further processing. Upon arrival, the umbilical cords were rinsed with PBS to remove blood residues and dissected into small segments. Tissue digestion was performed sequentially using a collagenase-dispase solution for one hour at 37°C, followed by trypsin for 30 minutes at 37°C. After each enzymatic step, tissue fragments were washed and centrifuged three times with PBS (1,500-2,000 rpm for 5 minutes per cycle). The resulting cell suspension was filtered through a 100 µm mesh strainer to separate single cells from debris. Isolated cells were seeded into flasks containing α-minimum essential medium (α-MEM; Gibco, USA) supplemented with 20% fetal bovine serum (Gibco, USA) and 1% penicillin-streptomycin. Cultures were maintained at 37°C in a humidified incubator with 5% CO_2. Non-adherent cells were removed after 24-48 hours, and the medium was refreshed twice weekly. When UC-MSCs reached 80% confluence in primary culture, adherent cells were harvested using 0.125% trypsin-EDTA and subcultured until passage 4, which typically took 3-4 weeks. The sterility of the final UC-MSC product was confirmed by endotoxin assay and qRT-PCR for bacteria and mycoplasma. Cell viability was assessed by trypan blue exclusion. Flow cytometry confirmed the MSC immunophenotype, showing positive expression of CD73, CD90, and CD105, and minimal expression of CD34 and CD45. Finally, UC-MSCs were suspended in saline and transported at 2-8°C to the clinical site.

Stem cell transplantation

All patients received concurrent IV infusions of allogeneic UC-MSCs in a clinical setting. Each infusion contained 1 × 10^8 UC-MSCs suspended in 50 ml of normal saline. The infusion was administered via a 22G intravascular cath-

eter connected to a syringe pump at a rate of 60 ml/h.

Patient follow-up

Patients with T2DM were evaluated three months before UC-MSC transplantation and then monitored for two-months. Safety was the primary focus of the study. Any adverse effects following IV administration of UC-MSCs were carefully observed. Patients' complaints about their medical condition and clinical symptoms were recorded to assess adverse effects. After transplantation, patients were monitored for immediate reactions, including systemic effects (such as allergic reactions, fever, sepsis) and local effects (pain, infection, urinary incontinence) for three days. During the one-day hospital stay, laboratory tests and continuous monitoring of vital signs (respiratory rate, heart rate, blood pressure, body temperature) were conducted. Serum biochemistry and complete blood counts were assessed on days 1 and 3 to rule out liver or kidney dysfunction, mineral imbalances, or infection. If no complications occurred, patients were discharged after one day and followed up regularly per the study protocol.

Outcomes measures

To evaluate the therapeutic effectiveness of UC-MSC transplantation, both clinical/metabolic indicators and molecular/inflammatory biomarkers were systematically assessed at baseline and two months post-treatment. Clinical efficacy endpoints included HbA1c, FBS, and fasting C-peptide. HbA1c was designated as the primary endpoint, with a clinically meaningful response defined as ΔHbA1c ≤ -0.5% and achievement of HbA1c < 7.0% regarded as a target outcome. FBS and C-peptide served as secondary endpoints, providing complementary information on short-term glycemic regulation and β-cell functional reserve. For inflammatory profiling, total RNA was extracted using the Parstous total RNA extraction kit (Lot No. 754088), followed by cDNA synthesis with the Parstous cDNA synthesis kit (Lot No. 753326). qRT-PCR analysis was performed using SYBR Green and primers targeting TNFα (Forward: 5-TCT TCT CCT TCC TGATCG TGG-3, Reverse: 5-GCT TGA GGG TTT GCT ACA AC-3), IL-6 (Forward: 5-GGCACTGGCAGAAAACAACC, Reverse: 5-ACCAGGCAAGTCTCCTCATTG), and IKBα (-F 5-GAAGAAGGAGCGGCTACTGG-3, Reverse: 5-GTCCTCGGTGAGCTGCTG-3), with GAPDH as the endogenous control. Gene expression fold changes were calculated using the 2^(-ΔΔCt) method.

Molecular efficacy endpoints were selected to capture the immunomodulatory effects of UC-MSCs. TNF-α and IL-6 were chosen as representative pro-inflammatory cytokines implicated in IR, whereas IKBα was evaluated as a negative regulator of NF-κB signaling, whose upregulation reflects suppression of inflammatory activity. Integrative analyses were performed to link molecular changes with clinical outcomes. Patients were stratified into mechanistic subgroups (insulin-sensitivity vs. insulin-secretion responders) using combined thresholds of ΔHbA1c and ΔC-peptide. Correlation analyses assessed associations between changes in inflammatory gene expression (IKBα, TNFα, IL-6) and metabolic parameters (HbA1c, FBS, C-peptide). Furthermore, multivariate regression was applied to determine whether combined changes in inflammatory markers predicted the magnitude of HbA1c reduction.

Statistical analysis

Statistical analyses were performed using R (version 4.5.0) with key packages including tidyverse, ggpubr, and cowplot. One-sample t-tests assessed whether post-therapy fold changes in IKBα, TNFα, and IL6 differed significantly from unity (no change). Results were visualized using boxplots with individual data points and annotated *p*-values. Safety profile evaluation employed paired t-tests compare pre- and post-therapy biomarker levels across lipid, hematological, inflammatory, and organ function parameters. *P*-values were adjusted for multiple comparisons using the Benjamini-Hochberg method. Pearson correlation analyzed associations between gene expression changes (fold changes in IKBα, TNFα, IL6) and metabolic improvements (ΔFBS, ΔHbA1c, ΔC-peptide). Scatter plots with regression lines and correlation coefficients illustrated these associations. Changes in clinical parameter (FBS, HbA1c, C-peptide) were analyzed by pairedt-tests and presented as boxplots showing individual trajectories. Multivariate linear

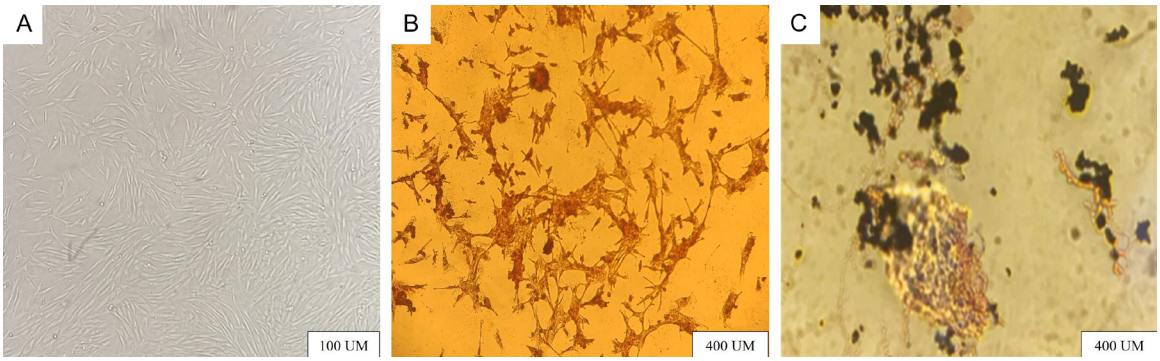

Figure 1. Microscopic view of cell cultures at different magnifications. (A) Umbilical cord-derived Mesenchymal Stem Cells (× 100 from Inverted phase microscope) passage 4, (B) Differentiation to osteocytes (× 400), (C) Differentiation to adipocyte (× 400).

regression modeled HbA1c reduction (ΔHbA1c) as a function of gene expression changes. Model significance was assessed by F-test and coefficient *p*-values. Patients were classified as responders (HbA1c < 7%) or non-responders. Mechanistic subgroups (improved insulin secretion vs. insulin sensitivity) were compared using ANOVA with Tukey post-hoc tests. All analyses assumed normality (Shapiro-Wilk test) and homogeneity of variance (Levene's test), with non-parametric alternatives (Wilcoxon signed-rank, Spearman correlation) applied where assumptions were violated. Statistical significance was set at $P < 0.05$, with exact *p*-values reported unless $P < 0.001$.

Results

Umbilical cord-derived MSCs isolation and characterization

In vitro, isolated UC-MSCs showed a spindle-shaped, fibroblast-like morphology under the microscope (**Figure 1A**). Their multilineage differentiation potential was confirmed by inducing osteogenic and adipogenic lineages. This was demonstrated by calcium deposition (**Figure 1B**) and lipid droplet formation (**Figure 1C**), respectively.

Flow cytometry further characterized the UC-MSCs immunophenotype (**Figure 2**). The cells highly expressed typical mesenchymal markers: CD73 (99.4%), CD90 (97.2%), and CD105 (96.9%), confirming their mesenchymal lineage. There was minor expression of the hematopoietic markers CD34 (2.3%) and CD45 (5.3%), indicating a small hematopoietic cell population or early-passage heterogeneity. A cell doubling time assay showed stable proliferation without signs of senescence. Cell viability before transplantation ranged from 95% to 98%. For therapy, 1 × 10^8 UC-MSCs were suspended in saline and delivered via IV injection.

Glycemic outcomes following stem cell therapy in T2DM

The cohort of 11 patients showed significant improvements in glycemic control parameters after stem cell therapy. HbA1c levels dropped from 10.3 ± 1.4% at baseline to 8.2 ± 1.5% post-therapy. The mean reduction was -2.1 ± 1.6% ($P = 0.00095$, paired t-test). FBS also decreased from 221.8 ± 43.2 mg/dL to 128.1 ± 58.6 mg/dL, with a mean reduction of -93.7 ± 67.6 mg/dL ($P = 0.00097$). However, C-peptide changes were not statistically significant, decreasing from 2.2 ± 1.7 ng/mL to 1.6 ± 0.9 ng/mL ($P = 0.18$) (**Figure 3**).

Safety profile result

The intervention demonstrated a favorable safety profile with selective hematologic and metabolic effects. Platelet counts increased significantly from baseline (289.5 ± 83.4 to 324.0 ± 86.7 × 10^3/μL; Δ = +34.5 ± 30.1 × 10^3/μL, $P = 0.0016$). Counts remained within the normal range (150-450 × 10^3/μL) in all patients (**Figure 4**). Red blood cell counts also increased (4.93 ± 0.62 to 5.08 ± 0.59 × 10^6/μL; Δ = +0.15 ± 0.13 × 10^6/μL, $P = 0.0031$), suggesting improved bone marrow function. Metabolic improvements included a significant decrease in total cholesterol (187.6 ± 38.1 to 170.6 ± 39.3 mg/dL; Δ = -17.0 ± 21.8 mg/dL, $P = 0.017$), indicating beneficial lipid modulation. Comprehensive safety monitoring showed no clinically significant changes (**Figure 4**). No se-

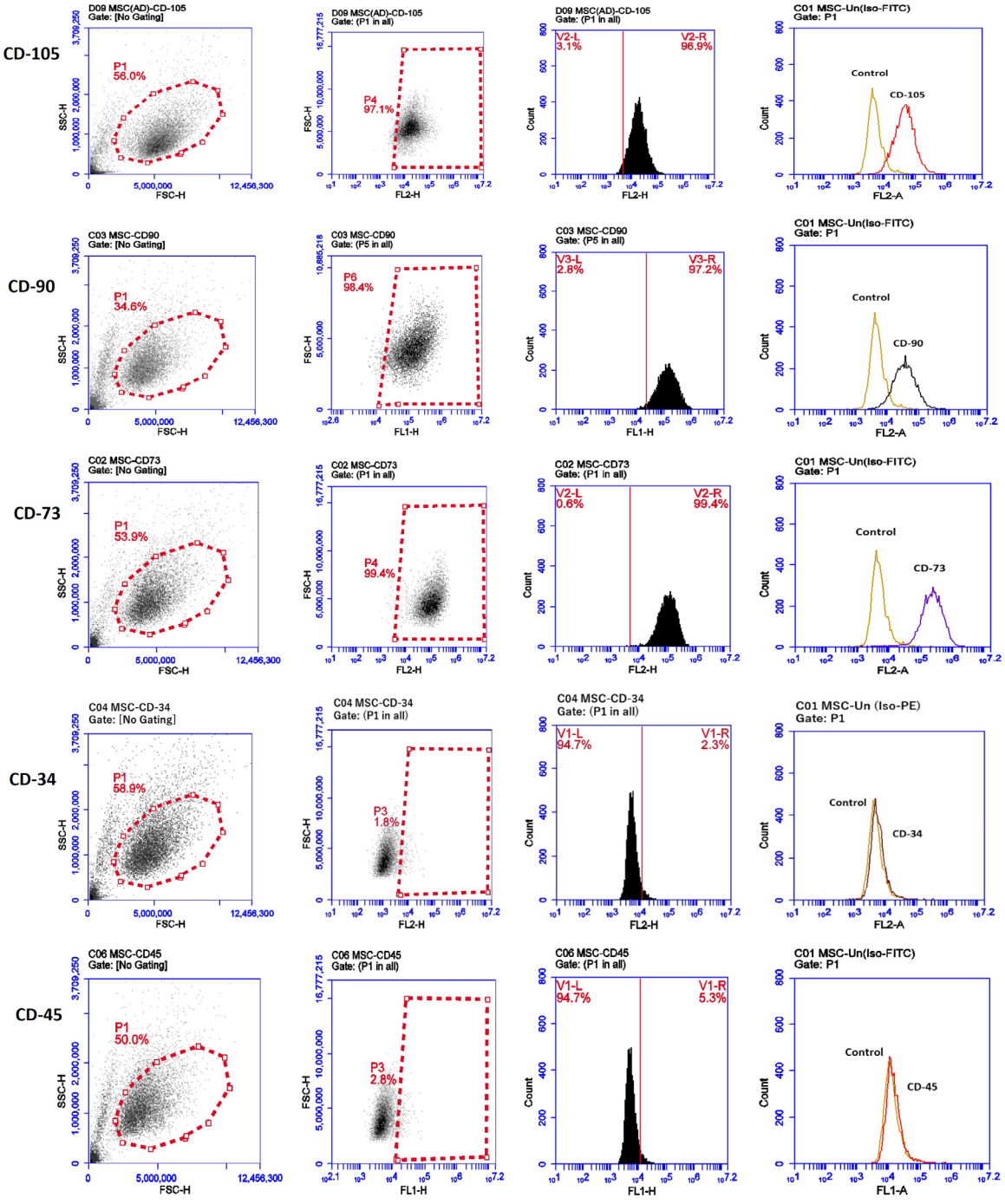

Figure 2. Immunophenotypic characterization of UC-MSCs by flow cytometry. Representative analysis demonstrated strong positivity for mesenchymal stem cell markers (CD73: 99.4%, CD105: 96.9%, CD90: 97.2%) and absence of hematopoietic lineage markers (CD34: 2.3%, CD45: 5.3%), confirming the MSC phenotype.

vere adverse events were reported. Transient fever occurred in 36.3% of patients (4 of 11), resolving spontaneously within 24-48 hours without intervention. Muscle pain was reported in 18.2% (2 of 11: P5, P11). One patient (P11, 9.1%) exhibited mild acute allergic reactions (pruritus without rash or respiratory compromise). There were no cases of infection, gastrointestinal disturbances, organ dysfunction, cardiovascular events, or nausea/vomiting. All side effects were self-limiting and required no therapeutic (**Table 1**).

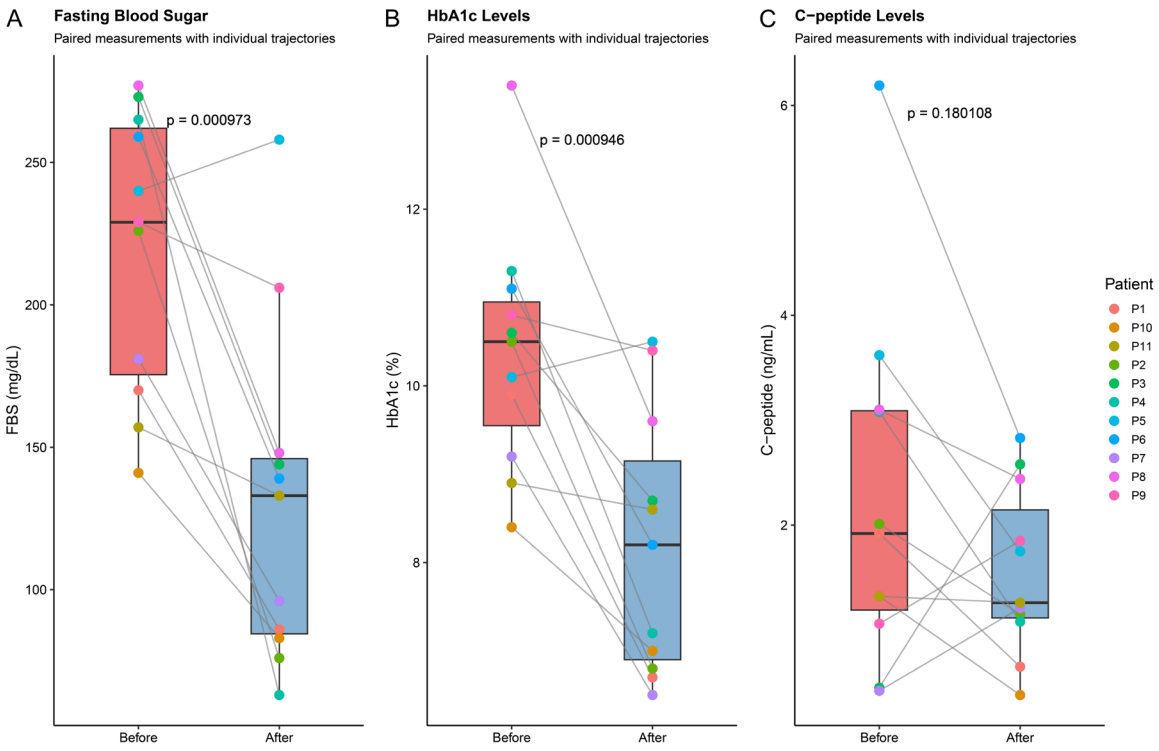

Figure 3. Glycemic parameter changes following stem cell therapy in T2DM patients. (A) Fasting blood sugar (FBS) levels. (B) HbA1c levels. (C) C-peptide levels. Data presented as mean ± SD (A-C) and individual patient trajectories. Statistical analysis by paired t-test.

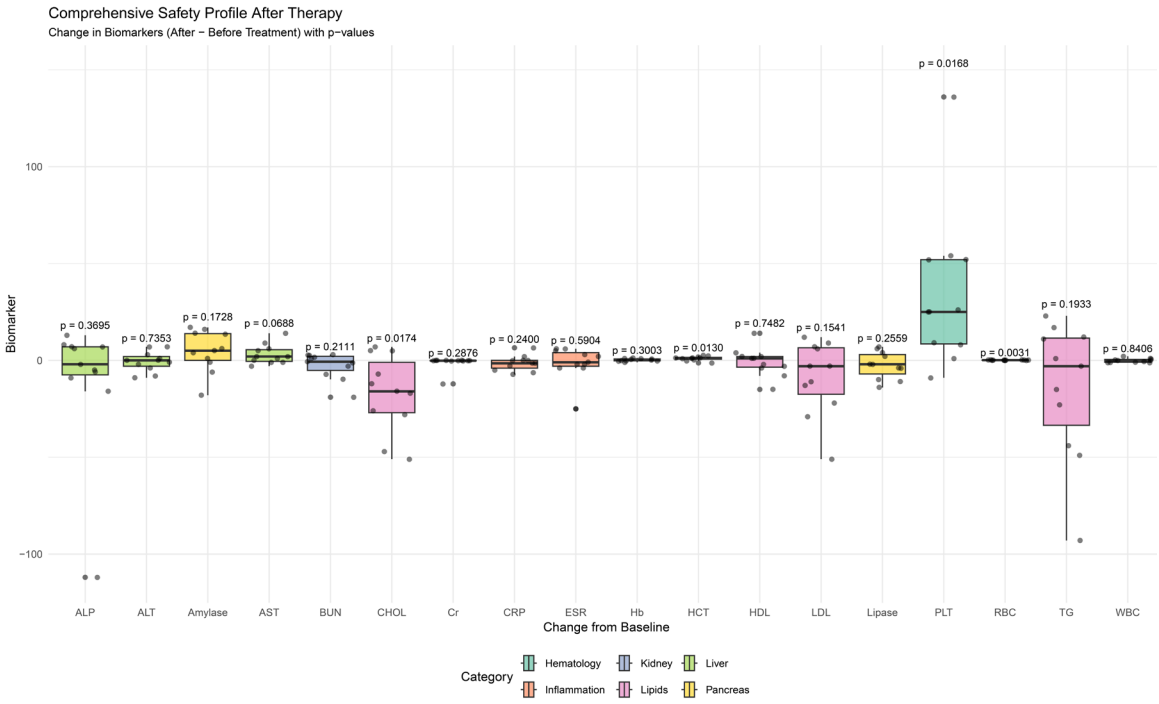

Figure 4. Safety profile following stem cell therapy. Data presented as mean ± SD with individual patient trajectories. Dashed lines indicate normal reference ranges.

Table 1. Summary of adverse events after umbilical cord-derived mesenchymal stem cells transplantation

P. NO	Fever	Muscle Pain	Acute and long-term Allergic Reactions	Infection	Gastrointestinal Disturbances	Organ Dysfunction	Cardiovascular Issues	Nausea/ Vomiting
P1	NA	NA	NA	NA	NA	NA	NA	NA
P2	NA	NA	NA	NA	NA	NA	NA	NA
P3	+	NA	NA	NA	NA	NA	NA	NA
P4	NA	NA	NA	NA	NA	NA	NA	NA
P5	+	+	NA	NA	NA	NA	NA	NA
P6	+	NA	NA	NA	NA	NA	NA	NA
P7	NA	NA	NA	NA	NA	NA	NA	NA
P8	NA	NA	NA	NA	NA	NA	NA	NA
P9	NA	NA	NA	NA	NA	NA	NA	NA
P10	NA	NA	NA	NA	NA	NA	NA	NA
P11	+	+	+	NA	NA	NA	NA	NA

Abbreviation: N/A, Not Applicable.

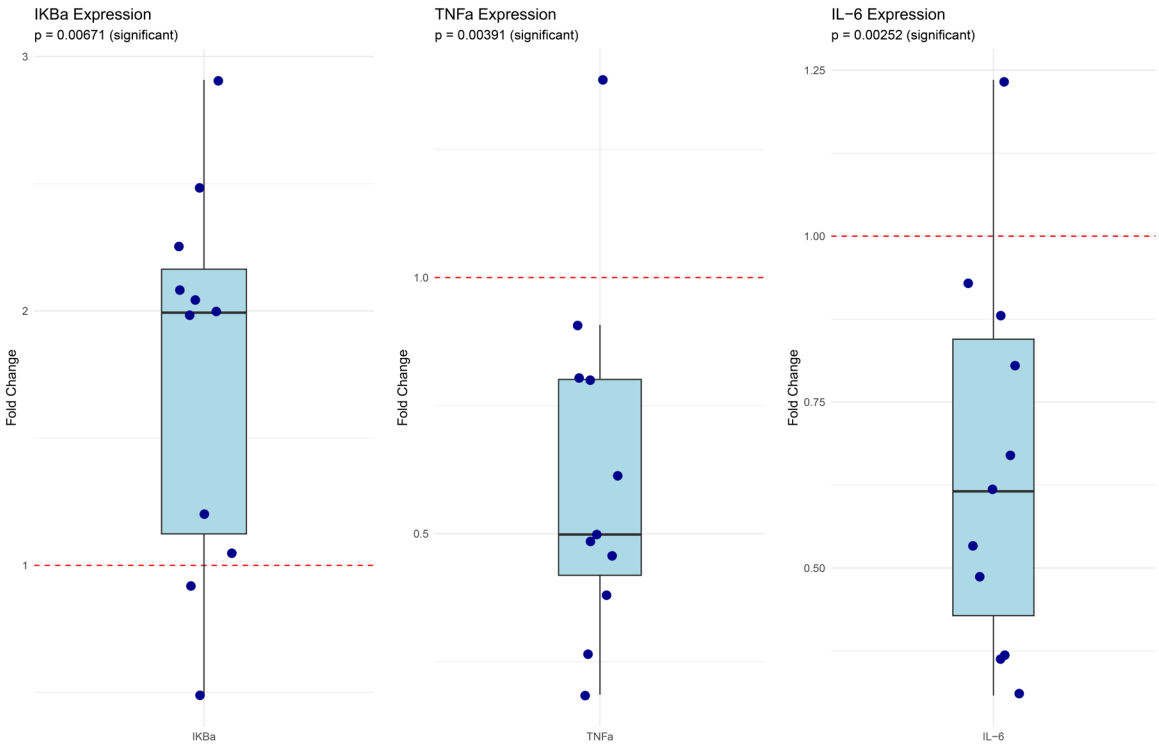

Figure 5. Inflammatory gene expression changes following stem cell therapy including IKBα, TNFα, IL-6. Data presented as mean fold change ± SEM relative to baseline. Dashed line indicates no change (fold change = 1). Individual patient responses shown as connected dots.

Gene expression changes following stem cell therapy

Quantitative analysis of inflammatory pathway genes showed significant transcriptional changes after stem cell therapy (**Figure 5**). The treatment triggered a coordinated anti-inflammatory response. First, IKBα expression increased by 1.76 ± 0.74-fold (P = 0.0067), indicating strong inhibition of the NF-κB signaling pathway. Second, TNFα expression decreased by 0.62 ± 0.34-fold (P = 0.0039), reflecting

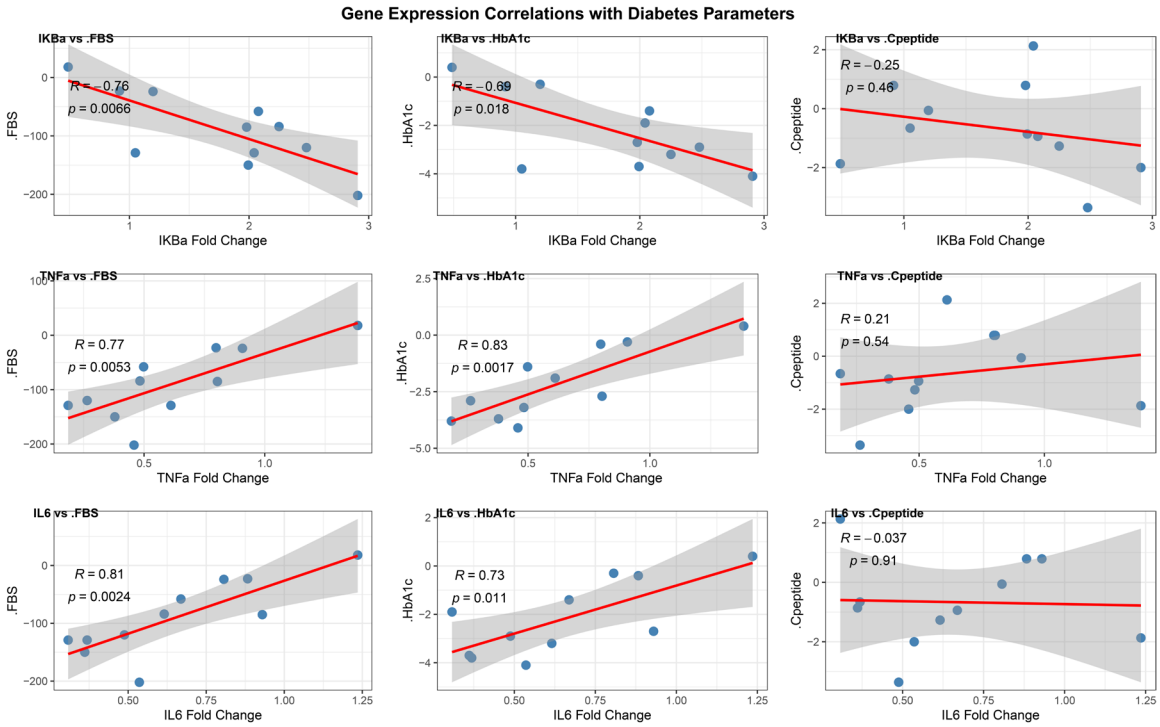

Figure 6. Correlation analysis of expression of IKBα, TNFα and IL-6 as inflammatory markers with glycemicparameter include ΔFBS, HbA1c, and C-peptide.

reduced pro-inflammatory cytokine production. Third, IL-6 levels declined by 0.65 ± 0.29-fold (P = 0.0025), suggesting attenuation of downstream inflammatory cascades.

Correlation analysis of gene expression of inflammatory markers and glycemic parameter

Our correlation analysis revealed three distinct molecular-metabolic interactions patterns after stem cell therapy (**Figure 6**). First, TNFα and IL-6 showed a strong positive correlation (r = 0.88, P < 0.01), indicating coordinated inflammatory pathway activation. Second, all three inflammatory markers correlated significantly with glycemic parameters IKBα correlated negatively with both ΔHbA1c (r = -0.69, P < 0.01) and ΔFBS (r = -0.76, P < 0.01). TNFα and IL-6 showed positive correlations with these parameters (TNFα-HbA1c: r = 0.83; TNFα-FBS: r = 0.77; IL6-HbA1c: r = 0.73; IL6-FBS: r = 0.81; all P < 0.01). Third, no significant correlations were observed between inflammatory markers and ΔC-peptide (all |r| < 0.25, P > 0.05), suggesting these pathways may not directly affect β-cell function recovery. The strong TNFα and IL-6 correlation may indicate co-regulation via common upstream pathways, such as NF-κB or JAK-STAT signaling.

Mechanistic basis of stem cell therapy response in T2DM

Stem cell therapy in diabetic patients resulted in three distinct metabolic response patterns based on changes in C-peptide and HbA1c levels: 1. Improved Insulin Secretion (n = 3/11; Patients 3, 7, 9): These patients showed increased C-peptide levels (Δ > 0 ng/mL) and decreased HbA1c (Δ < -0.5%), indicating restored β-cell function. 2. Improved Insulin Sensitivity (n = 7/11; Patients 1, 2, 4, 6, 8, 10, 11): This group had decreased HbA1c (Δ < -0.5%) despite stable or decreased C-peptide levels (Δ ≤ 0 ng/mL), suggesting enhanced glucose uptake and insulin action (**Figure 7A**). 3. Non-response (n = 1/11; Patient 5): This patient's HbA1c increased (+0.4%) and C-peptide declined, showing no therapeutic benefit.

Gene expression analysis showed significant downregulation of TNFα (median fold change [FC] = 0.45) and upregulation of IKBα (FC = 1.99) in the insulin sensitivity group compared

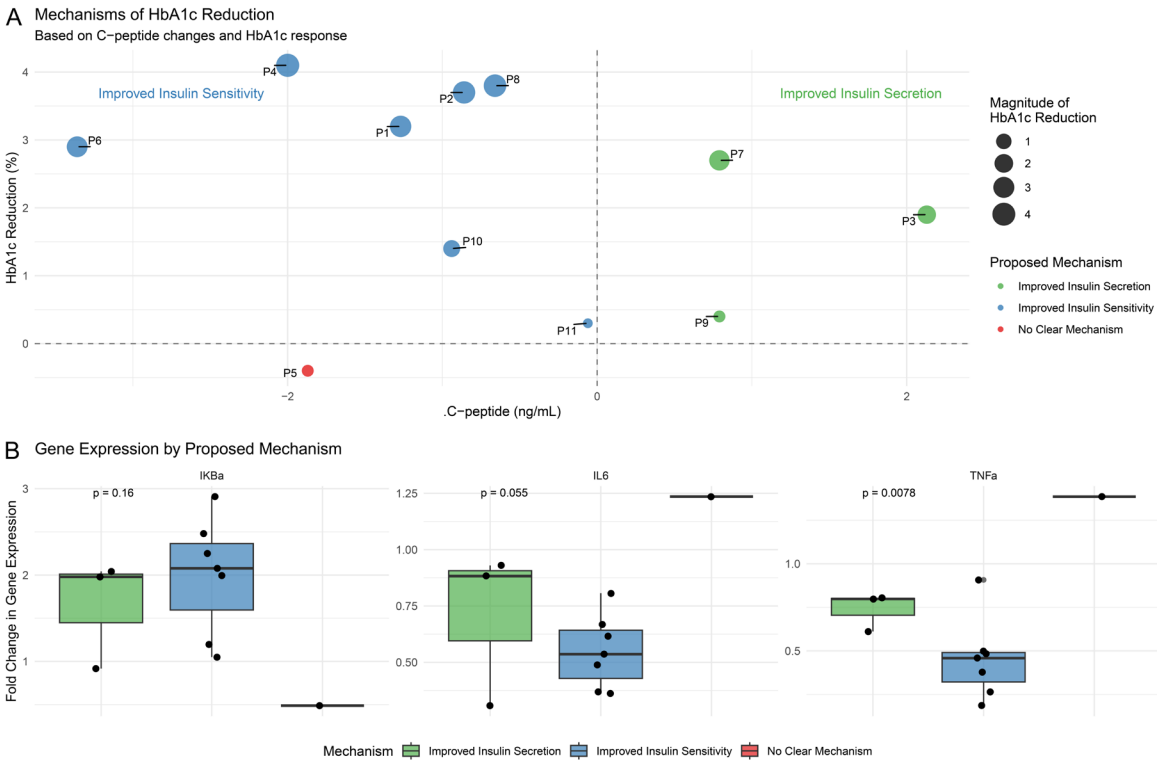

Figure 7. Bimodal mechanisms of therapeutic response. A. Patients clustered by therapeutic mechanism. Quadrants defined by ΔC-peptide (x-axis) and HbA1c reduction (y-axis). B. Fold changes in inflammatory genes by mechanism group. Boxplots show median/IQR; points = individual patients. Data presented as mean ± SEM with individual patient values overlaid. Statistical analysis by one-way ANOVA with Tukey post-hoc testing. Dashed lines indicate thresholds for clinical response (ΔHbA1c ≤ -0.5%) and β-cell functional improvement (ΔC-peptide > 0 ng/mL).

to the secretion group (TNFα FC = 0.74, IKBα FC = 1.65; P = 0.0078, P = 0.016). IL6 also tended to be downregulated (FC = 0.55 vs. 0.71; P = 0.055) (**Figure 7B**). The non-responder showed increased TNFα and IL6 expression and decreased IKBα, indicating ongoing inflammatory activity.

The study found that 64% of patients responded positively to stem cell therapy, mainly due to improved insulin sensitivity. This highlights the significant role of immune modulation, particularly through TNFα-NFκB axis regulation, as the primary therapeutic mechanism. A smaller group (27%) achieved glycemic control by enhancing β-cell function and insulin secretion, with less pronounced anti-inflammatory effects. The single non-responder underscores the importance of baseline inflammatory status as a potential predictor of treatment response. These results suggest that stem cell therapy reduces blood glucose levels via both metabolic (insulin sensitizing) and regenerative (β-cell restoration) pathways. Treatment effectiveness is influenced by individual inflammatory profiles.

Glycemic outcomes and molecular predictors of stem cell therapy in T2DM

Based on our results, 73% (8/11) of patients achieved a clinically significant HbA1c reduction of ≥ 0.5%. Additionally, 27% (3/11) reached the glycemic target of HbA1c < 7.0% (**Figure 8A**, **8B**). Multivariate regression analysis showed that combined changes in anti-inflammatory gene expression (IKBα, TNFα, and IL6) explained 74% of the variance in HbA1c improvement (R^2 = 0.74, P = 0.0186) (**Figure 8C**). Although no individual gene reached statistical significance, their regression coefficients showed distinct patterns. IKBα had a strong inverse relationship with HbA1c reduction (β = -0.641 per FC, P = 0.25), consistent with its role in reducing NF-κB-driven inflammation andIR. TNFα showed a paradoxical positive association (β = +3.049, P = 0.16), suggesting compensatory inflammatory

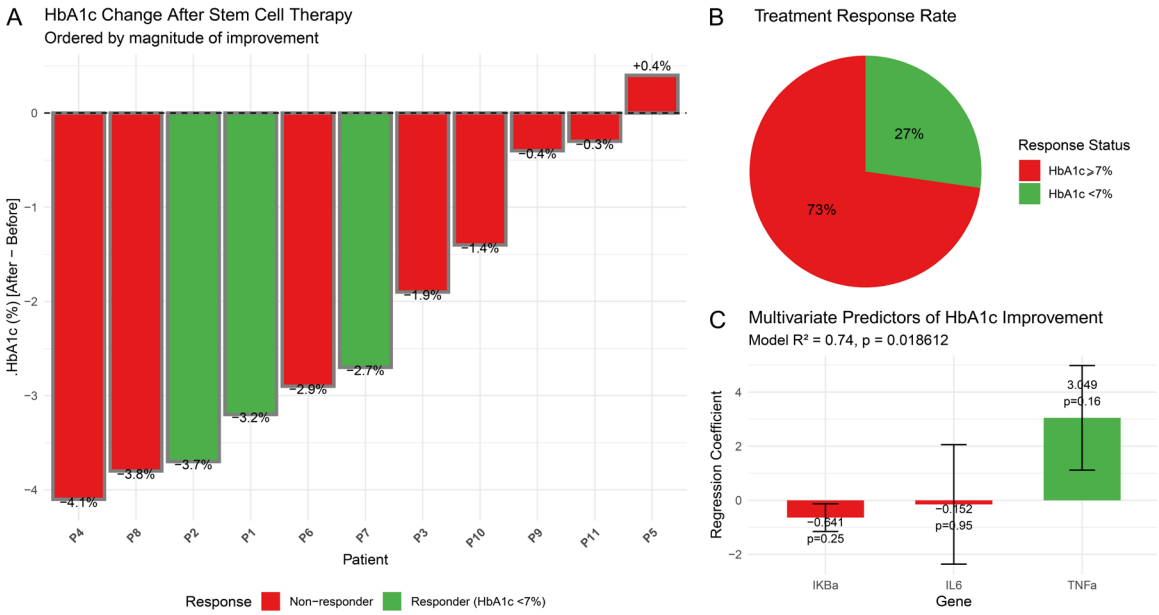

Figure 8. Glycemic outcomes and predictors of response. A. Waterfall plot of individual HbA1c changes. Green bars: patients achieving HbA1c < 7%. B. Response rates stratified by HbA1c targets. C. Multivariate coefficients for gene expression predictors.

mechanisms or context-dependent roles in glucose metabolism. IL6 showed no meaningful association (β = -0.152, P = 0.95).

Discussion

The current management of T2DM is based on lifestyle modification combined with stepwise pharmacotherapy. Metformin remains the first-line therapy, improving hepatic insulin sensitivity and being weight-neutral, but gastrointestinal intolerance and contraindications in patients with impaired renal function restrict its use. Additional drug classes include sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual incretin agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, sulfonylureas, thiazolidinediones, and insulin. While each class provides distinct metabolic benefits, all are associated with important drawbacks. For example, SGLT2 inhibitors confer cardiovascular and renal protection but increase the risk of genital infections and, rarely, euglycemic ketoacidosis. GLP-1 RAs and dual incretin agonists achieve robust reductions in HbA1c and body weight but are limited by gastrointestinal intolerance, discontinuation due to side effects, and the burden of injections. DPP-4 inhibitors are generally well tolerated but offer only modest glucose-lowering efficacy. Sulfonylureas are inexpensive and effective in lowering HbA1c, yet they are associated with hypoglycemia and weight gain. Thiazolidinediones improve insulin sensitivity but can cause edema, weight gain, fracture risk, and raise concerns regarding heart failure. Insulin remains the most potent glucose-lowering agent, but it carries the risks of hypoglycemia and weight gain, while daily self-management imposes a considerable treatment burden. Even metabolic or bariatric surgery, which can provide durable glycemic improvements in selected individuals, is limited by operative risks and eligibility criteria. Importantly, most of these therapeutic strategies primarily lower blood glucose but do not directly target the chronic low-grade inflammation that contributes to IR and β-cell dysfunction, and thus polypharmacy often becomes necessary over time.

Against this background, allogeneic UC-MSCs represent a mechanistically distinct therapeutic approach. UC-MSCs release immunomodulatory and trophic factors that suppress NF-κB-driven inflammatory signaling by downregulating TNF-α and IL-6 while upregulating IKBα. Through these pathways, UC-MSCs enhance insulin sensitivity and preserve β-cell function, thereby addressing key drivers of T2DM pathophysiology that conventional drugs largely leave untreated. Our study, consistent with previous

clinical investigations, demonstrated that IV infusion of UC-MSCs not only improved glycemic control, with significant reductions in HbA1c and fasting glucose, but also exhibited a favorable safety profile, with adverse events limited to transient fever and mild myalgia. Beyond their mechanistic advantages, UC-MSCs offer practical benefits, as the umbilical cord is an abundant and non-invasive source of high-quality cells that can be expanded under GMP conditions, providing an "off-the-shelf" product with low immunogenicity and consistent therapeutic properties. Collectively, these features suggest that UC-MSCs could complement existing guideline-based therapies and pave the way for precision approaches, in which biomarkers such as baseline C-peptide and inflammatory profiles may help identify patients most likely to benefit. Nonetheless, critical challenges remain, including uncertainties regarding the durability of clinical effects, optimal dosing and administration schedules, and the need for standardized criteria for patient selection. Larger, randomized controlled trials are therefore essential to define the long-term efficacy and to establish the place of UC-MSC transplantation within the therapeutic landscape of T2DM.

This clinical study shows that IV infusion of allogeneic UC-MSCs in patients with T2DM significantly improves glycemic control and modulates inflammatory pathways. It also demonstrates a favorable safety profile. Our findings add to the growing evidence supporting MSC-based therapies for T2DM. They provide new insights into anti-inflammatory regulation and variability in treatment response.

Our cohort showed a significant reduction in HbA1c (-2.1%, $P = 0.00095$) and FBS (-93.7 mg/dL, $P = 0.00097$), consistent with previous preclinical and clinical studies. For example, Zang et al. (2022) reported a 1.31% decrease in HbA1c ($P < 0.01$) in a Phase II trial of UC-MSCs. This aligns with our findings despite differences in cell dosage and administration frequency. Similarly, Liu et al. (2014) showed improved HbA1c and β-cell function after Wharton's jelly MSC (WJ-MSC) transplantation. However, their intrapancreatic delivery limits direct comparison [36]. Our results also agree with long-term data from Hu et al. (2012), who reported sustained improvements in HbA1c and C-peptide over 36 months after autologous bone marrow mononuclear cell (BM-MNC) implantation in T2DM patients [31]. Notably, our C-peptide levels remained stable, contrasting with Jiang et al. (2011), who found a significant increase after placental MSC treatment [37]. This discrepancy may result from our cohort's advanced β-cell dysfunction and shorter follow-up (2 vs. 24 months). Additionally, we interpret the overall stability of C-peptide as evidence that UC-MSCs predominantly act by enhancing insulin sensitivity rather than regenerating β-cell mass in patients with long-standing T2DM, where β-cell reserve is already limited. However, Wu et al., demonstrated that autologous BM-MNC (without hyperbaric oxygen) increased C-peptide AUC by 43.8% [32]. This suggests that hematopoietic progenitors in BM-MNCs may directly stimulate β-cell function more than the immunomodulatory effects of UC-MSCs. Mechanistically, we identified two distinct response phenotypes in our study. Seven of 11 patients showed improved insulin sensitivity, marked by reduced HbA1c without increased C-peptide. Three of 11 patients had improved insulin secretion, with increased C-peptide and reduced HbA1c. This bimodal response aligns with Bhansali et al. (2017), who reported that bone marrow MSCs enhanced insulin sensitivity via IRS-1 upregulation, while mononuclear cells increase C-peptide secretion [30]. Building on this, we propose a mechanistic model in which attenuation of NF-κB signaling decreases adipose-liver inflammatory crosstalk, relieves SOCS3-mediated impairment of IRS-1, and reduces hepatic gluconeogenesis and lipolysis-driven free fatty acid (FFA) flux. In this framework, the "insulin-sensitivity responder" profile observed in most patients indicates intact downstream insulin signaling once inflammatory tone is suppressed, whereas the "insulin-secretion responder" profile points to residual β-cell reserve that becomes unmasked in an improved metabolic milieu. The single non-responder likely reflects a baseline inflammatory set-point exceeding the paracrine immunomodulation achievable with standard UC-MSC dosing.

Our data further show that insulin sensitivity responders had significant TNFα suppression (FC = 0.45) and IKBα upregulation (FC = 1.99). This indicates preferential modulation of the NF-κB pathway. In contrast, secretion responders exhibited weaker anti-inflammatory effects. This suggests regenerative mechanisms independent of TNFα-NF-κB axis regulation. These

findings agree with Gao et al. (2018), who demonstrated that apelin-engineered WJ-MSCs improved insulin sensitivity and β-cell proliferation through distinct but simultaneous pathways [38]. Taken together, these bimodal patterns reinforce the importance of pre-treatment stratification using inflammatory gene panels alongside β-cell reserve indices to optimize patient selection, dosing, and clinical expectations.

A key finding of our study was the coordinated modulation of inflammatory pathways after UC-MSC transplantation. Pro-inflammatory genes, including TNFα (0.62-fold, P = 0.0039) and IL-6 (0.65-fold, P = 0.0025), were downregulated. At the same time, IKBα, a critical NF-κB pathway inhibitor, was upregulated (1.76-fold, P = 0.0067).

These molecular changes are significant as NF-κB suppression via IKBα improves insulin sensitivity by attenuating NF-κB-driven inflammation. This is supported by a strong inverse correlation between IKBα and HbA1c (r = -0.69, P < 0.01), consistent with preclinical evidence showing that NF-κB activation promotes serine phosphorylation of IRS-1, thereby impairing insulin signaling [7]. Our data quantitatively demonstrate this relationship clinically, with changes in IKBα accounting for 48% of the variance in HbA1c. Additionally, our findings reinforce the roles of TNFα and IL-6 in mediating IR, as both are positively correlated with HbA1c (r = 0.83 and r = 0.81, respectively). This aligns with preclinical evidence showing that NF-κB activation promotes serine phosphorylation of IRS-1, thereby impairing insulin signaling [7, 9, 10]. Furthermore, our findings support previous clinical observations by Kong et al. (2014), who reported increased Tregs following UC-MSC infusion [35]. Our gene-level data confirm the connection between TNFα and IL-6 suppression and HbA1c reduction. Additionally, we complement the study by Hu et al. (2016) on sustained anti-inflammatory effects of WJ-MSCs by identifying specific gene targets (IKBα, TNFα) and characterizing their temporal changes [39]. The lack of correlation between inflammatory markers and C-peptide levels aligns with the suggestion by Guan et al. (2015) that non-inflammatory pathways, such as VEGF secretion, may contribute to β-cell repair [40]. This implies that angiogenesis could represent an alternative mechanism for β-cell recovery.

The absence of severe adverse events in our study highlights the safety of allogeneic UC-MSCs, consistent with broader clinical trial evidence for MSC-based therapies. We interpret these safety signals as being most compatible with transient cytokine-related reactions rather than organ toxicity, since hematologic shifts remained within reference ranges and were not accompanied by thrombotic, renal, or cardiovascular complications. From a translational perspective, our data suggest two pragmatic optimization paths: (i) front-loading anti-inflammatory benefit (e.g., higher initial dose or early repeat dosing) in patients with high inflammatory burden to minimize non-response, and (ii) combining UC-MSCs with β-cell-trophic strategies (e.g., EV-enriched products or islet-directed delivery) in patients with demonstrable β-cell reserve. Collectively, these insights argue for biomarker-anchored, mechanism-specific trial designs rather than one-size-fits-all protocols. Transient fever occurred in 36.3% of our cohortand typically resolved spontaneously within 48 hours. This phenomenon was similarly reported by Liu et al. (2014) and Zang et al. (2022), who attributed it to immune cell activation rather than true infection [36, 41]. Our study also showed low immunogenicity, with only one mild allergic reaction among 11 patients. This supports the hypoimmunogenic profile of UC-MSCs [24]. These findings align with Skyler et al., who reported that allogeneic bone marrow-derived mesenchymal precursor cells (MPCs) did not cause donor-specific anti-HLA antibodies or sensitization, even at high doses [33]. The absence of renal, hepatic, or cardiovascular toxicity in both studies highlights the safety of MSCs in metabolically compromised patients. This contrast with conventional diabetes treatments, which pose risks of hypoglycemia, weight gain, and organ stress. This safety profile applies to different administration routes. For example, Ashoobi et al. reported no severe adverse events after intramuscular WJ-MSC delivery for critical limb ischemia [42]. Additionally, Skyler et al. found that 33% of high-dose MPC recipients achieved HbA1c levels below 7%, compared to 0% in placebo controls. This indicates that the observed safety is accompanied by potential metabolic benefits [33]. The heterogeneity in treatment response to UC-MSC therapy underscores the need for patient stratification strategies. Our study identified a non-responder with elevated TNFα and

IL-6 levels and suppressed IKBα expression. This suggests that baseline inflammatory may predict resistance by maintaining a pro-inflammatory environment that opposes MSC-mediated immunomodulation. Wang et al. (2024) found that preserved β-cell function, measured by high C-peptide AUC, predicts a positive response [43]. Our findings complement this by suggesting that inflammatory gene expression profiles mayserve as additional biomarkers for patient selection. Patients with intact β-cell function mightbenefit most from MSC-induced insulin sensitization, as shownby Bhansali et al. (2009) [30]. Conversely, patients with prominent inflammation may require adjunct anti-inflammatory therapies to enhance MSC efficacy. This difference in predictive markers may reflect disease stage. Early-stage patients respond mainly through insulin-sensitizing, while advanced cases need inflammation control. A thorough pre-therapeutic assessment of metabolic (C-peptide) and inflammatory (TNFα, IL-6, IKBα) markers could enable personalized treatments. When comparing UC-MSC therapy with other MSC sources and methods, it is important to consider the unique features and benefits of each approach. Our findings show both similarities and differences compared to studies using other MSCs sources. Unlike Liu et al. (2014) and Hu et al. (2016), who reported significant C-peptide improvements with Wharton's jelly-derived MSCs (WJ-MSCs), we did not observe such changes [36, 39]. This difference may result from their intrapancreatic delivery method, which likely enhances localized effects on β-cells, and from younger patient populations with greater regenerative capacity. Conversely, our results agree with placental MSC studies, such as Jiang et al. (2011), which reported similar metabolic improvements in some patients. This suggests common therapeutic mechanisms across different MSCs sources [37]. The study by Gao et al. (2018) on apelin-engineered WJ-MSCs offers valuable insights into enhancing MSC efficacy through genetic modification to overexpress metabolic regulators. This strategy could be applied to improve UC-MSC performance. Recent advances in extracellular vesicle (EV) technology, shown by Du et al. (2025), address current limitations by enabling targeted delivery of MSC-derived therapeutic factors. This approach may also reduce risks linked to whole-cell administration. These comparative suggest that while MSC source can influence outcomes, administration route, patient selection, and cellular engineering are key factors for therapeutic success. Our short-term, inflammation-linked glycemic improvements are directionally concordant with recent real-world registry data of allogeneic UC-MSC infusion in T2DM that reported durable metabolic and inflammatory benefits with a favorable safety profile. In parallel, a recent Cytotherapy study identified higher C-peptide AUC (and sex differences) as predictors of clinical response; our dataset complements this by highlighting inflammatory gene dynamics as orthogonal predictors tied to an insulin-sensitivity mode of benefit. Together, these reports support a precision framework that integrates β-cell reserve and inflammatory status for patient stratification and dosing. This study has several limitations. The small sample size (n = 11) and short follow-up (2 months) limit subgroups analysis, long-term effects assessment, and evaluation of β-cell mass changes. Without insulin clamp studies, we used indirect measures of insulin sensitivity. Also, the lack of a placebo control may have led to an overestimation of treatment effects. These issues highlight key areas for future research. Future studies use HbA1c reduction as the primary endpoint and stratify patients by IR and inflammation levels. Detailed mechanistic studies with hyperglycemic clamps and tissue analysis could provide direct evidence of β-cell changes. Validating biomarkers like IKBα, TNFα expression, and C-peptide levels may enable personalized treatment. Ultimately, tailoring regenerative interventions to address both metabolic (insulin sensitivity) and inflammatory axes may shift the treatment paradigm from glycemic management toward functional remission in T2DM.

Conclusion

This study demonstrates that allogeneic UC-MSC transplantation safely improves glycemic control in T2DM. The effect is mediated by suppression of NF-κB-driven inflammation through IKBα, leading to enhanced insulin sensitivity. The therapeutic response can be classified into insulin sensitivity and insulin secretion phenotypes. This underscores both the versatility of MSCs and the need for patient stratification. Our findings support previous evidence of MSC efficacy and add quantitative insights into how inflammatory pathway regulate metabolic out-

comes. Future studies should focus on larger and longer-term trials, ideally incorporating multi-omics approaches to refine patient selection and optimize treatment protocols. UC-MSC therapy shows potential as a disease-modifying strategy for T2DM, moving beyond symptomatic management towards a functional cure.

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Disclosure of conflict of interest

None.

Abbreviations

DM, Diabetes mellitus; T2DM, Type 2 Diabetes Mellitus; HbA1c, Glycated Hemoglobin A1c; FBS, Fasting Blood Sugar; NF-κB, Nuclear Factor-kappa B; IR, Insulin Resistance; MDS, Metabolic Dysfunction Syndrome; ERS, Endoplasmic Reticulum Stress; SOCS3, Suppressors of Cytokine Signaling 3; IRS-1, Insulin Receptor Substrates; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-Alpha; UC-MSC, Umbilical Cord-Derived Mesenchymal Stem Cells; IRCT, Iranian Registry of Clinical Trials; qRT-PCR, Quantitative Reverse Transcription Polymerase Chain Reaction; GMP, Good Manufacturing Practice; PBS, phosphate-buffered saline; α-MEM, Alpha Minimum Essential Medium; ISCT, International Society for Cellular Therapy; IV, Intravenous; FC, Fold Change; SD, Standard Deviation; SEM, Standard Error of the Mean; ANOVA, Analysis of Variance; Tregs, Regulatory T Cells; VEGF, Vascular Endothelial Growth Factor; HTLV I/II, Human T-Cell Lymphotropic Virus Type I/II; HBsAg, Hepatitis B Surface Antigen; HCV Ab, Hepatitis C Virus Antibody; HIV, Human Immunodeficiency Virus; ESR, Erythrocyte Sedimentation Rate; CRP, C - reactive protein; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; ALP, Alkaline Phosphatase; BUN, Blood Urea Nitrogen; SNPs, Single Nucleotide Polymorphisms; Cr, Creatinine; WBC, White Blood Cell; HLA, Human Leukocyte Antigen; BM-MNC, Bone Marrow Mononuclear Cell; EV, Extracellular Vesicle; AUC, Area Under the Curve; FFA, Free Fatty Acid.

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