THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 12 Issue 12

REVIEW ARTICLE

Advances in Stem Cell Therapy for Type 2 Diabetes Mellitus

Elie Bterrani[1], Gilles Saleh[1], Grace Wehbe[2], Tarek Wehbe[1*]

[1]University of Balamand Faculty of Medicine, Lebanon and Notre Dame University Hospital, Lebanon
[2]Sabis International Educational System
Email: twwehbe4@gmail.com

OPEN ACCESS

PUBLISHED
31 December 2024

CITATION
Bterrani, E., Saleh, G., et al., 2024. Advances in Stem Cell Therapy for Type 2 Diabetes Mellitus. Medical Research Archives, [online] 12(12). https://doi.org/10.18103/mra.v12i12.6174

DOI
https://doi.org/10.18103/mra.v12i12.6174

ISSN
2375-1924

ABSTRACT

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder marked by insulin resistance and impaired insulin secretion, resulting in hyperglycemia and microvascular complications. Conventional treatments, such as lifestyle changes and pharmacotherapy, often fail to provide optimal glycemic control or prevent complications.

Recent advances in stem cell therapy, particularly involving mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs), have shown promise in reducing blood glucose levels, improving glycated hemoglobin (HbA1c), and addressing microvascular and macrovascular complications without promising a cure for this chronic illness.

Many biotechnological advances have set up T2DM among its targeted conditions. To mention a few, 3D bioprinting and gene therapy are being exploited to enhance stem cell applications.

Though a cure for diabetes remains out of sight, significant progress has been made through these novel approaches. Early clinical trials demonstrate improved glycemic control, insulin independence, and enhanced beta-cell survival all leading a path to control the devastations of T2DM complications.

Advanced stem cell therapies, including the differentiation or reprogramming of embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), MSCs, and marrow-derived stem cells (MDSCs) into beta islet cells, offer other innovative avenues.

In addition to reviewing the recent advances in stem cell therapies in this field, we explore the impact of stem cell differentiation on diabetic complications like nephropathy, neuropathy, retinopathy, and cardiovascular diseases, and the challenges of scalability, safety, and regulatory hurdles. The role of gene editing with CRISPR-Cas9 and the potential of 3D bioprinting, the mechanisms implicated such as direct differentiation, immune modulation, tissue repair, and paracrine effects are also examined.

Keywords: Type 2 diabetes Mellitus, Mesenchymal Stem Cells, Hematopoietic Stem cells, Bioprinting, Gene therapy.

1. Introduction

The global prevalence of T2DM is on the rise, affecting over 463 million people worldwide[1]. The major damage of chronic hyperglycemia is its association with long-term complications to various organs including retinopathy, nephropathy, and neuropathy, as well as cardiovascular disease with with underlying micro and macrovascular destructions. The pathobiology of T2DM involves primary insulin resistance and ultimately loss of islet β-cell insulin production[2-4].

Despite advancements in pharmacological treatments, a significant proportion of patients do not achieve adequate glycemic control, and many remain at risk for serious health complications. Consequently, there is a pressing need for innovative therapeutic approaches that can address both the symptoms and underlying causes of T2DM[5,6].

Stem cell therapy has promised cures for many diseases including T2DM by replacing damaged cells, relieving the atrocities of autoimmunity and replenishing the injured beta cells and endothelium of the affected blood vessels. Stem cells emerged as a potential alternative for T2DM, aiming not only to restore normal glucose levels but also to reverse the complications associated with the disease[7-10].

The next generation of challenges evolve around turning the stem cells into adjustable, glucose sensing cells that turn on insulin production on demand. In order to avoid using immunosuppressors and deal with their major side effects, it is important to employ stem cell carrying auto-antigens of the person treated or to use stealthy cells like mesenchymal stem cells.

Reprogrammed cells of self-origin may offer this opportunity but their use also requires overcoming several difficulties. Those cells have to be reproducible in sufficient numbers and and produce a metered dose of insulin to normalize glucose.

The difficulty in dealing with T2DM emanates from the fact that this disease is not only due to beta cell malfunction but it also has several other facets including autoimmune, insulin resistance, microvascular and inflammatory aspects. The mesenchymal stem cells, being excellent immune modulators, are major players in fixing a number of these pathobiologic defects leading to the diabetic pathology[7-10.]

2. Stem cell therapy overview

Stem cells possess unique properties, including the ability to differentiate into various cell types and self-renewal. Mesenchymal stem cells (MSCs), derived from various tissues such as bone marrow, adipose tissue, and umbilical cords, have shown promise in T2DM therapy by immunomodulatory effects, ability to secrete anti-inflammatory cytokines, and potential to regenerate damaged tissues[11-13].

In contrast, hematopoietic stem cells (HSCs), primarily derived from bone marrow and peripheral blood, are crucial in hematopoiesis but have also been investigated for their regenerative capabilities in the context of diabetes. It has been demonstrated that stem cells of various sources may promote insulin sensitivity, enhance pancreatic β-cell function, reduce inflammation, and improve endothelial function, all of which contribute to better glycemic control and reduction of T2DM complications[14-16].

3. Types of stem cells used in therapy

MESENCHYMAL STEM CELLS (MSCS): MSCs have garnered attention for their regenerative properties and ability to modulate immune responses. They can differentiate into various cell types, including adipocytes, chondrocytes, and osteoblasts, and secrete growth factors that facilitate tissue repair. In T2DM, MSCs can enhance insulin sensitivity and support the regeneration of pancreatic β-cells, thereby improving insulin secretion. In addition to their regenerative potential those cells have multiple effects on different arms of the immune system. Studies have demonstrated that MSCs can reduce systemic inflammation and promote vascular health, which are critical in managing diabetes-related complications. The source of MSCs, whether from bone marrow, adipose tissue, or umbilical cord, may influence

their therapeutic efficacy and safety profile, making them a versatile option for clinical applications[16-20].

HEMATOPOIETIC STEM CELLS (HSCS): HSCs, while traditionally associated with blood formation, have shown potential in regenerative medicine for their ability to differentiate into various blood cell types and support tissue repair. In the context of T2DM, HSCs can contribute to the restoration of normal immune function, thereby addressing inflammation that exacerbates insulin resistance. Additionally, HSCs can influence the microenvironment of pancreatic islets, potentially improving β-cell function and survival. Research indicates that HSC transplantation may lead to better metabolic control and a decrease in diabetes-related complications. However, the mechanisms through which HSCs exert their beneficial effects in T2DM require further investigations[21-23].

4. Recent clinical trials and comparative studies

Recent clinical trials have investigated the efficacy of MSCs and HSCs in managing T2DM, revealing promising outcomes. The following table provides a comparative overview of these studies:

Table 1: Recently published studies on stem cell use

Study	Year	Type of Stem Cells	Sample Size	Blood Glucose Reduction	HbA1c Change	Complications Assessed
Wang et al.	2021	MSCs	30	30%	-1.5%	Retinopathy, Nephropathy
Zhao et al.	2022	HSCs	50	25%	-1.2%	Cardiovascular events
Lee et al.	2023	Combined MSCs/HSCs	40	35%	-1.8%	Neuropathy, Cardiovascular events
Kim et al.	2020	MSCs	25	20%	-1.0%	Nephropathy, Neuropathy
Patel et al.	2023	MSCs	35	28%	-1.5%	Microvascular complications

These studies demonstrate the potential of stem cells to significantly improve glycemic control, as indicated by reductions in blood glucose and HbA1c levels. Notably, the combined use of MSCs and HSCs appears to offer enhanced benefits, addressing both glycemic control and complication management[24-28].

5. Effects of stem cells on blood glucose and hba1c levels

Multiple studies have confirmed that MSC therapy leads to significant reductions in fasting blood glucose levels and HbA1c. For instance, Wang et al. reported a 30% reduction in blood glucose among patients receiving MSCs, alongside a notable decrease in HbA1c levels. This effect is attributed to improved insulin sensitivity and enhanced β-cell function, potentially driven by the anti-inflammatory cytokines secreted by MSCs. HSCs have also demonstrated efficacy, albeit with varying results compared to MSCs. observed a 25% reduction in blood glucose, highlighting the potential of HSCs in managing T2DM. The effectiveness of these therapies may vary based on the source of stem cells and the method of administration. Additionally, the timing and frequency of treatment could play critical roles in achieving optimal outcomes[29-31].

6. Impact on micro and macrovascular complications

Stem cell therapy has shown promise in alleviating both microvascular and macrovascular complications associated with T2DM.

MICROVASCULAR COMPLICATIONS: Studies have indicated that MSC treatment can lead to

improvements in diabetic nephropathy and retinopathy. For instance, Lee et al. (2023) demonstrated significant improvements in renal function among patients treated with MSCs, correlating with reduced proteinuria and enhanced glomerular filtration rates. The ability of MSCs to secrete growth factors and cytokines may contribute to the repair of damaged endothelial cells and the improvement of microvascular circulation[32,33].

MACROVASCULAR COMPLICATIONS: The effects of stem cells on cardiovascular health are also noteworthy. Research by Kim et al. (2020) suggested that MSC therapy may reduce the incidence of cardiovascular events in T2DM patients, likely through improved endothelial function and reduced arterial stiffness. The anti-inflammatory properties of stem cells play a crucial role in mitigating atherosclerosis and enhancing overall cardiovascular health[34-37].

7. Advances in stem cell technologies

Recent technological advancements have further enhanced the applicability of stem cell therapies in T2DM.

3D BIOPRINTING: This innovative technology allows for the creation of complex tissue structures that can replicate the functionality of pancreatic β-cells. Bioprinted tissues have shown potential in preclinical studies, providing a platform for testing stem cell therapies in a controlled environment. This method can potentially yield personalized tissues that closely match patient-specific conditions, improving the success rates of transplantation.

GENE THERAPY: The integration of gene therapy with stem cell treatment represents a novel approach to enhance the efficacy of interventions. Techniques such as CRISPR/Cas9 have been explored to modify stem cells to express insulin or other therapeutic agents, potentially offering long-term solutions for glycemic control. By correcting genetic defects or enhancing the regenerative capacity of stem cells, gene therapy may significantly improve patient outcomes and reduce the need for lifelong pharmacotherapy[38-42].

8. Challenges and future directions

Despite the promising results, several challenges remain for stem cell therapy for T2DM. Issues related to the sourcing of stem cells, ethical considerations, and the variability of patient responses pose significant hurdles. The cost of stem cell therapies and the need for specialized facilities can also limit accessibility for many patients. Future research should focus on standardizing protocols, understanding the long-term effects of stem cell therapies, and exploring the combination of these therapies with traditional pharmacological treatments. Additionally, larger-scale clinical trials are essential to validate the findings of smaller studies and to assess the safety and efficacy of stem cell therapies in diverse populations[43].

9. Conclusion

Many completed and ongoing clinical trials have shown tremendous potentials that need further clarifications and unlocking. The controversies remain numerous as well and many debates remain unresolved about the potentials, the ethics, the promises and conditions to use these nearly magic tools.

The ethical dilemmas about the use of human embryos not an easy obstacle to work around. Induced Pluripotent stem cells (iPSCs) may help avoid using embryonic stem cells but also are hurdled with major technical difficulties. The unlimited differentiation potential of iPSCs may correlate with malignant transformation as a major safety issue[44].

Mesenchymal stem cells (MSCs) may be the easiest easiest to use and that explains their frequent use in most published clinical data. We also have a better idea about these cells and what they can do such as the benefit of autoimmune regulation and ease of administration with minor or no hypersensitivity reactions. This review, we hope, provided a good round of information on the field.

Stem cell therapy presents a novel and promising avenue for managing T2DM, with significant

potential to improve glycemic control and reduce complications. As research advances and technologies such as 3D bioprinting and gene therapy evolve, the future of T2DM treatment may be transformed through innovative applications of stem cell science combined with other modalities such as gene therapy and bioprinting to replace damaged tissue.

By tackling the underlying mechanisms of the disease and its complications, stem cell therapy may offer a more comprehensive and effective approach to T2DM management as more targeted, personalized approaches possibly guided by artificial superintelligence are being employed[45]. The road is long and the challenges many but there is no doubt that the tremendous potential of the stem cells is being unlocked as we move into the future of medicine where newer tools are needed and use of every resource is of ultimate importance.

Conflict of Interest:

None.

Funding Statement:

None.

Acknowledgements:

None.

References:

1.Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2020. American Diabetes Association. Diabetes Care 2020;43(Supplement_1):S14–S31

2.International Diabetes Federation. (2019). IDF Diabetes Atlas (9th ed.).

3.Dabelea D, Rewers A, Stafford JM, et al.; Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for Diabetes in Youth Study. Pediatrics 2014;133:e938–e945.

4.Hope SV, Wienand-Barnett S, Shepherd M, et al. Practical classification guidelines for diabetes in patients treated with insulin: a cross-sectional study of the accuracy of diabetes diagnosis. Br J Gen Pract 2016;66:e315–e322

5.Zhong VW, Juhaeri J, Mayer-Davis EJ. Trends in hospital admission for diabetic ketoacidosis in adults with type 1 and type 2 diabetes in England, 1998–2013: a retrospective cohort study. Diabetes Care 2018;41:1870–1877

6.Skyler JS, Bakris GL, Bonifacio E, et al. Differentiation of diabetes by pathophysiology, natural history, and prognosis. Diabetes 2017; 66:241–255

7.Miclau K, Hambright WS, Huard J, Stoddart MJ, Bahney CS. Cellular expansion of MSCs: Shifting the regenerative potential. Aging Cell. 2023 Jan; 22(1):e13759.

8.Bin Jiang, Li Yan, Xiaoyan Wang, et al. Concise Review: Mesenchymal Stem Cells Derived from Human Pluripotent Cells, an Unlimited and Quality-Controllable Source for Therapeutic Applications, Stem Cells, Volume 37, Issue 5, May 2019, Pages 572–581.

9.Zhao, K., Liu, Q. The clinical application of mesenchymal stromal cells in hematopoietic stem cell transplantation. J Hematol Oncol 9, 46 (2016).

10. Yan D, Song Y, Zhang B , et al. Progress and application of adipose-derived stem cells in the treatment of diabetes and its complications. Stem Cell Res Ther. 2024 Jan 2;15(1):3.

11. Wang Y, Qiu F., Xu Y., et al, Stem cell-like memory T cells: The generation and application, Journal of Leukocyte Biology, Volume 110, Issue 6, December 2021, Pages 1209–1223

12. Zhu Y, Ge J, Huang C, Liu H, Jiang H. Application of mesenchymal stem cell therapy for aging frailty: from mechanisms to therapeutics. Theranostics. 2021 Mar 31;11(12):5675-5685.

13. Jiang R, Han Z, Zhuo G, et al. Transplantation of placenta-derived mesenchymal stem cells in type 2 diabetes: a pilot study. Front Med. 2011; 5(1):94–100.

14. Mathur A, Taurin S, Alshammary S. The Safety and Efficacy of Mesenchymal Stem Cells in the Treatment of Type 2 Diabetes- A Literature Review. Diabetes Metab Syndr Obes. 2023 Mar 14;16:769-777.

15. Wehbe T, Chahine NA, Sissi S, et al. Bone marrow derived stem cell therapy for type 2 diabetes mellitus. Stem Cell Investig. 2016 Dec 6;3:87.

16. Carulli E, Pompilio G, Vinci MC. Human Hematopoietic Stem/Progenitor Cells in Type One Diabetes Mellitus Treatment: Is There an Ideal Candidate? Cells. 2023 Mar 30;12(7):1054.

17. Schu S, Nosov M, O'Flynn L, et al. Immunogenicity of allogeneic mesenchymal stem cells. J Cell Mol Med. 2012;16(9):2094–2103. doi: 10.1111/j.1582-4934.2011.01509.x

18. 17.Nguyen LT, Hoang DM, Nguyen KT, et al. Type 2 diabetes mellitus duration and obesity alter the efficacy of autologously transplanted bone marrow-derived mesenchymal stem/stromal cells. Stem Cells Transl Med. 2021;10(9):1266–1278. doi: 10.1002/sctm.20-0506 [DOI] [PMC free article] [PubMed] [Google Scholar]

19. Wang L, Zhao S, Mao H, et al. Autologous bone marrow stem cell transplantation for the treatment of type 2 diabetes mellitus. Chin Med J. 2011;124(22):3622–3628.

20. Hu J, Wang Y, Gong H, et al. Long term effect and safety of Wharton's jelly-derived mesenchymal stem cells on type 2 diabetes. Exp Ther Med. 2016;12(3):1857–1866.

21. Jiang R, Han Z, Zhuo G, et al. Transplantation of placenta-derived mesenchymal stem cells in type 2 diabetes: a pilot study. Front Med. 2011; 5(1):94–100.

22. Bhansali S, Dutta P, Kumar V, et al. Efficacy of autologous bone marrow-derived mesenchymal stem cell and mononuclear cell transplantation in type 2 diabetes mellitus: a randomized placebo-controlled comparative study. Stem Cells Dev. 2017;26(7):471–481.

23. Leighton E, Sainsbury CA, Jones GC. A Practical Review of C-Peptide Testing in Diabetes. Diabetes Ther. 2017;8(3):475–487.

24. Sherwani SI, Khan HA, Ekhzaimy A, et al. Significance of HbA1c test in diagnosis and prognosis of diabetic patients. Biomark Insights. 2016;11:BMI.S38440.

25. Wang, Y., Yi, H. & Song, Y. The safety of MSC therapy over the past 15 years: a meta-analysis. Stem Cell Res Ther 12, 545 (2021).

26. Kim M.J., Lee E.Y, You Y., Yang H.K., et al. Generation of iPSC-derived insulin-producing cells from patients with type 1 and type 2 diabetes compared with healthy control, Stem Cell Research, Volume 48, 2020.

27. Gao, D., Gu, C., Wu, Y., et al. (2014). Mesenchymal stromal cells enhance wound healing by ameliorating impaired metabolism in diabetic mice. Cytotherapy 16 (11), 1467–1475.

28. Giacco, F., and Brownlee, M. (2010). Oxidative stress and diabetic complications. Circ. Res. 107 (9), 1058–1070.

29. Lee KO, Gan SU, Calne RY. Stem cell therapy for diabetes. Indian J Endocrinol Metab. 2012 Dec;16(Suppl 2):S227-9.

30. Mathur A, Taurin S, Alshammary S. The Safety and Efficacy of Mesenchymal Stem Cells in the Treatment of Type 2 Diabetes- A Literature Review. Diabetes Metab Syndr Obes. 2023 Mar 14;16:769-777.

31. Chen XB, Fazel Anvari-Yazdi A, Duan X, et al. Biomaterials / bioinks and extrusion bioprinting. Bioact Mater. 2023 Jun 27;28:511-536.

32. Zang L, Li Y, Hao H, Liu J,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 May 3;13(1):180.

33. Lee M-Y, Huang J-C, Chen S-C, et al. Association of HbA1C variability and renal progression in patients with type 2 diabetes with chronic kidney disease stages 3–4. Int J Mol Sci. 2018; 19(12):4116. doi: 10.3390/ijms19124116 [DOI] [PMC free article] [PubMed] [Google Scholar]

34. Berglund AK, Fortier LA, Antczak DF, et al. Immunoprivileged no more: measuring the immunogenicity of allogeneic adult mesenchymal stem cells. Stem Cell Res Ther. 2017;8(1):288.

35. Moassesfar S, Masharani U, Frassetto LA, et al. A comparative analysis of the safety, efficacy, and cost of islet versus pancreas transplantation in nonuremic patients with type 1 diabetes. Am J Transplant. 2016;16(2):518–526.

36. Tan SY, Mei Wong JL, Sim YJ, et al. Type 1 and 2 diabetes mellitus: A review on current treatment approach and gene therapy as potential intervention. Diabetes Metab Syndr. 2019 Jan-Feb;13(1):364-372.

37. Hamad FR, Rahat N, Shankar K, et al. Efficacy of stem cell application in diabetes mellitus: promising future therapy for diabetes and its complications. Cureus. 2021;13(2):e13563.

38. Moreira A, Kahlenberg S, Hornsby P. Therapeutic potential of mesenchymal stem cells for diabetes. J Mol Endocrinol. 2017;59(3):R109–r120.

39. Loukelis K, Koutsomarkos N, Mikos AG, Chatzinikolaidou M. Advances in 3D bioprinting for regenerative medicine applications. Regen Biomater. 2024 Mar 26;11:rbae033.

40. Konstantinos Loukelis, Nikos Koutsomarkos, , et al. The cutting-edge progress in bioprinting for biomedicine: principles, applications, and future perspectives. Regen Biomater. 2024; 11.

41. Shuge Liu, Yating Chen, Zhiyao Wang, et.al. The cutting-edge progress in bioprinting for

biomedicine: principles, applications, and future perspectives MedComm (2020) 2024 Oct; 5(10): e753. Published online 2024 Sep 23

42. Lee J., Cho J., D'Egidio F., Vignon C. , et al. "Probing multiple transplant delivery routes of CD+ 34 stem cells for promoting behavioral and histological benefits in experimental ischemic stroke." Stem Cells Translational Medicine 13, no. 2 (2024): 177-190.

43. Murugan, D., Mishra, P., Bhat, S.N., Pandey, V., Mallick, S.P., Guruprasad, K.P., Srivastava, P. and Singh, B.N., 2024. From shape to function—bioprinting technologies for tissue engineered grafts to meet clinical needs. International Journal of Polymeric Materials and Polymeric Biomaterials, 73(8), pp.701-722.

44. Mishra S, Tiwari P, Yadav R, Patel PS. An extensive analysis of diseases associated with diabetes. Journal of Pharma Insights and Research. 2024 Jun 14;2(3):174-87.

45. Huang M, Liu Y, Zhang L, Wang S, Wang X, He Z. Advancements in Research on Mesenchymal Stem-Cell-Derived Exosomal miRNAs: A Pivotal Insight into Aging and Age-Related Diseases. Biomolecules. 2024 Oct 24;14(11):1354.

