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Human-Umbilical Cord-Mesenchymal Stem Cells (hUC-MCSs) Therapy with Extra vesicles (EVs) Booster Improves Recovery in Type 2 Diabetes Mellitus with Cardiovascular Disease : a case report

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ABSTRACT

Background: Type 2 diabetes (T2DM) is a chronic metabolic disorder characterized by insulin resistance and β-cell dysfunction, leading to persistent hyperglycemia and complications. Studies have explored mesenchymal stem cell (MSC)-based therapies and their extracellular vesicles (EVs) as novel approaches for metabolic regulation and tissue repair. **Case:** A 43-year-old male patient exhibited symptoms including excessive thirst and hunger, frequent urination, fatigue, and intermittent blurry vision. He had type 2 diabetes and recently worsened symptoms. The obese patient had elevated blood glucose, HbA1c, triglycerides, and uric acid. He received umbilical cord-derived mesenchymal stem cells ($161{,}6 \times 10^6$ cells), followed by seven intramuscular EV injections (1.5 cc each), along with diet and antioxidant supplements. **Results:** Three months after the conclusion of treatment, laboratory test showed significant improvement, with fasting glucose levels measuring at 91 mg/dL, HbA1c levels at 5,1%, triglyceride levels at 151 mg/dL, uric acid levels at 4,9 mg/dL, and an erythrocyte sedimentation rate of 12 mm/hr. The clinical symptoms such as nocturia, fatigue, and neuropathic pain, demonstrated a substantial improvement, as well as led to the resolution of skin xerosis and heel fissures. **Conclusion:** This case suggests that combined UC-MSC and EV therapy, complemented by lifestyle modification, may contribute to metabolic stabilization and symptomatic relief in T2DM patients.

Keywords: Type 2 diabetes mellitus, mesenchymal stem cells, extracellular vesicles, regenerative therapy, metabolic disorder

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a highly prevalent metabolic disorder characterized by insulin resistance, chronic low-grade inflammation, progressive pancreatic beta cell dysfunction, and multiple metabolic disturbances, including dyslipidemia and hyperuricemia[1]. Long-term hyperglycemia and metabolic stress lead to microvascular and macrovascular complications, as well as impaired tissue repair. Although standard-of-care treatments (lifestyle changes, oral agents, GLP-1 receptor agonists, and insulin) reduce hyperglycemia and its associated complications, they often fail to restore β-cell function or reverse the underlying pathophysiology[2].

Mesenchymal stem cells (MSCs) are attractive for regenerative strategies in metabolic disorders due to their pleiotropic properties, which include immunomodulation, anti-inflammatory paracrine signaling, trophic support, and modest differentiation potential[3–5]. MSCs have been isolated from multiple tissues, including bone marrow, adipose tissue, and umbilical cord/Wharton's jelly. Umbilical cord-derived MSCs (UC-MSCs) are especially attractive due to their noninvasive collection, high proliferative capacity, and lower immunogenicity. Several clinical trials and systematic reviews/meta-analyses have reported improvements in glycemic indices (e.g., fasting glucose and HbA1c levels), reduced insulin requirements, and an acceptable short-term safety profile following MSCs transplantation in patients with T2DM[6,7].

Preclinical evidence suggests that the therapeutic effects of MSCs are primarily mediated by paracrine factors rather than durable engraftment. Among these factors, extracellular vesicles (EVs), including exosomes and small EVs, have emerged as key mediators[8,9]. MSC-derived EVs (MSC-EVs) carry microRNAs, proteins, lipids, and other cargo that have the capacity to modulate insulin signaling, suppress inflammation, promote survival and repair of pancreatic β cells, improve peripheral insulin sensitivity, and stimulate angiogenesis and nerve repair in cases of diabetic complications[10,11].

From a mechanistic perspective, MSCs and MSC-EVs may exert their effects through several pathways relevant to T2DM. These pathways include, but are not limited to: (1) reducing systemic and islet inflammation[12,13], (2) promoting β-cell survival and regeneration[14], (3) enhancing peripheral insulin signaling (PI3K/Akt pathway, GLUT4 translocation)[15,16], and (4) improving microvascular and neural repair that ameliorates diabetic complications such as neuropathy and poor wound healing[17]. These multifactorial effects may also positively modify metabolic parameters (triglycerides, uric acid) indirectly via improved insulin sensitivity and reduced systemic inflammation. This case contributes to the current understanding of regenerative strategies for metabolic disorders by documenting the combined use of UC-MSC infusion and sequential EVs injections in a patient with long-standing T2DM and metabolic abnormalities.

CASE PRESENTATION

A 43-year-old male with complaints of persistent thirst, hunger (polydipsia and polyphagia), frequent nocturia (which disrupted his sleep), generalized weakness despite rest, weight gain reaching the obesity category, episodic numbness and cramps in the legs, and episodic blurred vision (waxing and waning over recent weeks). On physical exam, the patient has weight: 101 kg; height: 167 cm; blood pressure: 120/80 mmHg, temperature: 36°C, pulse: 87 bpm, respiration: 22x/min, SpO_2: 98%. Baseline laboratory tests revealed the patient's fasting plasma glucose (FPG): 153 mg/dL; HbA1c: 7,2%; leukocytes: 11,6 × 10^3/µl; erythrocyte sedimentation rate (ESR): 25 mm/h; triglycerides: 704 mg/dL; uric acid: 9,0 mg/dL. All other routine biomarkers, including those assessing renal, hepatic, and electrolyte function, were within normal limits.

The patient's medical history revealed a diagnosis of type 2 diabetes mellitus (T2DM) for 5 years. However, it was observed that the patient's symptoms had deteriorated significantly over the course of the past two years. Over the prior year, he had developed recurrent muscle cramps associated with joint pain (notably toes), a history of hyperuricemia, and a recent acute gout attack (monosodium urate deposition) in the right hallux two weeks prior to presentation. His chronic medications included mecobalamin 500 µg twice daily (1-0-1); Canderin 8 mg twice daily (1-0-1); Diaglifoz 10 mg once daily (0-1-0); CPG 75 mg once daily (0-1-0); Lipanthyl Penta 145 mg.

Table 1. Laboratory follow-up before and after combined UC-MSC and EV therapy

Test	Test result	
	Before (26 April 2025)	**After (8 August 2025)**
Routine hematology		
Hemoglobin	15,3 g/dL	14,9 g/dL
Hematocrit	45,7%	45,5%
Erythrocytes	5,4	5,15
Leukocytes	11,6 × 10^3/µL	6,4 × 10^3/µL
Lymphocytes	34%	43%
Hemostasis function		
Erythrocyte Sedimentation Rate (ESR)	25 mm/h	12 mm/h
D-dimer	<31,6 ng/mL	157 ng/mL
Carbohydrate metabolism		
Fasting Blood Glucose (FBG)	153 mg/dL	91 mg/dL
HbA1c	7,2%	5,1%
Liver function		
SGOT	14 U/L	23 U/L
SGPT	15 U/L	23 U/L
Lipid profile		
Cholesterol total	198 mg/dL	185 mg/dL
Triglycerides	704 mg/dL	151 mg/dL
HDL	28 mg/dL	40 mg/dL
LDL	97 mg/dL	120 mg/dL
Kidney function		
Urea	27 mg/dL	31 mg/dL
Creatinine	0,74 mg/dL	1,04 mg/dL
eGFR	116	88
Gout (uric acid)	9,0 mg/dL	4,9 mg/dL
High Sensitivity C-Reactive Protein (hs-CRP)	1,23 mg/L	1,5 mg/L

On May 13, 2025, the patient received an intravenous infusion of UC-MSCs at a dose of 161,6 × 10^6 cells, along with a single intramuscular injection of EVs (1,5 cc). On days 2 and 3, the patient received the second and third intramuscular doses of EVs, respectively. Subsequent EV administrations (fourth to seventh doses) were administered via intramuscular injection at weekly intervals, for a total of seven EV treatments. The patient was also enrolled in a health promotion program with a diet plan for diabetes concerns. Furthermore, the patient was prescribed a herbal antioxidant supplement formulation comprising *Centella asiatica*. Following the first treatment, the patient reported an improvement in overall vigor, a reduction in fatigue, a decrease in nocturnal urination frequency, and enhanced appetite control. Three months after treatment, patients were retested and exhibited significant progress. The following laboratory values demonstrated notable enhancements: FPG: 91 mg/dL; HbA1c: 5,1%; leukocytes: 6,4 × 10^3/µL; ESR: 12 mm/h; and triglycerides: 151 mg/dL; and uric acid: 4,9 mg/dL.

Overall, the patient exhibited marked improvement in several areas of health. This included improved sleep quality, reduced fatigue levels, resolution of a gout flare in the patient's right big toe, more controlled food and water intake, and subjective improvements in skin texture and elasticity. It

is noteworthy that a heel fissure (associated with xerosis cutis) that had been present before treatment had resolved. No serious adverse events were observed during the follow-up period.

DISCUSSION

This case report highlights a metabolic and symptomatic improvement following a combined regimen of UC-MSC infusion and EV therapy in a moderately obese patient with long-standing T2DM and comorbid dyslipidemia and hyperuricemia. These results may offer insights into novel regenerative strategies in metabolic disease. Below, we discuss possible mechanisms, compare to existing literature, and outline limitations and future directions. Dyslipidemia, a condition marked by abnormal levels of lipids (fats) in the blood, is a prevalent complication among individuals with chronic kidney disease (CKD)[18,19]. This condition contributes to the development of both cardiovascular disease and the progression of renal damage. Research has demonstrated a correlation between elevated triglycerides, increased LDL/cholesterol-rich lipoproteins, decreased HDL, and the accumulation of lipoprotein remnants with a more precipitous decline in glomerular filtration rate (GFR). Therefore, in a patient with T2DM and severe hypertriglyceridemia (as in this case), dyslipidemia might predispose to or exacerbate renal injury even before clinically overt renal failure.

Emerging preclinical evidence suggests that UC-MSCs can modulate lipid metabolism via multiple pathways. In obese diabetic mouse models, multiple infusions of UC-MSCs reduced hepatic accumulation of triglycerides and cholesterol and attenuated hepatic steatosis. These effects were mediated by the upregulation of fatty acid β-oxidation genes (e.g. PPARα, ACOX1, CPT1b) and the downregulation of lipogenesis-associated genes (e.g. FASN, ACC1, ACC2, LXR) in the liver[20]. Similarly, in a model of exogenous Cushing's syndrome, MSCs lowered LDL cholesterol by inhibiting the liver X receptor α (LXRα)–inducible degrader of LDL receptor (IDOL) pathway, thus stabilizing LDL receptor expression in hepatocytes[21]. These findings may help explain the significant reduction in serum triglycerides observed in this patient (from approximately 704 mg/dL to 151 mg/dL), suggesting that UC-MSC/EV therapy may have improved lipid handling and metabolic balance through similar molecular routes.

Beyond metabolic regulation, inflammation is a major driver of insulin resistance, β-cell dysfunction, and tissue injury (including vascular, neural and renal)[22,23]. UC-MSCs have multiple demonstrated anti-inflammatory actions. In T2DM rat models, UC-MSC infusion reduces activation of the NLRP3 inflammasome in target tissues, leading to decreased levels of IL-1β, IL-18, and TNF-α, which are key mediators of islet inflammation and insulin resistance[24,25]. UC-MSCs also drive a phenotypic switch of adipose tissue macrophages from pro-inflammatory (M1) to anti-inflammatory (M2), involving mediators such as IL-6, IL-4R, and STAT6[26]. Another study showed that the spleen plays a key role after UC-MSC infusion. The UC-MSCs home to the spleen and enhance the function of regulatory T cells (Tregs). They also elevate IL-10, which modulates inflammation systemically and helps mitigate insulin resistance[27,28]. Moreover, suppression of the TLR4/NF-κB pathway by UC-MSCs further reduces tissue inflammation in the islets, liver, and adipose tissue[29]. Taken together, these mechanisms provide a plausible explanation for the improvements observed in this patient.

CONCLUSION

This case supports the idea that UC-MSC plus EV therapy can lower blood glucose and beneficially modulate lipid metabolism and inflammation. These are involved in the pathophysiology of T2DM and in preventing complications, such as renal damage. The rapid and broad improvements observed suggest that targeting metabolic and inflammatory pathways may lead to more complete

metabolic restoration. However, more studies are needed to validate efficacy, safety, and mechanistic underpinnings.

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Competing Interests

The authors declare that there is no conflict of interest.

REFERENCES

1. Gao S, Zhang Y, Liang K, Bi R, Du Y. Mesenchymal Stem Cells (MSCs): A Novel Therapy for Type 2 Diabetes. *Stem Cells Int*. 2022;2022:1-17. doi:10.1155/2022/8637493
2. Habiba UE, Khan N, Greene DL, Ahmad K, Shamim S, Umer A. Meta-analysis shows that mesenchymal stem cell therapy can be a possible treatment for diabetes. *Front Endocrinol (Lausanne)*. 2024;15. doi:10.3389/fendo.2024.1380443
3. Vizoso F, Eiro N, Cid S, Schneider J, Perez-Fernandez R. Mesenchymal Stem Cell Secretome: Toward Cell-Free Therapeutic Strategies in Regenerative Medicine. *Int J Mol Sci*. 2017;18(9):1852. doi:10.3390/ijms18091852
4. Ding DC, Shyu WC, Lin SZ. Mesenchymal Stem Cells. *Cell Transplant*. 2011;20(1):5-14. doi:10.3727/096368910X
5. Song N, Scholtemeijer M, Shah K. Mesenchymal Stem Cell Immunomodulation: Mechanisms and Therapeutic Potential. *Trends Pharmacol Sci*. 2020;41(9):653-664. doi:10.1016/j.tips.2020.06.009
6. de Klerk E, Hebrok M. Stem Cell-Based Clinical Trials for Diabetes Mellitus. *Front Endocrinol (Lausanne)*. 2021;12. doi:10.3389/fendo.2021.631463
7. Zang L, Li Y, Hao H, et al. Efficacy and safety of umbilical cord-derived mesenchymal stem cells in Chinese adults with type 2 diabetes: a single-center, double-blinded, randomized, placebo-controlled phase II trial. *Stem Cell Res Ther*. 2022;13(1):180. doi:10.1186/s13287-022-02848-6
8. Kuppa SS, Kim HK, Kang JY, Lee SC, Seon JK. Role of Mesenchymal Stem Cells and Their Paracrine Mediators in Macrophage Polarization: An Approach to Reduce Inflammation in Osteoarthritis. *Int J Mol Sci*. 2022;23(21):13016. doi:10.3390/ijms232113016
9. Zhang M, Wang L, Chen Z. Research progress of extracellular vesicles in type 2 diabetes and its complications. *Diabetic Medicine*. 2022;39(9). doi:10.1111/dme.14865
10. Jiao YR, Chen KX, Tang X, et al. Exosomes derived from mesenchymal stem cells in diabetes and diabetic complications. *Cell Death Dis*. 2024;15(4):271. doi:10.1038/s41419-024-06659-w
11. Sun F, Sun Y, Wu F, Xu W, Qian H. Mesenchymal Stem Cell-Derived Extracellular Vesicles: A Potential Therapy for Diabetes Mellitus and Diabetic Complications. *Pharmaceutics*. 2022;14(10):2208. doi:10.3390/pharmaceutics14102208
12. Liu J, Sun X, Zhang FL, et al. Clinical Potential of Extracellular Vesicles in Type 2 Diabetes. *Front Endocrinol (Lausanne)*. 2021;11. doi:10.3389/fendo.2020.596811

13. Sun F, Sun Y, Wu F, Xu W, Qian H. Mesenchymal Stem Cell-Derived Extracellular Vesicles: A Potential Therapy for Diabetes Mellitus and Diabetic Complications. *Pharmaceutics*. 2022;14(10):2208. doi:10.3390/pharmaceutics14102208
14. Wang L, Liu T, Liang R, et al. Mesenchymal stem cells ameliorate β cell dysfunction of human type 2 diabetic islets by reversing β cell dedifferentiation. *EBioMedicine*. 2020;51:102615. doi:10.1016/j.ebiom.2019.102615
15. van Gerwen J, Shun-Shion AS, Fazakerley DJ. Insulin signalling and GLUT4 trafficking in insulin resistance. *Biochem Soc Trans*. 2023;51(3):1057-1069. doi:10.1042/BST20221066
16. Li FXZ, Lin X, Xu F, et al. The Role of Mesenchymal Stromal Cells-Derived Small Extracellular Vesicles in Diabetes and Its Chronic Complications. *Front Endocrinol (Lausanne)*. 2021;12. doi:10.3389/fendo.2021.780974
17. Fan B, Chopp M, Zhang ZG, Liu XS. Treatment of diabetic peripheral neuropathy with engineered mesenchymal stromal cell-derived exosomes enriched with microRNA-146a provide amplified therapeutic efficacy. *Exp Neurol*. 2021;341:113694. doi:10.1016/j.expneurol.2021.113694
18. Kochan Z, Szupryczynska N, Malgorzewicz S, Karbowska J. Dietary Lipids and Dyslipidemia in Chronic Kidney Disease. *Nutrients*. 2021;13(9):3138. doi:10.3390/nu13093138
19. Daminova L, Muminova S, Nigmonov B. The state of lipid metabolism in patients with diabetic nephropathy. *Archives of Gerontology and Geriatrics Plus*. 2024;1(4):100095. doi:10.1016/j.aggp.2024.100095
20. Li B, Cheng Y, Yu S, et al. Human Umbilical Cord-Derived Mesenchymal Stem Cell Therapy Ameliorates Nonalcoholic Fatty Liver Disease in Obese Type 2 Diabetic Mice. *Stem Cells Int*. 2019;2019:1-12. doi:10.1155/2019/8628027
21. Kim YH, Jeong S, Cho KA, Woo SY, Han SH, Ryu KH. Reduction of Low-Density Lipoprotein Cholesterol by Mesenchymal Stem Cells in a Mouse Model of Exogenous Cushing's Syndrome. *Tissue Eng Regen Med*. 2025;22(2):237-248. doi:10.1007/s13770-024-00697-3
22. de Luca C, Olefsky JM. Inflammation and insulin resistance. *FEBS Lett*. 2008;582(1):97-105. doi:10.1016/j.febslet.2007.11.057
23. Rohm T V., Meier DT, Olefsky JM, Donath MY. Inflammation in obesity, diabetes, and related disorders. *Immunity*. 2022;55(1):31-55. doi:10.1016/j.immuni.2021.12.013
24. Li L, Li J, Guan H, Oishi H, Takahashi S, Zhang C. Human umbilical cord mesenchymal stem cells in diabetes mellitus and its complications: applications and research advances. *Int J Med Sci*. 2023;20(11):1492-1507. doi:10.7150/ijms.87472
25. Sun X, Hao H, Han Q, et al. Human umbilical cord-derived mesenchymal stem cells ameliorate insulin resistance by suppressing NLRP3 inflammasome-mediated inflammation in type 2 diabetes rats. *Stem Cell Res Ther*. 2017;8(1):241. doi:10.1186/s13287-017-0668-1
26. Xie Z, Hao H, Tong C, et al. Human umbilical cord-derived mesenchymal stem cells elicit macrophages into an anti-inflammatory phenotype to alleviate insulin resistance in type 2 diabetic rats. *Stem Cells*. 2016;34(3):627-639. doi:10.1002/stem.2238
27. Xue J, Gao J, Gu Y, et al. Human umbilical cord-derived mesenchymal stem cells alleviate insulin resistance in diet-induced obese mice via an interaction with splenocytes. *Stem Cell Res Ther*. 2022;13(1):109. doi:10.1186/s13287-022-02791-6
28. Zang L, Hao H, Liu J, Li Y, Han W, Mu Y. Mesenchymal stem cell therapy in type 2 diabetes mellitus. *Diabetol Metab Syndr*. 2017;9(1):36. doi:10.1186/s13098-017-0233-1
29. Li L, Li J, Guan H, Oishi H, Takahashi S, Zhang C. Human umbilical cord mesenchymal stem cells in diabetes mellitus and its complications: applications and research advances. *Int J Med Sci*. 2023;20(11):1492-1507. doi:10.7150/ijms.87472