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Stem cell therapy in diabetes mellitus; a mini-review on recent trends

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Abstract
Stem cells, particularly human pluripotent stem cells, can be effectively differentiated into functional insulin-producing beta cells that mimic native cells in structure and glucose responsiveness. These cells have demonstrated the ability to reverse diabetes in animal models upon transplantation, either through further in- vivo maturation or as fully matured cells generated in-vitro. Activation of endogenous pancreatic progenitors also offers a complementary regenerative approach. Despite these advances, clinical application requires overcoming immune rejection, ensuring safety, and validating long-term efficacy in humans.
Keywords: Stem cells, Type 1 diabetes, Beta cells, Type 2 diabetes, Bone marrow, Glycemic control
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Introduction

Stem cell therapy is an emerging and promising approach to treat diabetes mellitus, directing principally to regenerate or replace the insulin-producing beta cells in the pancreas across with modulate the immune environment to improve disease outcomes (1). In this method, the main therapeutic goal is to restore insulin production by regenerating pancreatic beta cells or transplanting insulin-secreting cells derived from stem cells (2). These cells also repair tissue damage caused by diabetes while modulate immune responses, especially in type 1 diabetes where autoimmune destruction of beta cells occurs (3). Clinical studies show that hematopoietic stem cells (HSCs), particularly CD34+ bone marrow-derived HSCs, have demonstrated significant efficacy in type 1 diabetes (T1DM) (4). Preliminary finding shows 58.9% of treated patients achieved insulin independence for an average of 16 months, since other studies showed substantial insulin reduction (5). Meanwhile, mesenchymal stem cells (MSCs), principally those derived from umbilical cord tissue, also show beneficial effects in improving C-peptide levels as a marker of beta-cell function along with reducing HbA1c, though their effects are generally less pronounced than HSCs (6). In this type of diabetes, early intervention after diagnosis tends to yield better outcomes, with stem cell therapy being more effective when applied in the early stages of diabetes (7). Likewise, stem cell therapy in T2DM (type 2 diabetes) primarily aims to improve insulin sensitivity and regenerate beta cells to strengthen endogenous insulin production (8). Several studies show that, mesenchymal stem cells and bone marrow mononuclear cells have been shown to reduce HbA1c levels, decrease insulin requirements, and improve C-peptide levels in this type of diabetes (9). Results showed, a stabilized blood glucose, reduced symptoms like thirst and frequent urination, improved wound healing, and better overall quality of life (10). A recent breakthrough study by Wu et al, from Shanghai reported the first-ever cure for T2DM using autologous stem cell-derived pancreatic islet transplantation, demonstrating functional restoration of insulin secretion in a patient with long-standing diabetes (11). This mini-review sought to study the most recent findings on stem cell therapy in diabetes mellitus individuals.

Search strategy

For this study, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ) and Embase, using different keywords including stem cells, type 1 diabetes, beta cells, type 2 diabetes, bone marrow and glycemic control

Effectivity of stem cells

Stem cells have shown significant ability in regenerating insulin-producing beta cells in the pancreas, however their efficiency varies depending on the stem cell type, differentiation protocols, and the stage of maturity of the derived cells (12). Human pluripotent stem cells,

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Implication for health policy/practice/research/ medical education

Stem cell therapy for diabetes mellitus offers a promising modality to improve glycemic control, reduce insulin dependence, and potentially achieve long-term remission or cure, mainly with advances in stem cell-derived islet transplantation. However, more large-scale randomized clinical trials are required to confirm efficacy, optimize protocols, and establish long-term safety.

including embryonic stem cells (ESCs); that induced pluripotent stem cells (iPSCs), can be directed to differentiate into pancreatic beta-like cells that produce insulin (13). Advanced differentiation protocols mimic pancreatic development stages, producing cells that express key beta cell markers (e.g., PDX1, NKX6.1, MAFA) and secrete insulin in response to glucose (12). Early protocols often yielded immature, polyhormonal cells with limited insulin secretion (14). However, newer methods generate monohormonal, glucose-responsive beta cells with ultrastructural features similar to native beta cells, capable of ameliorating hyperglycemia in diabetic mice shortly after transplantation (15). In-vivo maturation after transplantation is also a critical step (16). Transplanted pancreatic progenitors derived from stem cells can continue differentiating into mature beta cells in animal models, with detectable human C-peptide appearing soon, post-transplant and lasting for several months, effectively reversing diabetes in these models (17,18). Recent developments include the generation of fully functional stem cell-derived beta cells in-vitro which respond to glucose like human donor islets (19). Moreover, pancreatic stem-like progenitor cells within the pancreas can be activated by growth factors such as BMP-7 to regenerate insulin-producing beta cells, even in type 1 diabetes patients, indicating that endogenous regeneration pathways remain functional and can be harnessed therapeutically (20).

Focus on the types of stem cells

Hematopoietic stem cells typically resulting from bone marrow or from mobilized peripheral blood (CD34+ cells) (21). This transplantation, particularly autologous nonmyeloablative bone marrow CD34+ HSCs, has shown the most robust clinical outcomes in type 1 diabetes (T1DM) (22). Approximately 58.9% of treated patients achieved insulin independence for an average of 16 months, with sustained increases in C-peptide levels indicating preserved or restored beta-cell function (5). Hematopoietic stem cells have been associated with increased beta-cell mass and proliferation in animal studies, leading to improved glucose tolerance after few weeks of post-transplantation (23,24). This cells also modulate immune responses beneficially, which is critical in autoimmune T1DM (25). On the other hand, MSCs, which is originated from bone marrow and umbilical cord tissue, or adipose tissue are found to improve glycemic control relatively fast, commonly within seven days in animal models; though this procedure does not significantly increase beta-cell mass or islet morphology (26). Recent clinical trials and meta-analysis displayed MSC transplantation reduces HbA1c, lowers insulin requirements, and reasonably improves C-peptide levels in both T1DM and T2DM without major adverse effects (27). Importantly these cells tend to provide better outcomes than BM-MSCs in T1DM. It is possible that, MSCs act through paracrine effects, immunomodulation, and improving insulin sensitivity rather than direct beta-cell regeneration (28). Another option is umbilical cord blood (UCB) cells, while infusion of these cells has shown poor clinical efficacy in improving beta-cell function or insulin independence in T1DM (29). Possible reasons include mixed cell populations, freezing-thawing processes, and lower engraftment potential compared to freshly isolated BM-HSCs (30). Recent studies also talk about induction of pluripotent stem cells (iPSCs) (31). These cells can be differentiated into insulin-producing beta-like cells that normalize blood glucose and an increase in insulin level in diabetic animal models for extended periods (32). It should remember that, iPSC-derived beta cells offered a promising renewable source for autologous transplantation (33). A recent study converted patient's fat cells into pluripotent stem cells, across with differentiating them into insulin-producing islet cells with its transplantation into the abdomen (34). These results led to insulin independence for over a year, demonstrating the potential of autologous pluripotent stem cell-derived islet transplantation (35).

Conclusion

Bone marrow-derived CD34+ hematopoietic stem cells currently show the most consistent and robust outcomes in regenerating beta-cell function and achieving insulin independence in T1DM, while mesenchymal stem cells improve glycemic control mainly through immunomodulatory and supportive mechanisms. Umbilical cord blood cells have shown limited efficacy, and pluripotent stem cell-derived beta cells represent a promising frontier with recent clinical successes but require further validation. These differences highlight the importance of stem cell source, preparation, and mechanism of action in determining therapeutic outcomes for diabetes treatment.

Conflicts of interest

The author declares that she has no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to

refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

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