INTERNATIONAL JOURNAL OF PHARMA PROFESSIONAL'S RESEARCH

Exploring the Role of Stem Cell Therapy in Diabetes: From Benchside Research to Clinical Applications and Beyond

*Manisha Walde, Priti S Bhoyar, Ujwala Wasnik, Sharad Bhandarkar
Taywade Institute of Diploma in Pharmacy Koradi Nagpur Maharashtra

ABSTRACT

The chronic metabolic disease known as diabetes mellitus, which is defined by hyperglycemia, presents enormous difficulties to the health of people all over the world due to the prevalence of the condition and the consequences it causes. Although they are efficient in treating symptoms, traditional treatments do not address the pathophysiological factors that are occurring beneath the surface. Because it can restore normal glucose metabolism and heal damaged tissues, stem cell treatment has emerged as a possible alternative solution. Within the scope of this review, the function of stem cell therapy in diabetes is investigated in depth, with a focus on its progression from bench-top research to clinical applications. Embryonic stem cells, induced pluripotent stem cells, and adult stem cells are some of the types of stem cells that are discussed here. We highlight the distinctive characteristics of these stem cells as well as their possible treatments. Not only are preclinical studies indicating efficacy in diabetes models being investigated, but also important developments in stem cell technology, such as differentiation procedures and gene editing, are being investigated. Considerations about safety, efficacy, and ethics are taken into account during the critical evaluation of the transition to clinical trials. In addition, we discuss the difficulties and restrictions that are associated with the present forms of stem cell therapy, such as immunological rejection, tumorigenicity, and scalability. In addition, prospects and emerging trends are examined, with a particular focus on the incorporation of stem cell therapy with other new treatments such as gene therapy and tissue engineering. A full overview of the current state of stem cell therapy in diabetes is the goal of this review. Additionally, the study hopes to stimulate future research and clinical improvements in this promising field.

Keywords: *Diabetes mellitus, stem cell technology, immunological rejection, tumorigenicity, and scalability*

Corresponding Author-
Manisha Walde
Email. Id: manishawalde123@gmail.com
Taywade Institute of Diploma in Pharmacy Koradi Nagpur Maharashtra

Volume 15, Issue 3, 2024, Received: 15 May 2024**, Accepted:** 10 June 2024**, Published:** 30 July 2024,
DOI: 10.69580/IJPPR.15.3.2024.68-83

1. Introduction

Hyperglycemia, which can occur in either the fasting or postprandial phases, is the defining characteristic of diabetes. Several organs and tissues, including the retina, kidney, nerves, heart, and blood vessels, are susceptible to injury, dysfunction, and failure as a result of the persistent hyperglycemia that is characteristic of diabetes mellitus (DM). A total of 366 million people were estimated to have diabetes mellitus in the world in 2011, according to the International Diabetes Federation (IDF), and it is anticipated that this number will increase to 552 million by the year 2030. [1]

1.1 Types of Diabetes

The Diabetes Management Center at Alton Memorial Hospital provides prevention, diagnosis, treatment and management services to patients who think they have or have diabetes. Below is an overview of the various types of diabetes. The types of diabetes include type 1, type 2, prediabetes and gestational diabetes.

1.1.1 Type 1 Diabetes:

Immune-mediated diabetes is the most common form of type 1 diabetes, and the one generally referred to as type 1 diabetes.

1.1.1.1 Two Forms of Type 1 Diabetes:

- Idiopathic type 1 diabetes. This refers to rare forms of the disease with no known cause.
- Immune-mediated diabetes. An autoimmune disorder in which the body's immune system destroys, or attempts to destroy, the cells in the pancreas that produce insulin.[2]

1.1.2 Type 2 Diabetes:

Type 2 diabetes is a metabolic disorder resulting from the body's inability to make enough insulin for the degree of insulin resistance (body's inability to properly use insulin). It used to be called non-insulin-dependent diabetes mellitus, or maturity-onset diabetes mellitus (NIDDM).

Without adequate production or utilization of insulin, the body cannot move blood sugar into the cells. It is a chronic disease that has no known cure. It is the most common type of diabetes.[3]

1.1.3 Prediabetes:

Type 2 diabetes is commonly preceded by prediabetes. In prediabetes, blood glucose levels are higher than normal but not high enough to be defined as diabetes. However, many people with prediabetes develop type 2 diabetes within 10 years, states the National Institute of Diabetes and Digestive and Kidney Diseases.

Prediabetes also increases the risk of heart disease and stroke. With modest weight loss and moderate physical activity, people with prediabetes can delay or prevent type 2 diabetes.

1.1.4 Gestational Diabetes:

Gestational diabetes is a condition in which the glucose level is elevated and other diabetic symptoms appear during pregnancy in a woman who has not previously been diagnosed with diabetes. Diabetes disappears following delivery. All diabetic symptoms disappear following delivery.

Unlike type 1 diabetes, gestational diabetes is not caused by an absolute lack of insulin, but rather by the effects of hormones released during pregnancy on the insulin that is produced, a condition referred to as insulin resistance.[4]

2. Current treatment limitations for diabetes

Individuals who have type 1 diabetes are dependent on insulin and must undergo daily injections or pump therapy. This requires continual monitoring and bears the risk of hypoglycemia throughout treatment. This method is effective in managing symptoms, but it does not address the autoimmune death of beta cells that is happening behind the surface. The progressive nature of type 2 diabetes causes a deterioration in beta cell function and a reduction in the efficacy of medicine over time. Treatments for type 2 diabetes often entail the use of oral hypoglycemic medications and insulin. There is a significant amount of individual heterogeneity in treatment response due to genetic, lifestyle, and environmental factors, and both forms of diabetes require frequent monitoring of blood glucose levels and strict adherence to food and lifestyle, respectively. There are considerable challenges, particularly in areas with limited resources, such as high costs and limited access to innovative treatments and technologies. Long-term pharmaceutical use can produce severe consequences, including damage to the liver and kidneys, and elaborate treatment

regimens that are difficult to follow might lead to non-compliance. There is a need for more effective and comprehensive treatment approaches, such as stem cell therapy, which aims to address the root causes of diabetes and provide potential long-term solutions. Current strategies are more focused on management than prevention, and early detection continues to be difficult. This highlights the need for more effective and diverse treatment approaches.[5,6]

3. Stem Cells

Stem cells are unspecialized cells in the human body that are capable of becoming specialized cells, each with new specialized cell functions. The best example of a stem cell is the bone marrow stem cell that is unspecialized and able to specialize into blood cells, such as white blood cells and red blood cells, these new cell types have special functions, such as being able to produce antibodies, act as scavengers to combat infection and transport gases. Thus, one cell type stems from the other hence the term "stem cell." A stem cell remains uncommitted until it receives a signal to develop into a specialized cell. Stem cells have the remarkable properties of developing into a variety of cell types in the human body. They serve as a repair system by being able to divide without limit to replenish other cells. When a stem cell divides, each new cell has the potential to either remain as a stem cell or become another cell type with new special functions, such as blood cells, brain cells, etc.[7]

3.1 Classification of Stem Cells

The easiest way to categorize stem cells is by dividing them into two types: Early or embryonic and mature or adult. Early stem cells, often called embryonic stem cells, are found in the inner cell mass of a blastocyst after approximately five days of development. Mature stem cells are found in specific mature body tissues as well as the umbilical cord and placenta after birth.[8]

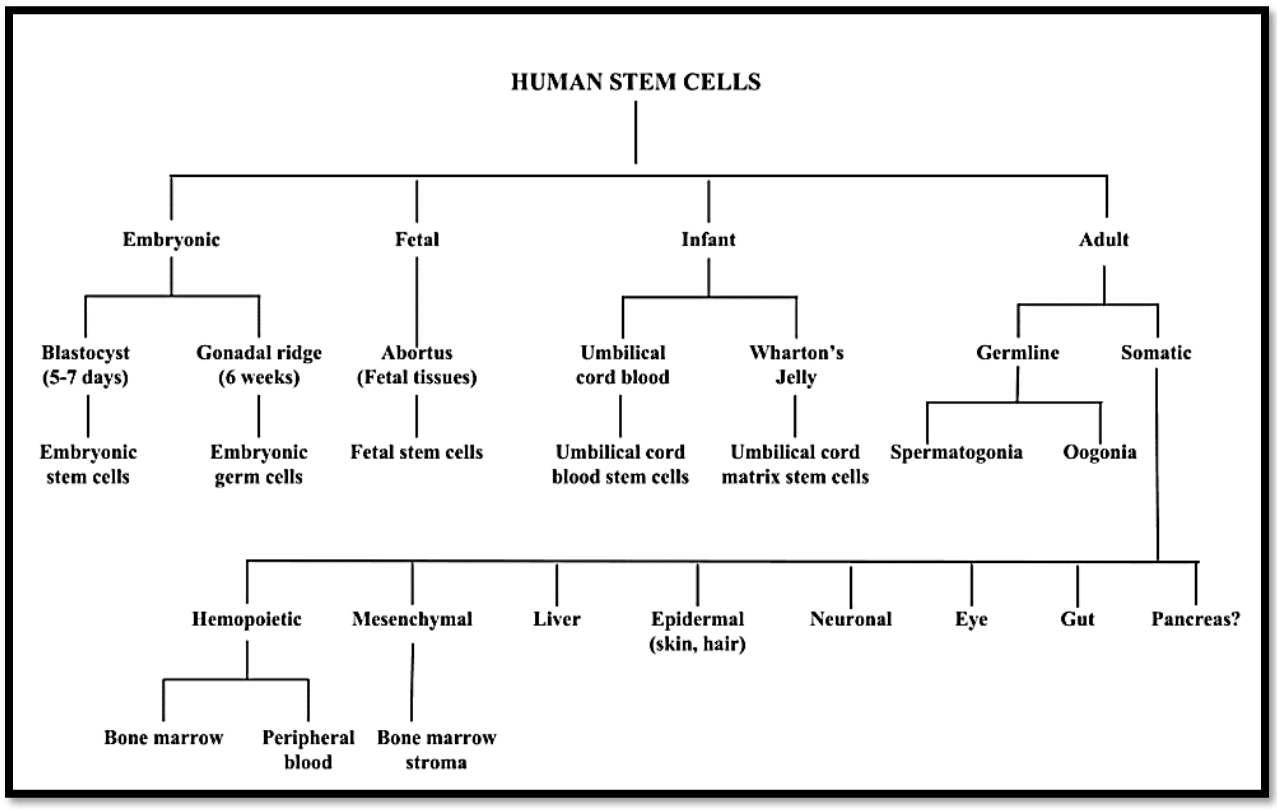

Figure 1: Classifications of human stem cells

3.2 Adult Stem Cells (ASCs):

ASCs are undifferentiated cells found living within specific differentiated tissues in our bodies that can renew themselves or generate new cells that can replenish dead or damaged tissue. You may also see the term "somatic stem cell" used to refer to adult stem cells. The term "somatic" refers to non-reproductive cells in the body (eggs or sperm). ASCs are typically scarce in native tissues which have rendered them difficult to study and extract for research purposes.

Resident in most tissues of the human body, discrete populations of ASCs generate cells to replace those that are lost through normal repair, disease, or injury. ASCs are found throughout ones lifetime in tissues such as the umbilical cord, placenta, bone marrow, muscle, brain, fat tissue, skin, gut, etc. The first ASCs were extracted and used for blood production in 1948. This procedure was expanded in 1968 when the first adult bone marrow cells were used in clinical therapies for blood disease.

Studies proving the specificity of developing ASCs are controversial; some showing that ASCs can only generate the cell types of their resident tissue whereas others have shown that ASCs may be able to create other tissue types than those they reside in. More studies are necessary to confirm the dispute.[9]

3.2.1 Types of Adult Stem Cells:

- Hematopoietic Stem Cells (Blood Stem Cells)
- Mesenchymal Stem Cells
- Neural Stem Cells
- Epithelial Stem Cells
- Skin Stem Cells

3.3 Embryonic Stem Cells (ESCs):

During days 3-5 following fertilization and before implantation, the embryo (at this stage, called a blastocyst), contains an inner cell mass capable of generating all the specialized tissues that make up the human body. ESCs are derived from the inner cell mass of an embryo that has been fertilized *in vitro* and donated for research purposes following informed consent. ESCs are not derived from eggs fertilized in a woman's body.

These pluripotent stem cells have the potential to become almost any cell type and are only found during the first stages of development. Scientists hope to understand how these cells differentiate during development. As we begin to understand these developmental processes, we may be able to apply them to stem cells grown in vitro and potentially regrow cells such as nerve, skin, intestine, liver, etc for transplantation. [10]

3.4 Induced Pluripotent Stem Cells (iPSCs)

Induced pluripotent stem cells are stem cells that are created in the laboratory, a happy medium between adult stem cells and embryonic stem cells. iPSCs are created through the introduction of embryonic genes into a somatic cell (a skin cell for example) that cause it to revert to a "stem cell-like" state. These cells, like ESCs, are considered pluripotent Discovered in 2007, this method of genetic reprogramming to create embryonic-like cells, is novel and needs many more years of research before use in clinical therapies. [11]

3.5 Mesenchymal stem cells (bone marrow stroma)

Mesenchymal stem cells (MSCs) are found postnatally in the non- hematopoietic bone marrow stroma. Marrow stromal tissue is made up of a heterogenous population of cells, which include reticulamcells, adipocytes, osteogenic cells, smooth muscle cells, endothelial cells and macrophages. In a steady state or response to injury, turnover of stromal tissue and repair occurs through the participation of a population of stem cells found in the stromal tissue. Apart fm bone marrow stroma, MSCs can also be derived from periosteum, fat and skin. MSCs are multipotent cells that are capable of differentiating into cartilage, bone, muscle, tendon, ligament and fat. There is some recent evidence that there is a rare cell within MSC cultures that is pluripotent and can give rise not only to mesodermal but to endodermal tissues. The authors have called this a Multipotent Adult Progenitor Cell.[12]

3.6 Neuronal stem cells

It has been suggested that a continuous neurogenic turnover occurs in some limited areas of the central nervous system (CNS). Two neurogenic regions of the adult mammalian CNS are supposed to be involved in this process: the subventricular zone (SVZ) of the forebrain and the dental gyrus of the hippocampus which are considered reservoirs of new neural cells. Thus, neural stem cells (NSCs) are known to reside in these two areas and they consistently generate new neurons, In vivo, endogenous NSCs seem to be able to produce almost exclusively neurons, while a single NSC in vitro is competent to generate neurons, astrocytes and oligodendrocytes. NSCs are multipotent progenitoir cells that have self-renewal activity. Although it seems clear that the bona fide NSC is the subventricular zone B cells, the search for self-renewing, multipotent NSCs is in progress and conflicting information is available in the literature. There has been data to suggest that the SVZ NSC is an ependymal cell, while others have demonstrated that the SVZ astrocyte is the NSC. It was also demonstrated that ependymal cells were unipotent giving rise to only glial cells, whereas SVZ astrocytes were able to produce multipotent neurospheres that yielded both neurons and glia. The final fate of the NSC is under tight environmental control and a stem cell niche has been postulated for the adult mammalian brain.[7,10]

4. Relevance to Diabetes

Diabetes affects millions of people in the world and is caused by the abnormal metabolism of insulin. Normally, insulin is produced and secreted by the cellular structures called the islets of Langerhans in the pancreas. Recently, insulin-expressing cells from mouse stem cells have been generated. In addition, the cells self-assemble to form structures, which closely resemble normal pancreatic islets and produce insulin. Future research will need to investigate how to optimize conditions for insulin production to provide a stem cell-based therapy to treat diabetes to replace the constant need for insulin injections.[13,14]

5. Mechanisms of Action

5.1 Beta Cell Regeneration

Beta cell regeneration involves three primary mechanisms:

- **Neogenesis**: This process refers to the formation of new beta cells from stem cells or progenitor cells. It is a promising avenue for restoring beta cell mass, particularly in patients with diabetes.
- **Duplication of Existing Beta Cells**: This mechanism emphasizes the self-replication of existing beta cells. Research has shown that this is a significant contributor to maintaining and expanding the beta cell population, especially under physiological conditions such as pregnancy or obesity.
- **Transdifferentiation**: This involves converting other pancreatic cell types, particularly alpha cells, into beta cells. Recent studies highlight the potential of transdifferentiation as a therapeutic strategy, as it avoids ethical concerns associated with stem cell use and minimizes the risk of immune rejection.[15,16]

5.2 Immunomodulation

Immunomodulation plays a crucial role in beta cell regeneration, especially in the context of autoimmune diseases like Type 1 diabetes. Strategies to modulate the immune response can help protect existing beta cells from autoimmune destruction and promote their regeneration. This can involve the use of immunosuppressive therapies or agents that enhance the tolerance of the immune system towards beta cells.[17]

5.3 Tissue Repair and Regeneration

The repair and regeneration of pancreatic tissue are influenced by various signaling pathways and factors. Key pathways include the PI3K/Akt/mTOR and JAK2/STAT5 pathways, which are essential for cellular proliferation and survival. Additionally, factors such as lactogens, hepatokines, and gut hormones can modulate the regenerative processes in the pancreas, suggesting a complex interplay between different signaling molecules in promoting tissue repair.[18]

6. Preclinical Studies

6.1 Animal Models

Preclinical studies often utilize rodent models to investigate beta cell regeneration mechanisms. These models can be classified into classical models, which involve the surgical or chemical ablation of beta cells, and genetic models, which are engineered to exhibit specific features of diabetes. Recent advancements include the use of humanized mouse models that incorporate human immune cells, allowing for more relevant evaluations of regenerative therapies.[19]

Recent findings from preclinical studies have underscored the potential of various regenerative strategies:

- **Transdifferentiation** of alpha cells into beta cells has emerged as a particularly promising approach, with several studies demonstrating its feasibility and effectiveness in animal models.
- **Pharmaceutical agents** that stimulate beta cell replication and regeneration have shown encouraging results, leading to increased beta cell mass and improved glycemic control in diabetic models.[20]

7. Challenges and Limitations

Despite promising results, several challenges remain in the field of beta cell regeneration:

- **Variability in Response**: Different animal models exhibit varying degrees of response to regenerative therapies, complicating the translation of findings to human subjects.
- **Immune Rejection**: In the case of transplanted cells or tissues, the risk of immune rejection remains a significant hurdle, particularly for therapies involving foreign cells or tissues.

- **Complexity of Human Disease**: The multifactorial nature of diabetes, including genetic, environmental, and lifestyle factors, poses challenges in developing universally effective therapies.[21,22]

8. Translational Research

8.1 From Lab to Clinic

Translational research is a crucial approach that aims to bridge the gap between scientific discoveries and real-world applications, particularly in the field of medicine. It involves a systematic and multidirectional process of applying knowledge gained from basic research to improve human health and well-being.

8.2 Bridging the Gap

The gap between basic science and clinical research has widened despite unprecedented opportunities in both fields. Translational research challenges investigators to move beyond the traditional training of laboratory scientists and clinicians. Efficient collaboration among researchers, clinicians, and industry partners is crucial to rapidly translate discoveries into clinical applications.[23,24]

8.3 Regulatory Pathways and Ethical Considerations

As translational research progresses from basic science to preclinical and clinical stages, researchers must navigate regulatory pathways and address ethical considerations. Clinical trials are carefully designed studies that follow strict protocols to gather data on how potential treatments interact with human subjects. Outcomes research assesses the effectiveness of these interventions in real-world settings and evaluates their long-term effects on patient outcomes and quality of life.[25,26]

9. Innovative Techniques in Translational Research

9.1 Gene Editing (e.g., CRISPR-Cas9)

Gene therapies deliver functional copies of missing or faulty genes, while RNA-based therapies can help restore normal protein production from dysfunctional genes. The approval of nusinersen, an RNA-based drug for spinal muscular atrophy, marked a significant milestone in the field of gene therapy. Adeno-associated viruses (AAVs) and lipid nanoparticles (LNPs) are being explored as delivery methods for DNA and RNA-based therapeutics.[27]

9.2 Scaffold and Biomaterials

Scaffolds and biomaterials play a crucial role in tissue engineering and regenerative medicine. These materials provide a structural support for cells to grow and organize into functional tissues.[28]

9.3 3D Bioprinting

3D bioprinting is an innovative technique that allows the fabrication of complex, three-dimensional structures using living cells, biomaterials, and growth factors. This technology holds great potential for creating customized tissue grafts and organ replacements for patients.[29,30]

10. Clinical Applications

Diabetes stem cell therapy is a rapidly developing subject that is now undergoing a large number of clinical trials at a variety of phases. Pancreatic islet cells, embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSCs) are the primary targets of clinical trials for the treatment of type 1 diabetes. These cells are being used to restore insulin-producing β-cells. Mesenchymal stem cells (MSCs) are currently being investigated for their potential to improve insulin sensitivity and reduce inflammation in patients with type 2 diabetes. Among the noteworthy clinical trials currently underway, ViaCyte's PEC-Direct and PEC-Encap are being conducted to investigate the implantation of embryonic stem cell (ESC)-derived pancreatic progenitor cells in patients diagnosed with Type 1 diabetes. Additionally, Sanofi and Evotec's iPSC-derived β-cells are being investigated to determine the safety and effectiveness of iPSC-derived β-cells in restoring insulin production.[31,32]

Pancreatic islet transplants, which have resulted in insulin independence for some patients with type 1 diabetes, and mesenchymal stem cell therapy, which has shown promise in lowering systemic inflammation and improving metabolic control in type 2 diabetes, are two examples of successful treatments. There are, however, ongoing hurdles that include assuring the long-term survival of transplanted cells without immune rejection, locating sources of stem cells that are trustworthy and scalable, and monitoring for potential tumorigenicity and other long-term side effects.[33]

Autologous and allogeneic transplants are two types of therapeutic techniques that are utilized in stem cell therapy for the treatment of diabetes. The use of the patient's own stem cells in autologous transplants reduces the likelihood of immunological rejection; yet, the transplant's success may be contingent on the patient's overall health and the quality of the cells. Allogeneic transplants, which make use of donor stem cells, offer a supply that is more easily accessible; yet, immunosuppression is necessary in order to prevent recipient rejection. It is possible to reduce the risk of donated cells being rejected by the body by combining immunosuppressants and stem cell therapy. The use of immunomodulatory medicines that induce immunological tolerance to transplanted cells and encapsulation technologies that protect transplanted cells from the immune system while permitting insulin release are two examples of innovative techniques.[34]

Stem cell therapy for diabetes has shown promising results in terms of its efficacy, safety, and potential to improve patients' quality of life. The major objective is to reestablish the production of endogenous insulin, which will result in a significant improvement in glycemic control in both type 1 and type 2 diabetes, and may also result in a reduction or elimination of the requirement for exogenous insulin injections. When opposed to allogeneic transplants, which are associated with the dangers associated with the use of immunosuppressants for an extended period of time,

autologous transplants typically have a lower risk of adverse consequences. Patients may experience improvements in their mental health and general quality of life as a result of improved glycemic control and a lower disease load. This can also result in a large reduction in the amount of daily management chores and an improvement in psychosocial well-being.[35]

11. Challenges and Limitations in Stem Cell Research and Therapy

11.1 Technical and Biological Challenges

11.1.1 Stem Cell Source and Quality:

- **Source Variability**: Stem cells can be derived from various sources, including embryonic, fetal, and adult tissues, each with unique properties and potential. The variability in sources can affect the consistency and quality of stem cells obtained for therapeutic purposes.
- **Quality Control**: Ensuring the purity, potency, and viability of stem cells is critical. Contaminants or differentiated cells can compromise the efficacy and safety of stem cell-based therapies.
- **Scalability**: Producing a sufficient quantity of high-quality stem cells for therapeutic applications remains a challenge. Scaling up production while maintaining quality is complex and resource-intensive.[36,37]

11.1.2 Delivery Methods:

- **Targeting Accuracy**: Effective delivery of stem cells to the specific site of injury or disease is crucial. Poor targeting can lead to reduced efficacy and potential side effects.
- **Survival and Integration**: Ensuring that transplanted stem cells survive, integrate with host tissues, and function properly is challenging. Many stem cells may die or fail to integrate post-transplantation.
- **Controlled Differentiation**: Inducing stem cells to differentiate into the desired cell type in vivo or in vitro before transplantation requires precise control. Uncontrolled differentiation can lead to teratoma formation or other adverse outcomes.[38,39]

11.1.3 Immune Rejection:

- **Host Immune Response**: The host's immune system may recognize transplanted stem cells as foreign and mount an immune response, leading to rejection and failure of the therapy.
- **Immunosuppression**: Using immunosuppressive drugs to prevent rejection can expose patients to infections and other complications. Developing methods to induce immune tolerance without lifelong immunosuppression is a significant hurdle.[40]

12. Regulatory and Ethical Issues

12.1 Approval Processes:

- **Regulatory Hurdles**: Navigating the regulatory landscape for stem cell therapies is complex and time-consuming. Obtaining approval from agencies like the FDA or EMA requires extensive preclinical and clinical data to demonstrate safety and efficacy.
- **Clinical Trial Design**: Designing and conducting robust clinical trials that meet regulatory standards while addressing the unique aspects of stem cell therapies is challenging. Ensuring adequate patient recruitment, control groups, and long-term follow-up adds complexity.[41,42]

12.2 Cost and Accessibility:

- **High Development Costs**: The research, development, and manufacturing of stem cell therapies are expensive, leading to high treatment costs. This can limit accessibility for patients who need these therapies.
- **Insurance and Reimbursement**: Securing coverage and reimbursement from insurance providers for stem cell therapies can be difficult. The high costs may not be fully covered, placing a financial burden on patients and healthcare systems.[43,44]

12.3 Ethical Debates Surrounding Stem Cell Use:

- **Embryonic Stem Cells**: The use of embryonic stem cells (ESCs) raises ethical concerns regarding the destruction of human embryos. This has led to polarized views and restrictions in funding and research in some regions.
- **Informed Consent**: Obtaining informed consent from donors, particularly for embryonic and fetal tissues, involves ethical considerations. Ensuring that donors are fully aware of the potential uses and implications of their donations is critical.
- **Equity in Access**: Ensuring equitable access to stem cell therapies across different populations and socioeconomic groups poses an ethical challenge. Addressing disparities in access and ensuring that therapies are available to all who need them is a key consideration.[45]

13. Future Directions

Future directions in stem cell research and therapy are poised to overcome current challenges and open new avenues for treatment. Advances in stem cell research include the discovery of new stem cell sources and improved differentiation protocols, enhancing the quality and applicability of stem cells for various therapies. Personalized medicine approaches are becoming more prominent, allowing for treatments tailored to individual patients' genetic and molecular profiles, which can significantly improve efficacy and reduce adverse effects. Integrating stem cell therapies with other treatments, such as pharmacotherapy, can enhance therapeutic outcomes. For instance, combining stem cell therapy with advanced monitoring technologies like continuous glucose monitoring could provide more precise and effective management of conditions such as diabetes. Looking at the long-term prospects, there is potential for stem cell research to contribute to cures

for currently incurable diseases. Sustainable and scalable therapies are also on the horizon, as ongoing research aims to develop cost-effective methods for producing and delivering stem cell treatments, making them more accessible to a broader population. These future directions highlight the promise of stem cell research in transforming medical treatments and improving patient outcomes.[46,47]

14. Conclusion

The field of stem cell research has achieved significant milestones, demonstrating its transformative potential in medicine. Benchside research has seen remarkable progress, including advancements in stem cell isolation, characterization, and manipulation, which have led to a deeper understanding of stem cell biology and their therapeutic capabilities. Clinical applications have similarly progressed, with several promising treatments emerging from clinical trials and moving towards practical use. These advancements include successful applications in regenerative medicine and preliminary successes in treating complex diseases, underscoring the transformative potential of stem cell therapies.

Despite these achievements, numerous hurdles remain. Technical challenges related to stem cell sourcing, quality control, and effective delivery continue to complicate the development and implementation of therapies. Regulatory and ethical issues, including stringent approval processes and debates surrounding the use of certain types of stem cells, pose additional barriers that must be navigated carefully. Addressing these issues requires sustained effort and innovation.

The outlook for stem cell therapy in diabetes is particularly promising. Advances in stem cell research offer hope for more effective and personalized treatments, potentially transforming diabetes management and offering solutions for cases resistant to conventional therapies. Innovations in stem cell technology, combined with advancements in related fields such as continuous glucose monitoring and pharmacotherapy, hold the promise of creating integrated treatment approaches that improve patient outcomes.

Looking forward, it is crucial to emphasize the importance of continued research and collaboration. Interdisciplinary efforts that bring together scientists, clinicians, and policymakers will be essential to overcoming existing challenges and translating breakthroughs into real-world applications. By fostering a collaborative environment and prioritizing ongoing research, the potential of stem cell therapies can be fully realized, paving the way for innovative treatments that could significantly impact the management and treatment of diabetes and other challenging conditions.

15. Conflict of interest

The authors have no conflict of interest.

16. Acknowledgement

Authors are highly thankful to their Universities/Colleges for providing library facilities for the literature survey.

References

1. Bastaki S. Diabetes mellitus and its treatment _ International Journal of Diabetes and Metabolism _ Karger Publishers. Published online 2019.
2. Agarwal S, Simmonds I, Myers AK. The Use of Diabetes Technology to Address Inequity in Health Outcomes: Limitations and Opportunities. *Curr Diab Rep*. 2022;22(7):275-281. doi:10.1007/s11892-022-01470-3
3. Alam U, Asghar O, Azmi S, Malik RA. *General Aspects of Diabetes Mellitus*.; 2014.
4. Kaul K, Tarr JM, Ahmad S 1, Kohner' EM, Chibber' R. *Introduction to Diabetes Mellitus*.; 2012.
5. Angiolillo D. Antiplatelet therapy in diabetes: Efficacy and limitations of current treatment strategies and future directions. *Diabetes Care*. 2009;32(4):531-540. doi:10.2337/dc08-2064
6. Ali S, Drucker DJ. Benefits and limitations of reducing glucagon action for the treatment of type 2 diabetes. *Am J Physiol Endocrinol Metab*. 2009;296(3). doi:10.1152/ajpendo.90887.2008
7. Kalra K, Tomar PC. *Stem Cell: Basics, Classification and Applications*.; 2014. www.ajpct.org
8. 2021. *Types of Stem Cell*.; 2021. https://www.unmc.edu/stemcells/educational-resources/types.html
9. Ariff Bongso & Eng Hin Lee. Stem Cells_ From Bench To Bedside - Google Books. Published online 2005.
10. Daniel Murrell MD. *What Are Stem Cells, and What Do They Do?*; 2023. https://www.medicalnewstoday.com/articles/323343#types
11. *NIH Stem Cell Information Stem Cell Basics*.; 2016. https://stemcells.nih.gov/info/basics/stc-basics
12. Ding DC, Shyu WC, Lin SZ. Mesenchymal stem cells. *Cell Transplant*. 2011;20(1):5-14. doi:10.3727/096368910X
13. Noguchi H. Journal of Stem Cells Stem Cell Applications in Diabetes. 2012;7(4).
14. Fadini GP, Ciciliot S, Albiero M. Concise Review: Perspectives and Clinical Implications of Bone Marrow and Circulating Stem Cell Defects in Diabetes. *Stem Cells*. 2017;35(1):106-116. doi:10.1002/stem.2445
15. Liu C, Wu H. From beta cell replacement to beta cell regeneration: Implications for antidiabetic therapy. *J Diabetes Sci Technol*. 2014;8(6):1221-1226. doi:10.1177/1932296814540611
16. Bouwens & Luc. Beta Cell Regeneration_ Ingenta Connect. Published online 2006.
17. English K. Mechanisms of mesenchymal stromal cell immunomodulation. *Immunol Cell Biol*. 2013;91(1):19-26. doi:10.1038/icb.2012.56
18. Li HH, Fu X. Mechanisms of action of mesenchymal stem cells in cutaneous wound repair and regeneration. *Cell Tissue Res*. 2012;348(3):371-377. doi:10.1007/s00441-012-1393-9

19. Clare Njoki Kimani et al. CIMB _ Free Full-Text _ Regeneration of Pancreatic Beta Cells by Modulation of Molecular Targets Using Plant-Derived Compounds_ Pharmacological Mechanisms and Clinical Potential. Published online 2023.
20. King A, Bowe J. Animal models for diabetes: Understanding the pathogenesis and finding new treatments. *Biochem Pharmacol*. 2016;99:1-10. doi:10.1016/j.bcp.2015.08.108
21. Thi Van Anh Bui et al. KoreaMed Synapse. Published online 2021.
22. Inanç B, Elçin YM. Stem Cells in Tooth Tissue Regeneration-Challenges and Limitations. *Stem Cell Rev Rep*. 2011;7(3):683-692. doi:10.1007/s12015-011-9237-7
23. Rubio DMG, Schoenbaum EE, Lee LS, et al. Defining translational research: Implications for training. *Academic Medicine*. 2010;85(3):470-475. doi:10.1097/ACM.0b013e3181ccd618
24. Mayrink NNV, Alcoforado L, Chioro A, et al. Translational research in health technologies: A scoping review. *Front Digit Health*. 2022;4. doi:10.3389/fdgth.2022.957367
25. Baker HB, McQuilling JP, King NMP. Ethical considerations in tissue engineering research: Case studies in translation. *Methods*. 2016;99:135-144. doi:10.1016/j.ymeth.2015.08.010
26. Baker HB, McQuilling JP, King NMP. Ethical considerations in tissue engineering research: Case studies in translation. *Methods*. 2016;99:135-144. doi:10.1016/j.ymeth.2015.08.010
27. Sparmann A, Vogel J. RNA -based medicine: from molecular mechanisms to therapy . *EMBO J*. 2023;42(21). doi:10.15252/embj.2023114760
28. Khorkova O, Stahl J, Joji A, Volmar CH, Wahlestedt C. Amplifying gene expression with RNA-targeted therapeutics. *Nat Rev Drug Discov*. 2023;22(7):539-561. doi:10.1038/s41573-023-00704-7
29. Uddin F, Rudin CM, Sen T. CRISPR Gene Therapy: Applications, Limitations, and Implications for the Future. *Front Oncol*. 2020;10. doi:10.3389/fonc.2020.01387
30. Hernández-Juárez J, Rodríguez-Uribe G, Borooah S. Toward the Treatment of Inherited Diseases of the Retina Using CRISPR-Based Gene Editing. *Front Med (Lausanne)*. 2021;8. doi:10.3389/fmed.2021.698521
31. Verhoeff K, Henschke SJ, Marfil-Garza BA, Dadheech N, Shapiro AMJ. Inducible pluripotent stem cells as a potential cure for diabetes. *Cells*. 2021;10(2):1-25. doi:10.3390/cells10020278
32. Tahbaz M, Yoshihara E. Immune Protection of Stem Cell-Derived Islet Cell Therapy for Treating Diabetes. *Front Endocrinol (Lausanne)*. 2021;12. doi:10.3389/fendo.2021.716625
33. Ashe S, Hebrok M. Role of Cell-Based Therapies in T2D. *Semin Nephrol*. 2023;43(3). doi:10.1016/j.semnephrol.2023.151432
34. Park SJ, Kim YY, Han JY, Kim SW, Kim H, Ku SY. Advancements in Human Embryonic Stem Cell Research: Clinical Applications and Ethical Issues. *Tissue Eng Regen Med*. 2024;21(3):379-394. doi:10.1007/s13770-024-00627-3

35. Inoue R, Nishiyama K, Li J, et al. The feasibility and applicability of stem cell therapy for the cure of type 1 diabetes. *Cells*. 2021;10(7). doi:10.3390/cells10071589

36. Wnorowski A, Yang H, Wu JC. Progress, obstacles, and limitations in the use of stem cells in organ-on-a-chip models. *Adv Drug Deliv Rev*. 2019;140:3-11. doi:10.1016/j.addr.2018.06.001

37. Jankowski M, Machatkova M, Ventruba P, et al. Challenges of stem cell application in research and clinical practice – an update. *Medical Journal of Cell Biology*. 2021;9(4):160-164. doi:10.2478/acb-2021-0022

38. Jotwani G. et al. National_Guidelines_StemCellResearch-2017. Published online 2017.

39. Hoang DM, Pham PT, Bach TQ, et al. Stem cell-based therapy for human diseases. *Signal Transduct Target Ther*. 2022;7(1). doi:10.1038/s41392-022-01134-4

40. McKee C, Chaudhry GR. Advances and challenges in stem cell culture. *Colloids Surf B Biointerfaces*. 2017;159:62-77. doi:10.1016/j.colsurfb.2017.07.051

41. Bashor CJ, Hilton IB, Bandukwala H, Smith DM, Veiseh O. Engineering the next generation of cell-based therapeutics. *Nat Rev Drug Discov*. 2022;21(9):655-675. doi:10.1038/s41573-022-00476-6

42. Van Schothorst M, Weeda J, Schiffers K, Oortwijn W, Hoekman J, De Bruin ML. European Commission Study on the regulation of advanced therapies in selected jurisdictions. Published online 2014. doi:10.2818/74841

43. *Experimental Treatments*.; 2014. https://www.ncbi.nlm.nih.gov/books/NBK223198/

44. El-Kadiry AEH, Rafei M, Shammaa R. Cell Therapy: Types, Regulation, and Clinical Benefits. *Front Med (Lausanne)*. 2021;8. doi:10.3389/fmed.2021.756029

45. Devi K, Joga R, Srivastava S, et al. *Regulatory Landscape and Challenges in CAR-T Cell Therapy Development in the US, EU, Japan, and India*.; 2024. https://doi.org/./j.ejpb..

46. Liu G, David BT, Trawczynski M, Fessler RG. Advances in Pluripotent Stem Cells: History, Mechanisms, Technologies, and Applications. *Stem Cell Rev Rep*. 2020;16(1):3-32. doi:10.1007/s12015-019-09935-x

47. Dardano M, Lebek T, Tsang IHC. Exploring stem cell frontiers: definitions, challenges, and perspectives for regenerative medicine. *Biol Open*. 2024;13(4). doi:10.1242/bio.060245