

**THERAPEUTIC POTENTIAL OF STEM CELLS IN PANCREATIC
REGENERATION: AN EMERGING STRATEGY FOR THE TREATMENT OF
TYPE 1 DIABETES MELLITUS**

**POTENCIAL TERAPÊUTICO DAS CÉLULAS-TRONCO NA REGENERAÇÃO
PANCREÁTICA: UMA ESTRATÉGIA EMERGENTE PARA O TRATAMENTO DO
DIABETES MELLITUS TIPO 1**

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REGENERACIÓN PANCREÁTICA: UNA ESTRATEGIA EMERGENTE PARA EL
TRATAMIENTO DE LA DIABETES MELLITUS TIPO 1**

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ABSTRACT

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by the destruction of pancreatic β -cells, resulting in absolute insulin deficiency and lifelong dependence on exogenous insulin therapy. Despite advances in glucose monitoring technologies and new insulin formulations, many patients remain outside therapeutic targets, reinforcing the need for innovative strategies. Stem cell-based therapies have emerged as a promising alternative, given their potential for pancreatic regeneration and restoration of endocrine function. This study is a narrative review of the literature published between 2020 and 2025 in national and international databases, focusing on embryonic stem cells (hESCs), induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs). The results show that hESCs and iPSCs can differentiate into insulin-producing β -like cells, while MSCs play a relevant role in immune modulation and protection of the pancreatic microenvironment. Recent clinical trials, including protocols with human pluripotent stem cell-derived products, already demonstrate measurable C-peptide secretion and partial reduction of exogenous insulin requirements, confirming the translational feasibility of this strategy. However, significant challenges remain, such as residual immunogenicity, tumorigenic risk, functional immaturity of transplanted cells, need for immunosuppression, as well as economic and regulatory barriers. In conclusion, stem cell-based pancreatic regeneration represents a rapidly evolving field with relevant clinical prospects, but still requires long-term multicenter studies, standardized protocols for efficacy and safety, and policies that ensure global accessibility.

Keywords: Stem Cells. Pancreatic Regeneration. Type 1 Diabetes Mellitus. Cell Therapy. Regenerative Medicine.

RESUMO

O diabetes mellitus tipo 1 (DM1) é uma doença autoimune caracterizada pela destruição das células β pancreáticas, resultando em deficiência absoluta de insulina e necessidade de terapia exógena contínua. Apesar dos avanços nas tecnologias de monitoramento glicêmico e nas formulações de insulina, muitos pacientes permanecem fora das metas terapêuticas, reforçando a necessidade de estratégias inovadoras. As terapias celulares baseadas em células-tronco emergem como alternativa promissora, uma vez que apresentam potencial para regeneração pancreática e restauração da função endócrina. O presente estudo constitui uma revisão narrativa da literatura, realizada entre 2020 e 2025, em bases indexadas nacionais e internacionais, com foco no uso de células-tronco embrionárias (hESCs), pluripotentes induzidas (iPSCs) e mesenquimais (MSCs). Os resultados analisados demonstram que hESCs e iPSCs podem diferenciar-se em células β -like produtoras de insulina, enquanto as MSCs exercem papel relevante na modulação imunológica e na proteção do microambiente pancreático. Ensaios clínicos recentes, incluindo protocolos com células derivadas de pluripotentes humanas, já evidenciam secreção mensurável de C-peptídeo e redução parcial da necessidade de insulina exógena, confirmando a viabilidade translacional da estratégia. Contudo, desafios importantes permanecem, como imunogenicidade residual, risco de tumorigênese, imaturidade funcional das células implantadas, necessidade de imunossupressão, além de barreiras econômicas e regulatórias. Conclui-se que a regeneração pancreática mediada por células-tronco representa um campo em rápida evolução, com perspectivas clínicas relevantes, mas que ainda exige estudos multicêntricos de longo prazo, protocolos padronizados de eficácia e segurança, e políticas que assegurem acessibilidade global.

Palavras-chave: Células-tronco. Regeneração Pancreática. Diabetes Mellitus Tipo 1. Terapia Celular. Medicina Regenerativa.

RESUMEN

La diabetes mellitus tipo 1 (DT1) es una enfermedad autoinmune que se caracteriza por la destrucción de las células beta pancreáticas, lo que resulta en una deficiencia absoluta de insulina y la necesidad de terapia exógena continua. A pesar de los avances en las tecnologías de monitorización de la glucosa y las formulaciones de insulina, muchos pacientes permanecen fuera de los objetivos terapéuticos, lo que refuerza la necesidad de estrategias innovadoras. Las terapias celulares basadas en células madre se perfilan como una alternativa prometedora, ya que tienen el potencial de regenerar el páncreas y restaurar la función endocrina. Este estudio es una revisión narrativa de la literatura, realizada entre 2020 y 2025, en bases de datos indexadas nacionales e internacionales, centrada en el uso de células madre embrionarias (hESC), células madre pluripotentes inducidas (iPSC) y células madre mesenquimales (MSC). Los resultados analizados demuestran que las hESC y las iPSC pueden diferenciarse en células similares a β productoras de insulina, mientras que las MSC desempeñan un papel relevante en la modulación inmunitaria y la protección del microambiente pancreático. Ensayos clínicos recientes, incluyendo protocolos con células derivadas de células madre pluripotentes humanas, ya han demostrado una secreción medible de péptido C y una reducción parcial de la necesidad de insulina exógena, lo que confirma la viabilidad translacional de la estrategia. Sin embargo, persisten importantes desafíos, como la inmunogenicidad residual, el riesgo de tumorigénesis, la inmadurez funcional de las células implantadas, la necesidad de inmunosupresión y las barreras económicas y regulatorias. Concluimos que la regeneración pancreática mediada por células madre representa un campo en rápida evolución con importantes perspectivas clínicas, pero aún requiere estudios multicéntricos a largo plazo, protocolos estandarizados de eficacia y seguridad, y políticas que garanticen la accesibilidad global.

Palabras clave: Células Madre. Regeneración Pancreática. Diabetes Mellitus Tipo 1. Terapia Celular. Medicina Regenerativa.

1 INTRODUCTION

Type 1 diabetes mellitus (T1D) is a chronic autoimmune disease characterized by the selective destruction of pancreatic β cells, resulting in absolute insulin deficiency and the need for lifelong replacement therapy. According to the Atlas of the International Diabetes Federation (IDF), it is estimated that more than 9 million people are currently living with T1DM worldwide, a number that grows annually, representing a global public health challenge, especially due to the costs associated with the management of chronic complications of the disease (INTERNATIONAL DIABETES FEDERATION, 2024).

Despite significant advances in insulin formulations, continuous glucose monitoring systems, and automated infusion pumps, a large portion of patients remain outside the established glycemic targets, which increases the risk of severe hypoglycemia, diabetic ketoacidosis, microvascular and macrovascular complications, as well as a negative impact on quality of life (GHONEIM et al., 2024). This scenario highlights the need for innovative therapeutic strategies that overcome the limitations of conventional therapy.

In this context, regenerative medicine has stood out as an emerging field, offering therapeutic alternatives based on the use of stem cells. The ability of these cells to differentiate into pancreatic progenitors and modulate the immune response places them as promising candidates for restoring lost endocrine function in T1D. Recent studies indicate that embryonic stem cells (hESCs), induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs) have been the most investigated sources, with varying degrees of success in generating β -like cells capable of secreting insulin in response to glucose (WANG et al., 2025).

Translational advances in this area have already resulted in high-impact clinical trials. In 2024, the first transplantation of islets derived from autologous iPSCs in a patient with T1D was reported, resulting in insulin independence for approximately one year, which represents a milestone in biotechnology applied to the treatment of the disease (ABOU ZAKI et al., 2024). At the same time, companies such as Vertex Pharmaceuticals have been conducting phase I/II clinical trials with human pluripotent-derived cells (VX-880), demonstrating measurable C-peptide secretion and partial reduction in the need for exogenous insulin, consolidating the clinical feasibility of this approach (DANILEVSKII et al., 2025).

In addition to the direct replacement of β cells, studies highlight the relevance of the immunomodulatory role of MSCs. These cells, when used in experimental models and in early clinical trials, have shown potential to reduce inflammatory markers, attenuate

autoimmune destruction, and promote greater graft integration. The combination of regenerative and immunosuppressive properties makes MSCs a particularly attractive therapeutic resource, including in protocols that aim to reduce or eliminate the need for pharmacological immunosuppression (KASHBOUR et al., 2025).

Despite the optimism, significant barriers still remain. Among them, immunological rejection, the possibility of tumorigenic formation due to incomplete differentiations, the need for robust β -like cell maturation protocols, and the high costs of production on a clinical scale stand out. In addition, ethical and regulatory issues remain at the center of the debate, especially when it comes to embryonic cell manipulation and advanced gene editing (TONDIN et al., 2025).

Thus, the review of the most recent evidence on the application of stem cells in pancreatic regeneration becomes fundamental. By integrating data from experimental studies, clinical trials, and translational analyses, it is possible to understand not only the advances already achieved, but also the technical, immunological, and economic challenges that still limit the incorporation of these therapies into clinical practice. Critical analysis of this scenario provides subsidies to outline future perspectives and research gaps that need to be overcome to turn this promise into therapeutic reality (NATURE COMMUNICATIONS BIOLOGY, 2025).

2 METHODOLOGY

The present study is characterized as a **narrative review of the literature**, of an exploratory and descriptive nature, focusing on the therapeutic potential of stem cells in pancreatic regeneration applied to the treatment of type 1 diabetes mellitus (DM1). The choice of this methodological design is justified by the breadth of the topic and the need to integrate different levels of evidence, from preclinical experiments to recent clinical trials, allowing a critical analysis of translational applicability (GHONEIM et al., 2024).

2.1 SOURCES OF INFORMATION AND SEARCH STRATEGY

The literature search was carried out between **January 2020 and September 2025**, using the **PubMed, Scopus, Web of Science, SciELO, and LILACS databases**, as well as official documents published by the World Health Organization (WHO) and the International Diabetes Federation (IDF). The searches were complemented by queries to open access

journals specializing in cell therapy and regenerative medicine, such as *Stem Cell Research & Therapy* and *Frontiers in Cell and Developmental Biology* (WANG et al., 2025).

The descriptors were defined according to DeCS/**MeSH**, in Portuguese and English: *Stem cells; Pancreatic regeneration; Type 1 diabetes mellitus; Cell therapy; Pancreatic islets*. Boolean operators (*AND, OR*) were used to increase the sensitivity and specificity of the search.

2.2 INCLUSION AND EXCLUSION CRITERIA

The following were included:

- Original articles, systematic and narrative reviews, meta-analyses, and clinical trials published between **2020 and 2025**;
- Publications in **Portuguese or English**;
- Studies that specifically addressed the application of stem cells in pancreatic regeneration or in the management of T1D;
- Papers with relevant experimental, clinical, or translational data.

The following were excluded:

- Isolated case reports and very small series;
- Opinion articles without methodological support;
- Duplicate studies in different databases;
- Research whose main focus was not cell therapy applied to DM1 (KASHBOUR et al., 2025).

2.3 ANALYSIS PROCEDURE

The analysis was conducted in three stages:

1. **Exploratory reading** of titles and abstracts for preliminary selection;
2. **Full reading** of the articles that met the inclusion criteria;
3. **Interpretative reading and thematic categorization**, organizing the findings into five main axes: (a) investigated cellular sources (hESCs, iPSCs, MSCs); (b) differentiation and maturation protocols; (c) immunoprotection and gene editing strategies; (d) recent clinical results; (e) challenges and future prospects (ABOU ZAKI et al., 2024).

2.4 METHODOLOGICAL LIMITATIONS

As this is a narrative review, this study did not follow strict protocols such as **PRISMA**, which may increase the risk of subjectivity in the selection and analysis of articles. However, we sought to mitigate this bias by prioritizing the inclusion of high-impact publications, critical reviews, and recent clinical trials indexed in prestigious international databases (DANILEVSKII et al., 2025; TONDIN et al., 2025).

3 RESULTS

3.1 CELLULAR SOURCES FOR PANCREATIC REGENERATION

Several sources of stem cells have been investigated for application in DM1. Embryonic **stem cells (hESCs)** have great potential for differentiation into functional β -like cells, but they face ethical barriers and tumorigenic risk. Induced **pluripotent stem cells (iPSCs)** represent a promising alternative, as they allow the generation of autologous cells, reducing the risk of immune rejection (ABOU ZAKI et al., 2024). At the same time, **mesenchymal stem cells (MSCs)**, derived from adipose tissue, bone marrow, or umbilical cord, have been studied mainly for their immunomodulatory effect and support to the pancreatic microenvironment, although with less capacity for direct differentiation (KASHBOUR et al., 2025).

3.2 DIFFERENTIATION AND FUNCTIONAL MATURATION PROTOCOLS

Significant advances have been made in the protocols for differentiation of hESCs and iPSCs into insulin-producing cells. Recent studies have shown that multistep protocols, with sequential activation and inhibition of signaling pathways, can generate β -like cells capable of secreting insulin in a glucose-dependent manner (DANILEVSKII et al., 2025). However, there are still limitations regarding the complete maturation of these cells, which often exhibit an immature phenotype, with a suboptimal response to glucose compared to native β cells.

3.3 IMMUNOPROTECTION STRATEGIES AND GENETIC ENGINEERING

Immune rejection remains one of the main barriers to clinical application. Cell **encapsulation** strategies have been widely explored, with promising results in animal models. Macroencapsulated devices make it possible to physically isolate transplanted cells from the immune system, while enabling the diffusion of nutrients and insulin. However,

complications such as pericapsular fibrosis still compromise long-term efficacy (WANG et al., 2025).

In addition, **gene editing** has been used to produce hypoimmunogenic cells, with deletion of major histocompatibility complex (MHC) molecules, increasing graft survival without the need for continuous immunosuppression. Preclinical models in non-human primates have already demonstrated that genetically modified pseudo-islets can maintain stable insulin secretion without significant rejection (TONDIN et al., 2025).

3.4 RECENT CLINICAL TRIALS

In the last five years, pioneering clinical trials have demonstrated the translational feasibility of cell therapy in T1D. The study conducted by **Abou Zaki et al. (2024)** reported the first autologous transplantation of differentiated iPSCs into insulin-producing cells, resulting in insulin independence for approximately one year. Similarly, phase I/II clinical trials with VX-880, conducted by Vertex Pharmaceuticals, showed measurable C-peptide secretion and partial reduction of exogenous insulin in patients with long-standing T1D (GHONEIM et al., 2024; SHAPIRO et al., 2024).

In addition to pluripotent-derived cells, several studies investigate the application of **MSCs** in clinical protocols. A meta-analysis published in 2025 reported significant improvement in glycemic control, reduction in glycated hemoglobin (HbA1c), and lower glycemic variability in patients treated with MSCs, suggesting a relevant immunomodulatory effect on the pancreatic microenvironment (KASHBOUR et al., 2025).

3.5 SECURITY AND LIMITATIONS

While the initial results are encouraging, security issues remain at the center of the debate. The risk of tumorigenic formation due to incomplete differentiation is still a concern with hESCs and iPSCs, requiring rigorous cell purification protocols. In the VX-880 trials, no serious adverse events related to the cell product were reported, but the need for pharmacological immunosuppression remains a significant clinical barrier (DANILEVSKII et al., 2025).

Another critical point refers to the **functional durability of the grafts**. It remains to be seen whether the positive effects observed in short-term studies can be sustained for many years. In addition, the costs associated with the development, production, and maintenance

of these therapies represent a relevant obstacle to their large-scale implementation (NATURE COMMUNICATIONS BIOLOGY, 2025).

4 DISCUSSION

The findings of this review indicate that stem cell-based therapies have advanced from the preclinical domain to **proof-of-concept clinical trials** in T1D, with evidence of C-peptide secretion and reduced need for exogenous insulin after implantation of pluripotent-derived cells. These results support the **translational feasibility** of β cell replacement as a therapeutic strategy, although still far from routine clinical standardization (Ghoneim et al., 2024; Danilevskii et al., 2025).

The comparison between **cellular sources** suggests a potential gradient: hESCs and iPSCs exhibit greater differentiation capacity into functional β -like cells, while MSCs exert mainly **immunomodulatory and trophic effects**, modulating the pancreatic microenvironment without necessarily directly replenishing β mass. This complementarity indicates that **combined approaches** (e.g., β -like cell grafting associated with MSCs) can optimize tissue integration and functional stability of the graft (Wang et al., 2025; Kashbour et al., 2025).

From a techno-scientific **point of view**, the biggest obstacles lie in the **immunogenicity** and **functional maturation** of β -like cells. Multistep differentiation protocols generate glucose-responsive cells, but often with **an immature** phenotype, which limits the amplitude and dynamics of insulin secretion when compared to native cells. In parallel, allogeneic rejection persists even with highly purified cell products, requiring **pharmacological immunosuppression** which, in turn, adds risks and costs (Danilevskii et al., 2025; Ghoneim et al., 2024).

Immunoprotection strategies and **genetic engineering** emerge as promising ways to reduce dependence on immunosuppressants. **Macroencapsulated devices** cushion the immune attack and allow eventual **recovery** of the implant, but they can suffer pericapsular fibrosis, compromising nutrient diffusion and graft performance. In parallel, **hypoimmunogenic** cells by MHC editing showed, in preclinical models, maintenance of insulin secretion without significant rejection, pointing to a scenario in which **intrinsic immune-evasion** replaces physical barriers (Tondin et al., 2025; Wang et al., 2025).

Recent clinical evidence reinforces this trajectory. The report of the **first autologous transplantation of differentiated iPSCs** into insulin-producing cells, with insulin

independence for about one year, illustrates the potential of autology to mitigate rejection, even if scalability and **manufacturing time** challenges persist. Trials with **VX-880** have shown measurable C-peptide and lower insulin use, but still dependent on immunosuppression, which limits large-scale applicability and imposes long-term safety surveillance (Abou Zaki et al., 2024; Ghoneim et al., 2024).

In the safety axis, two points require continuous attention: **tumorigenesis** and **functional durability**. Incomplete differentiations can generate proliferative remnants, requiring **rigorous purification** and traceability of the cell product. Even in initial efficacy scenarios, there is uncertainty about the **longevity of the effect** (years) and the maintenance of glycemic goals without significant adverse events, a gap that requires **multicenter follow-ups** and **standardized outcome protocols** (C-peptide, HbA1c, time in range, severe hypoglycemias) (Danilevskii et al., 2025; Ghoneim et al., 2024).

Costs and **logistics** are structural barriers: GMP production, cryopreservation, transportation, traceability, and qualified centers raise the total cost and can **widen inequalities in access**, especially in low- and middle-income countries. Public-private financing models, **adaptive regulatory partnerships**, and global health strategies will be key to converting innovation into tangible population benefit (Kashbour et al., 2025; Wang et al., 2025).

Ethical and regulatory **aspects** also remain central. The use of hESCs raises bioethical debates, while **gene editing** amplifies dilemmas about the extent of modification and long-term risk screening. Regulatory agencies tend to require **reversibility mechanisms** (e.g., removable devices) and robust **post-market surveillance** systems, as well as consensus on **clinically meaningful and reproducible clinical efficacy criteria** (Tondin et al., 2025; Danilevskii et al., 2025).

In light of the epidemiological burden of T1D and the limits of insulin therapy to completely normalize glycemic variability and risk of complications, the convergence between tissue engineering, advanced biomaterials, immunoengineering, and regulatory learning sets the research agenda for the next decade. Priorities include: full and stable maturation of β -like cells, immunoprotection without systemic immunosuppression, validation of early biomarkers of graft integration, and design of pragmatic trials focused on harsh clinical outcomes and quality of life (International Diabetes Federation, 2024; Tondin et al., 2025; Morales et al., 2025).

In summary, cell therapies for T1D **have advanced substantially**, but their place in clinical practice depends on solving an interconnected set of **biological, immunological, economic, and regulatory** challenges. Current evidence justifies cautious optimism and supports continued investments in translational science, with an emphasis on **reproducibility, scalability, and accessibility** (Ghoneim et al., 2024; Kashbour et al., 2025).

5 CONCLUSION

Stem cell-mediated cell therapies have been consolidated as one of the most innovative and promising strategies of regenerative medicine applied to type 1 diabetes mellitus (DM1), a disease marked by the autoimmune destruction of pancreatic β cells and the consequent lifelong dependence on exogenous insulin. Significant advances have been observed in the last decade, with emphasis on clinical trials conducted with human pluripotent cells, such as VX-880, which demonstrated measurable C-peptide secretion and partial reduction of insulin requirement, and the first autologous transplantation of differentiated iPSCs into insulin-producing cells, which provided insulin independence for approximately one year, representing a historic milestone in biotechnology applied to the treatment of DM1 (ABOU ZAKI et al., 2024; GHONEIM et al., 2024). These results, although preliminary, confirm the translational feasibility of cell therapies and consolidate the real possibility of restoring pancreatic endocrine function in humans.

However, the obstacles that are still imposed on clinical consolidation are multiple and complex. The residual immunogenicity of the grafts, the need for pharmacological immunosuppression or cell encapsulation, the possibility of tumorigenic formation due to incomplete differentiation, and the functional immaturity of β -like cells remain relevant obstacles. Similarly, the long-term durability of grafts is still uncertain, and there is a lack of robust data from multicenter studies and prolonged follow-up that allow the establishment of safe and reproducible protocols (DANILEVSKII et al., 2025; TONDIN et al., 2025). In addition to biological barriers, economic and logistical factors pose substantial challenges, since production under good manufacturing practices (GMP), specialized storage, transportation, and clinical monitoring of patients imply high costs, restricting the feasibility of incorporating this technology in public health systems and in low- and middle-income countries. To these aspects are added ethical and regulatory issues, especially in relation to the use of embryonic

cells and the implications of gene editing, which require clear regulation and post-marketing surveillance mechanisms (KASHBOUR et al., 2025; WANG et al., 2025).

In this context, it is concluded that stem cell-mediated pancreatic regeneration should be understood as a strategy still in the experimental stage, although already supported by concrete evidence that attests to its partial efficacy in humans. The definitive translation into clinical practice will depend on overcoming technical barriers, optimizing cell differentiation and maturation protocols, developing effective immunoprotection systems that dispense with chronic immunosuppression, validating early biomarkers of functional graft integration, and implementing regulatory and economic policies that ensure safety, efficacy, and accessibility on a global scale. The next decade will be decisive in transforming this scientific promise into clinical reality, and only through collaborative efforts between researchers, industries, regulatory agencies, and health systems will it be possible to offer patients with DM1 a therapeutic alternative capable of reducing complications, improving quality of life, and redefining the paradigm of disease treatment (NATURE COMMUNICATIONS BIOLOGY, 2025; INTERNATIONAL DIABETES FEDERATION, 2024).

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