Preservation of β-Cells as a Therapeutic Strategy for Diabetes

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ABSTRACT

The preservation of pancreatic islet β-cells is crucial in diabetes mellitus, encompassing both type 1 and type 2 diabetes. β-cell dysfunction, reduced mass, and apoptosis are central to insufficient insulin secretion in both types. Research is focused on understanding β-cell characteristics and the factors regulating their function to develop novel therapeutic approaches. In type 1 diabetes (T1D), β-cell destruction by the immune system calls for exploring immunosuppressive therapies, non-steroidal anti-inflammatory drugs, and leukotriene antagonists. Islet transplantation, stem cell therapy, and xenogeneic transplantation offer promising strategies for type 1 diabetes treatment. For type 2 diabetes (T2D), lifestyle changes like weight loss and exercise enhance insulin sensitivity and maintain β-cell function. Additionally, various pharmacological approaches, such as cytokine inhibitors and protein kinase inhibitors, are being investigated to protect β-cells from inflammation and glucotoxicity. Bariatric surgery emerges as an effective treatment for obesity and T2D by promoting β-cell survival and function. It improves insulin sensitivity, modulates gut hormones, and expands β-cell mass, leading to diabetes remission and better glycemic control. In conclusion, preserving β-cells offers a promising approach to managing both types of diabetes. By combining lifestyle modifications, targeted pharmacological interventions, and advanced therapies like stem cell transplantation and bariatric surgery, we have a significant chance to preserve β-cell function and enhance glucose regulation in diabetic patients.

Introduction

The pancreatic islet β-cells are crucial to diabetes mellitus pathophysiology. Both type 1 and type 2 diabetes are characterized by inadequate insulin secretion, which is a result of β-cell dysfunction, apoptosis, and decreased mass. Obviously, novel therapeutic methods were created by better understanding the essential characteristics of β-cells. Hopefully, more promising therapeutic targets are in the pipeline, based on a better analysis of the factors controlling β-cells [1].

While β-cells are responsible for producing and secreting insulin, the mass of functional β-cells directly affects the pancreatic capacity of insulin secretion. Thus, a hallmark of both T1D and T2D is the reduction of β-cell mass. Recent advancements in understanding diabetes mellitus have revealed crucial milestones in the pathophysiology spectrum of the disease. A key focus has been on β-cell dedifferentiation, which significantly contributes to β-cell dysfunction/failure [2]. This process involves a complex interplay of metabolic and epigenetic alterations, intricately disrupting the precise regulation of insulin secretion. Noteworthy, findings suggest a potential avenue for reprogramming dedifferentiated β-cells, offering a promising therapeutic for diabetes management and intervention [3].

In T1D, the immune system attacks and destroys β-cells, whereas in T2D, the β-cells progressively lose their responsiveness to glucose, resulting in impaired insulin secretion to face the demands [3, 4]. As a result, β-cell regenerative capacity is highly important to maintain glucose homeostasis. On the other hand, chronic exposure of β-cells to high glucose levels induces endoplasmic retic-

ulum (ER) stress in the β-cells, leading to activation of unfolded protein response. Prolonged ER stress leads to β-cell dysfunction and apoptosis, thus perpetuating the pathophysiology of diabetes. Incretin hormones can improve β-cell function. Noteworthy, in T2D, the aggregation of islet amyloid polypeptide in the pancreatic islets can lead to β-cell apoptosis and dysfunction. The risk of developing diabetes is influenced by specific genetic variables that alter β-cell mass and function. Disease vulnerability is influenced by variations in genes associated with β-cell formation, insulin production, and glucose sensing.

Adding to the complexity of the disease pathology, the ectopic pancreatic adipose tissue (ePAT), a distinctive adipose entity surrounding pancreatic islets, has gained great attention for its role in diabetes mellites [5]. It has been reported that ePAT expansion is linked with inflammation, insulin resistance, and β-cell dysfunction [6, 7].

Both central and peripheral nervous systems contribute to regulating pancreatic islet function. This includes sympathetic efferent innervation, which is activated during hypoglycemia, parasympathetic, which is activated during the cephalic pre-absorptive phase of insulin secretion and sensory neural pathways that are comprised of spinal and vagal afferent innervation and increase blood glucose. The role of entero-pancreatic innervation is still not fully elucidated. Advanced technologies provide deep insight into the anatomical detail and physiological aspects related to pancreatic islet innervation. Such technologies, including 3D imaging of pancreatic innervation and targeted in vivo neuromodulation, provide further insights [8].

Noradrenergic fibers (NAF) are significantly increased in the islets of diabetic subjects, and this positively correlates with β-cell dedifferentiation score. The correlation between in vivo insulin secretion parameters and pancreatic noradrenergic fibers' density reflects a potentially significant involvement of NAF in the diabetes pathogenesis [9]. Pancreatic innervation and its role in the pathophysiology of diabetes have been previously reviewed [10].

These milestones in understanding the pathophysiology of diabetes mellitus pave the way for developing novel therapeutic strategies that target the underlying mechanisms of β-cell dysfunction and insulin resistance. By dissecting these fundamental pathophysiological processes, strides toward effective and sustainable diabetes management. In this review, we outlined different strategies for preserving β-cells in T1D and T2D.

Preservation of β-cells in T1D

Immunomodulation

Immunosuppressive therapy

Several immunosuppressive medications, including corticosteroids and cyclosporine, have been investigated, aiming to preserve β-cell function [11].

Non-steroidal anti-inflammatory drugs

NSAIDs impact various ion channel functions, and they may result in hypoglycemia by impairing ion channel activity in β-cells that secrete insulin. In INS-1 cells bathed in low (but not high) glucose solutions, Mefenamic Acid (MFA) can elicit a fast depolarization. It stimulates the cells by blocking ATP-sensitive potassium channels (KATP). The same applies to acetylsalicylic acid (ASA) and flufenamic acid (FFA) [12].

Leukotriene Antagonists

A pro-inflammatory cytokine; IL-1 has been linked to the death of β-cells in T1D [13, 14]. Leukotrienes are produced through the 5-LOX and lead to increased inflammation, vasoconstriction, and non-vascular smooth muscle contraction [15]. Interestingly, the 5-LOX pathway is upregulated in obese subjects, and thus 5-LOX inhibition can improve insulin sensitivity [14]. Cysteinyl leukotrienes (Cyst-LTs) are among the potent bioactive lipids generated by the 5-LOX pathway, provoking inflammation. The inflammatory effects occur via acting on Cyst-LT receptors are expressed in the pancreas and can reduce insulin secretion [16]. The leukotriene receptor antagonist; Montelukast, suppresses the neutrophilic infiltration, decreases oxidative stress, and several inflammatory mediators release. Accordingly, it has shown promising results in several diseases, including inflammatory bowel diseases [17], non-alcoholic steatohepatitis [18], some cardiovascular disorders [19], and recently, COVID-19 [20].

Islet transplantation in T1D

One of the promising strategies for T1D treatment is islet transplantation. The most common type is islet allotransplantation (Allogenic islet transplantation). The procedure involves procurement of a deceased donor pancreas, with islets isolated from the donated pancreas returned to the patient via an intraportal infusion for intrahepatic engraftment. The liver provides an optimal environment for the survival of transplanted islets. An important part of caring for the islet recipient includes maintaining normoglycemia (essential for islet survival until revascularization and engraftment are completed), reducing inflammation and cutting down on thrombotic and bleeding hazards. Allo-islet recipients benefit from ameliorating hypoglycemia, on-target glycemic control and improved quality of life, with more than 50 % of patients will become insulin-independent. However, islets from more than one donor pancreas are often required to achieve and maintain insulin independence [21, 22].

Another approach is autologous islet transplantation, which is usually adopted in patients undergoing total pancreatectomy for severe pancreatitis or other pancreatic conditions associated with intractable pain or complications. Auto-islet recipients benefit from ameliorating pain, improved quality of life, and on-target glycemic control. More than 30 % of patients will enjoy insulin independence, whereas some may experience postprandial hypoglycemia [23].

A third strategy is xenogeneic islet transplantation, using the islets from another species, typically pigs, as they have anatomical and physiological similarities to humans, making their islets a potential alternative source for transplantation. The advantages and disadvantages of each strategy followed for islet transplantation are shown in ▶ **Table 1**.

Noteworthy, encapsulation involves enclosing islets in a protective barrier or capsule to protect them from the recipient's immune system while allowing the passage of nutrients and insulin. Encapsulated islets can be transplanted into various sites in the body, such as the subcutaneous tissue. Encapsulation provides a physical barrier against immune attack, reducing the need for immunosup-

▶ **Table 1** Advantages and challenges of various islet transplantation strategies.

Islet transplantation strategy	Advantages	Challenges
Allogenic islet transplantation	Availability of donor islets from deceased donors.	Limited donor availability, leading to long waiting lists.
	Established protocols and techniques for isolation and transplantation.	Need for lifelong immunosuppressive therapy to prevent graft rejection.
	Potential for long-term insulin independence.	Variable and unpredictable outcomes, with some patients experiencing gradual loss of graft function over time.
Autologous islet transplantation	Eliminates the need for immunosuppressive therapy since the patient's own cells are used.	Requires a specialized islet isolation facility to process the patient's pancreas.
	Allows for precise control over islet isolation and transplantation processes.	Limited availability of healthy islets in patients with chronic pancreatitis or extensive pancreatic damage.
	Can alleviate pain and improve quality of life in select patients.	Variable outcomes, with some patients requiring supplemental insulin despite transplantation.
Xenogeneic islet transplantation	Potential for an abundant and readily available source of islets.	The risk of immunological rejection due to the differences between human and pig tissues.
	Overcomes the limitations of donor shortage in allogeneic transplantation.	The potential for transmission of porcine viruses to human recipients.
	May reduce or eliminate the need for immunosuppression with advancements in immunomodulatory techniques.	Ongoing research is needed to optimize xenogeneic transplantation techniques and overcome immunological barriers.

pressive drugs, allowing for retrievability and replacement of encapsulated islets if needed, and offering the potential for long-term graft survival and function. However, this strategy requires ensuring optimal oxygen and nutrient supply to the encapsulated islets, maintaining the viability and function of the encapsulated islets over time [24].

Further advancements in encapsulation technologies and materials are ongoing. In addition, novel approaches are investigated to alleviate the consequences of peri-transplant inflammation on intrahepatic islet engraftment outcomes. For allogeneic transplanted islets, calcineurininhibitor–free immunosuppression has been studied to minimize the adverse effects on kidney function [25].

β-Cell regeneration in T1D

Stem cell

Stem cell therapy for islet regeneration holds great promise as a potential treatment for T1D. Stem cells possess the unique ability to self-renew and differentiate into various cell types, including β-cells. The concept behind stem cell therapy is to utilize the regenerative capacity of stem cells to generate functional insulin-producing β-cells and restore normal glucose regulation. Several strategies are being explored in stem cell therapy for islet regeneration in T1D. Here, we outline some of the key strategies:

Embryonic stem cells (ESCs)

Embryonic stem cells are derived from early-stage embryos and have the capacity to differentiate into all cell types in the body, including insulin-producing β-cells. A step-by-step approach was developed to direct cell differentiation through four sequential stages – pancreatic epithelium, endocrine progenitors, definitive endoderm, and β-like cells. Researchers are exploring methods to direct the differentiation of ESCs into β-cells by mimicking the developmental processes that occur in the pancreas [26].

Induced pluripotent stem cells (iPSCs)

iPSCs are adult cells reprogrammed to a pluripotent state, meaning they regain the ability to differentiate into various cell types. iPSCs can be derived from a patient's own cells, such as skin cells, and then differentiated into β-cells. This approach offers the advantage of patient-specific cells, reducing the risk of immune rejection [27, 28].

Adult stem cells

Adult stem cells exist in various tissues, including the pancreas. These cells can potentially differentiate into β-cells under certain conditions. Research is being conducted to identify and isolate adult stem cells within the pancreas and induce their differentiation into functional β-cells [29].

Combination approaches

Stem cell therapy for islet regeneration may involve combining different types of stem cells or utilizing additional factors to enhance the differentiation and maturation of β-cells. For example, combining ESC-derived or iPSC-derived β-cells with supportive cells or factors that promote their survival and function can improve their therapeutic potential [30].

Transplantation and encapsulation

Once stem cell-derived β-cells are generated, they can be transplanted into the recipient's body. Strategies include transplanting individual cells, cell clusters, or encapsulated cells. Encapsulation techniques aim to protect transplanted cells from the immune system while allowing the exchange of nutrients and insulin [31].

Ensuring the safety and immune compatibility of stem cell-derived β-cells is very crucial. Researchers are developing techniques to eliminate any remaining undifferentiated stem cells to minimize the risk of tumor formation. Additionally, immunomodulatory approaches are being investigated to reduce the immune response and prevent rejection of the transplanted cells [32].

It is important to note that while stem cell therapy for islet regeneration shows significant potential, there are still challenges to overcome, including the efficient generation of fully functional β-cells, ensuring their long-term survival, and addressing the immune response in T1D. Ongoing research and clinical trials are focused on optimizing these strategies and translating stem cell therapy into a viable treatment option for T1D.

Preserving β-cells in T2D

Lifestyle modification

Obesity is a major risk factor for T2D, causing insulin resistance and increased β-cell workload. Weight loss and exercise interventions increase insulin sensitivity, reducing T2D risk. The US Diabetes Prevention Program achieved 58 % lower T2D incidence with 7 % body weight reduction [33]. The Finnish Diabetes Prevention Study also showed a 58 % reduction in T2D incidence through lifestyle intervention, preserving β-cell function by improving insulin sensitivity [34].

Pharmacological approaches

Several pharmacological agents have been used to inhibit β-cell dysfunction and death, targeting two main factors; inflammation and glucotoxicity. To suppress inflammation as a mechanism of β-cell dysfunction and loss, several cytokine antibodies, anti CD3, anti-IL-β1, kinase inhibitors, histone deacetylase inhibitors and antioxidants have been investigated. The latter three interventions can also combat the effect of glucotoxicity on β-cells. In addition, other agents that can ameliorate the effect of gluco- and glucose-lipotoxicity on β-cells include thioredoxin-interacting protein (TXNIP) inhibitors, endoplasmic reticulum stress inhibitors and triglyceride synthase inhibitors, angiotensin-converting enzyme inhibitors, adipokines, vitamin D receptor/BRD9 association inhibitors and voltage-dependent anion channel-1 inhibitors.

Other mechanisms that may lead to β-cell dysfunction and/or loss include: proteotoxicity, β-cell senescence, and hyperglucagonemia. In addition, a number of anti-diabetic agents can preserve the function and survival of β-cells including metformin, glucagon-like peptide 1 agonists, dipeptidyl peptidase inhibitors, selective sodium glucose co-transporter 2 inhibitors. The following section will discuss the most thoroughly investigated agents with substantial evidence of favorable effects on β-cells.

Cytokine inhibitors

In T1D, β-cell death and dysfunction are mediated through immune cells that invade the endocrine pancreas and release proinflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and other mediators [35]. In clinical trials, blocking IL-1 signaling with antibodies like canakinumab [36] or anakinra [37] resulted in better β-cell function, lower HbA1c levels, and less need for insulin. These findings highlight the function of IL-1 in the etiology of T1D and the possibility of immunomodulation by IL-1 targeting. A recent clinical trial concluded that montelukast adjuvant therapy is superior to metformin-only therapy in diabetes control and weight loss. The investigators explained that this finding is most likely due to its increased insulin sensitivity and the anti-inflammatory properties of the leukotriene antagonist. The combined use of metformin and montelukast was well tolerated, with no significant adverse effects (NCT04075110) [38].

Canakinumab and anakinra were previously investigated in clinical trials for T1D (NCT00947427 and NCT00711503). Both were safe but ineffective as single immunomodulatory drugs in recent-onset T1D. IL-1 blockade might be more effective when combined with treatments targeting adaptive immunity [39].

Furthermore, in T2D, treatment with canakinumab over a median period of 3.7 years did not reduce diabetes incidence. However, canakinumab treatment had a favorable effect on major cardiovascular events among those with and without diabetes. (Canakinumab Anti-inflammatory Thrombosis Outcomes Study; CANTOS, (NCT01327846). Similarly, anakinra improved β-cell function and, subsequently, controlled hyperglycemia. In addition, anakinra reduced markers of systemic inflammation (NCT00303394). To date, there is no approved treatment for diabetes with anti-IL-1 β antibodies.

Interestingly, combined treatment with anti-TNF-α and anti-T-cell receptor (TCR) can increase β-cell proliferation, reduces apoptosis leading to a restoration of β-cell mass and function associated with decreased immune cell infiltration in the LEW.1AR1-iddm T1D rat model [40]. Similarly, the combined anti-IL-17 and anti-TCR therapy can increase the β-cell proliferation and mass. In addition, IL-2 and F5111.2 induced remission of T1D in the NOD mouse mode.

The triple combination therapy (anti- IL-2, anti- IL-17 and anti-TCR) achieved a complimentary anti-autoimmune and anti-inflammatory action, resulting in sustained normoglycaemia [41]. Combination of anti-IL-21 antibody and the GLP-1 agonist; liraglutide preserved β-cell function in recently diagnosed T1D patients. Efficacy and safety of this combination deserve to be evaluated in a phase 3 trial program [42].

By blocking apoptosis and boosting β-cell survival, fingolimod (FTY720), a sphingosine-1-phosphate receptor modulator, is described to avoid islet damage and to preserve β-cell mass. Fingolimod combined with an antibody targeting T cells' TCR/CD3 complex raised β-cell bulk, prevented islet invasion, and effectively reversed T1D in the LEW.Rat 1AR1-iddm [43].

Another example of cytokine inhibitors is 5Z-7-oxozeaenol; an inhibitor of the serine/threonine kinase transforming growth factor-β activated kinase-1 (TAK1, or MAP3kinase 7). It is well known that the JNK and NFκB signaling pathways are activated by the serine/threonine kinase transforming growth factor-β activated kinase-1 (TAK1, or MAP3kinase 7), a member of the mitogen-activated protein kinase kinase (MAP3K) family. TAK1 is also known as MAP3Kase 7 [44]. Interestingly, non-specific tyrosine kinase inhibitors may reverse diabetes in animal models, for example, imatinib treatment prevented hyperglycemia in streptozotocin-injected rats [45].

Protein kinase inhibitors

Several molecules are notorious for mediating β-cell dysfunction and death. There is a myriad of examples in this direction. The serine/threonine kinase mammalian sterile 20-like kinase 1 (MST1) is a key molecule that induces β-cell apoptosis. MST1 is upregulated upon exposure of β-cells to cytokines and high glucose concentrations, resulting in activation of downstream JNK kinases and apoptotic pathways, thus impairing insulin secretion through proteasomal degradation of the β-cell transcription factor pancreatic and duodenal homeobox 1 (PDX1). PDX1 is essential for insulin production [46]. Neratinib, an approved medication that targets the HER2/EGFR dual kinases, was discovered to be a powerful MST1 inhibitor and demonstrated to prevent β-cells damage resulting from the autoimmune process in T1D [47].

Others

Oxidative stress has been also proposed as an inducer of β-cell dysfunction and loss. Hesperidin, a flavanone glycoside found in all citrus fruits, was investigate for its possible therapeutic benefits in T1D.

β-Cells benefited from the actions of hesperidin. Enhancing antioxidant SOD and GPx activity, lowering nitrotyrosine and malondialdehyde levels, upregulating antiapoptotic Bcl-xL, and downregulating pro-apoptotic Bax and cleaved caspase-3 to reduce oxidative stress. Hesperidin treatment decreased hyperglycemia and raised blood and pancreatic insulin levels in streptozotocin-diabetic rats. As a result of the hesperidin treatment, TNF-α levels and the expression of the ER stress proteins CHOP and GRP78 were also shown to be reduced in the pancreas [48].

Histone deacetylase inhibitors HDACs were suggested as potential therapeutic targets for T1D and T2D, particularly HDAC 1 and 3. Among tens of HDACs, givinostat [49] and sodium butyrate (NaB) [50] have been investigated in diabetes. Noteworthy, NaB is a short-chain fatty acid with HDAC inhibition activity. BRD3308 is an HDAC3 inhibitor that showed a protective effect on β-cell function and survival, enhanced β-cell proliferation, decreased mononuclear cell infiltration of the islets, and reduced the emergence of diabetes in NOD mice [51].

Administration of oral givinostat with humanized CD3 antibodies (otelixizumab) have a synergistic effect that serves to suppress islet inflammation in NOD mice [52], whereas the combination of HDAC inhibitor vorinostat with the dipeptidyl peptidase-4 (DPP-4) inhibitor (MD-626) increased β-cell mass; however, did not mount to prevent diabetes [53].

Combatting glucotoxicity and lipotoxicity

Chronic exposure of β-cells to hyperglycemia and elevated saturated fatty acids leads to glucotoxicity and lipotoxicity, contributing to β-cell dysfunction and apoptosis [54, 55]. Chronic exposure to high glucose increases reactive oxygen species (ROS) formation, contributing to β-cell damage [56]. Antioxidants like naringin, found in citrus species, have been shown to reduce ROS accumulation and protect against islet dysfunction and diabetes [55]. On the other hand, activation of the tumor suppressor protein p53 by oxidative stress induces mitochondrial dysfunction, leading to β-cell death. Inhibitors of p53, such as pfithrin-α, have been found to improve mitochondrial function and glucose intolerance in diabetic mice [57]. Increased iron content in β-cells can catalyze ROS formation. Iron chelators like deferoxamine and deferasirox have been shown to reduce ROS formation and β-cell apoptosis. Higher levels of iron-carrying plasma protein transferrin have been associated with a risk of developing diabetes [57, 58].

Protein kinase inhibitors

Glycogen synthase kinase-3 (GSK3) and IKKβ play crucial roles in β-cell dysfunction induced by chronic hyperglycemia and fatty acids. Inhibitors of GSK3, such as valproate, TDZD-8, and KICG1338, preserve β-cell function and improve insulin secretion [56]. As previously mentioned, the kinase MST1 has been identified as a key regulator of β-cell apoptotic death and dysfunction under diabetogenic conditions. Neratinib, an MST1 inhibitor, has shown promise in preserving β-cell mass and function in diabetic mouse models [59].

Endoplasmic reticulum stress inhibitors

Endoplasmic reticulum (ER) stress has been linked to β-cell dysfunction and death in T2D. Various inhibitors exist for key molecules involved in ER stress, such as IRE1, PERK, and ATF6. Tauroursodeoxycholic acid, a chemical chaperone, has been shown to reduce ER stress and protect β-cells from apoptosis [60].

TXNIP Expression Inhibitors

Thioredoxin-interacting protein (TXNIP) is critical in regulating β-cell dysfunction and death. Inhibitors of TXNIP, such as SRI-37330 and verapamil, have been shown to protect β-cells and improve glucose homeostasis in animal models of diabetes [61].

Histone Deacetylase Inhibitors

HDAC3 inhibitors, like RGFP966 and MS-275, enhance insulin secretion and synthesis, preventing palmitate-induced β-cell death. Sodium butyrate and other HDAC inhibitors also protect β-cells from dysfunction and death [62, 63].

Others

Diacylglycerol acyltransferase 1 (DGAT1) inhibitors have shown promise in improving β-cell survival and function, reducing inflammation and ER stress. However, gastrointestinal side effects in clinical trials raise questions about the usefulness of DGAT1 inhibition as a treatment for diabetes [64]. Interestingly, inhibition of the renin-angiotensin system has been associated with delaying the onset of T2D. Angiotensin receptor blockers, such as losartan and telmisartan, protect β-cells against glucotoxicity and improve insulin secretion [65, 66]. Adipsin/complement factor D increases insulin secretion and protects β-cells from apoptosis. Inhibitors of the phosphatase Dusp26, which negatively regulates β-cell identity genes, show potential in improving hyperglycemia and protecting against apoptosis [67].

The vitamin D receptor (VDR) can bind to bromodomain-containing protein 9 (BRD9 protein). Inhibiting BRD9 promotes the activation of a VDR-dependent transcriptional programming β-cell survival [68]. Inhibition of BRD9 promotes the activation of the vitamin D receptor (VDR)-dependent transcriptional program, promoting β-cell survival and glucose homeostasis. Vitamin D supplementation has shown mixed results in clinical trials [69, 70].

Inhibition of VDAC1 conductance using metformin and specific VDAC1 inhibitors has been shown to restore ATP generation and glucose-stimulated insulin secretion in T2D pancreatic islets, protecting β-cells from glucotoxicity [71].

Inhibition of β-cell dysfunction and death induced by proteotoxicity

Amyloid deposition derived from amyloid polypeptide (IAPP) is frequently found in pancreatic islets of T2D patients [72]. IAPP forms insoluble fibrils, leading to β-cell failure and apoptosis. Several molecules have been explored to inhibit IAPP aggregation and protect β- cells. The IAPP inhibitory peptide D-ANFLVH disrupts the aggregation of hIAPP, preventing amyloid deposition and preserving β-cell area, leading to improved glucose tolerance [73].

Intravenous immunoglobulin treatment improves glucose control, insulin sensitivity and prevents β-cell apoptosis by lowering toxic IAPP oligomer levels, attenuating islet inflammation, and activating autophagy [74]. Similarly, an autophagy enhancer (MSL-7) reduces IAPP oligomer accumulation and oligomer-mediated apoptosis in β-cells, improving glucose tolerance and β-cell function in transgenic mice [75].

Alpha1-antitrypsin (AAT) treatment improves glucose tolerance, restores insulin secretory response, and prevents the formation of amyloid deposits and apoptosis induced by high glucose concentrations. AAT also protects β-cells against the cytotoxic effects of hIAPP [76]. In addition, selenium-containing phycocyanin, azadirachtin, and chitosan oligosaccharides have been found to inhibit IAPP fibrillation and reduce oxidative and ER stress, improving glucose-stimulated insulin secretion [77, 78].

Inhibition of β-cell dysfunction and death induced by senescence

Senescent β-cells have been observed in T1D development. Selective elimination of these cells using Bcl-2 inhibitors prevents immune-mediated β-cell destruction and diabetes, suggesting clearance of senescent β-cells as a potential therapeutic approach [79].

Inhibition of β-cell Dysfunction and Death Induced by Hyperglucagonemia

Hyperglucagonemia is present in all forms of diabetes and blocking glucagon and/or its receptor (GCGR) has been proposed as a therapeutic strategy. Treatment with an anti-glucagon receptor (anti-GCGR) monoclonal antibody (Ab-4) improves glycemia, promotes β-cell survival, and enhances the formation of functional β-cell mass in T1D mouse models [80]. The liver-derived fibroblast growth factor 21 (FGF21) was shown to be involved in GCGR antagonism-induced β-cell regeneration [81].

Protecting β-cells from dysfunction and death requires a multi-faceted approach targeting various pathways and mechanisms. Inhibition of IAPP aggregation, clearance of senescent β-cells, and blocking glucagon action are potential strategies to preserve β-cell function and mass. These therapeutic approaches show promise in preventing and treating T1D and T2D, and further research and clinical trials are needed to assess their efficacy and safety in human subjects. Ultimately, a comprehensive understanding of the underlying mechanisms will pave the way for effective and innovative treatments for diabetes mellitus.

Role of bariatric surgery and weight reduction in β-cell preservation

Bariatric surgery has emerged as an effective and sustainable treatment option for obesity and its associated comorbidities, including T2D. Over the past two decades, extensive research and clinical trials have demonstrated the profound effects of bariatric surgery on metabolic health and glucose homeostasis. One of the remarkable outcomes of bariatric surgery is its ability to preserve β-cell survival and function, leading to improved glycemic control and diabetes remission in many patients.

Enhanced insulin sensitivity

Bariatric surgery, such as Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy, induces significant weight loss and improves insulin sensitivity. Reduced adiposity and improved insulin sensitivity reduce the demand on β-cells to produce excessive amounts of insulin, preventing β-cell exhaustion and apoptosis [82].

Gut hormone modulation

Bariatric surgery alters the gut hormone profile, including increased glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) secretion. GLP-1 is known to enhance β-cell survival and function while promoting β-cell proliferation [83]. The upregulation of GLP-1 and PYY levels after bariatric surgery contributes to improved glycemic control and β-cell preservation.

Remission of diabetes

Clinical trials have consistently shown that bariatric surgery can lead to remission of T2D in a substantial proportion of patients. The Swedish Obese Subjects (SOS) study demonstrated that RYGB and vertical banded gastroplasty were associated with diabetes remission in 72 % and 36 % of patients at 2-year follow-up [84]. The Diabetes Surgery Study (DSS) reported 95 % diabetes remission rates after RYGB and 75 % after laparoscopic adjustable gastric banding (LAGB) at 2 years [85].

β-Cell mass expansion

Bariatric surgery has been shown to increase β-cell mass, promoting insulin secretion and glucose regulation. In a rodent study, RYGB significantly increased β-cell mass through neogenesis and hypertrophy, contributing to enhanced insulin secretion [86].

Glycemic Control Improvement: The rapid improvement in glycemic control after bariatric surgery often precedes significant weight loss, suggesting that mechanisms beyond weight reduction play a role in β-cell preservation [87]. Improved glycemic control is likely a result of improved β-cell function and sensitivity to glucose, independent of weight loss.

Impact on Glucose Variability: Bariatric surgery has been associated with reduced glucose variability and postprandial excursions. Stable glucose levels contribute to β-cell preservation and protect against oxidative stress and inflammation, which can damage β-cells [88]. ▶ **Table 2** presents examples of bariatric surgery studies and their outcomes [89–95].

Bariatric surgery has proven to be a highly effective intervention for weight loss and metabolic improvement in obese individuals,

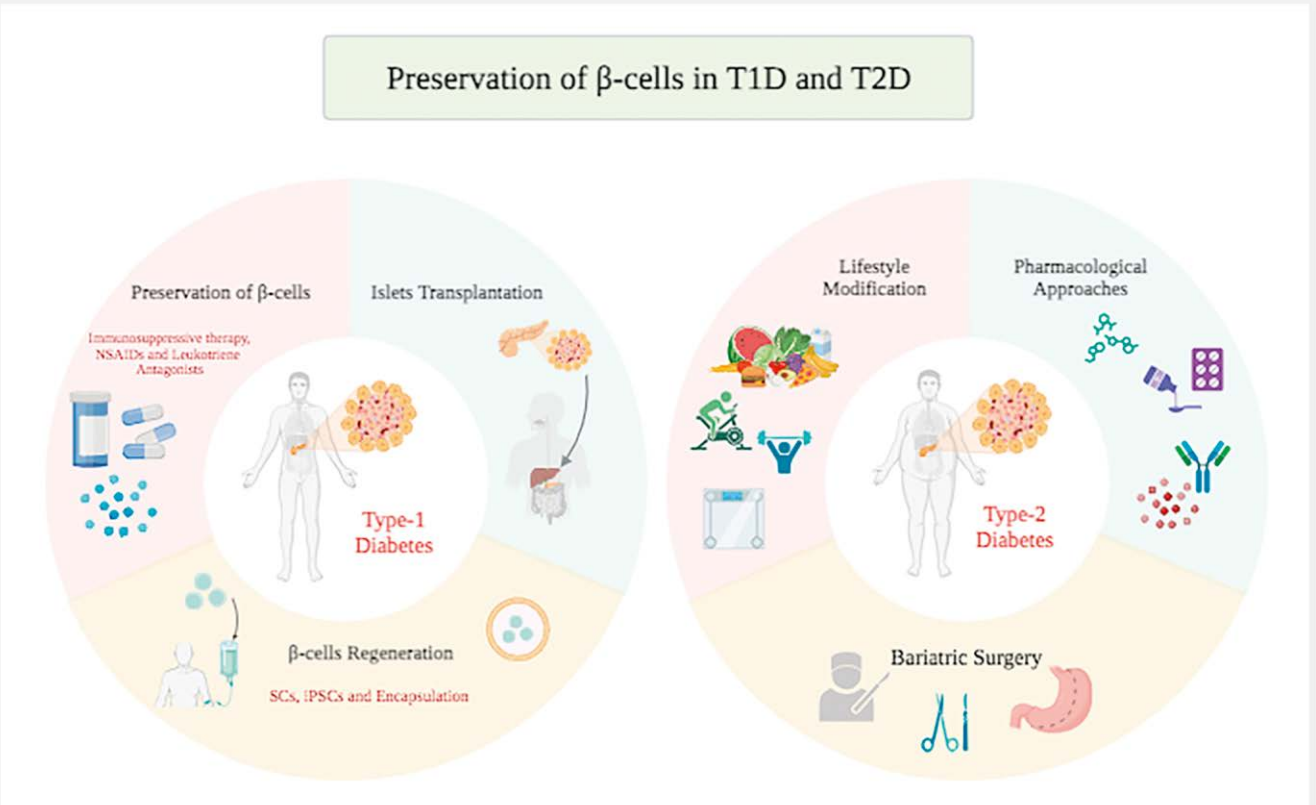
▶ **Table 2** Outcome of bariatric surgery studies.

Study design	Inclusion criteria	Exclusion criteria	Intervention	Outcome	Ref
Prospective cohort	Adults with T2D	Prior bariatric surgery	Roux-en-Y Gastric Bypass (RYGB)	Improved β-cell function and insulin sensitivity	[89]
	BMI ≥ 35 kg/m² and inadequately controlled	Severe hepatic, renal, or pulmonary			
	glycemia despite standard treatments	disease, or history of drug/ alcohol			
	HbA1c ≥ 53 mmol/mol	abuse			
	and C-peptide ≥ 1.0 ng/ml				
Randomized controlled trial	Adults with T2D and BMI 30–39.9 kg/m²	History of bariatric surgery	Intensive medical therapy	Greater improvement in β-cell function	[90]
	HbA1c 53–75 mmol/mol and C-peptide ≥ 1.0 ng/ml	Significant diabetic complications	vs. Roux-en-Y Gastric Bypass	and remission of diabetes with RYGB	
	C-peptide response to mixed meal ≤ 2.0 ng/ml	Significant psychiatric or	or Sleeve Gastrectomy (SG)	compared to medical therapy	
	Age 25–55 years	neurologic disorders			
Randomized controlled Trial	Adults with T2D and BMI 27–43 kg/m²	Prior bariatric surgery or major	Intensive medical therapy	RYGB led to remission of T2D and improved	[91]
	HbA1c 64–86 mmol/mol and C-peptide ≥ 1.0 ng/ml	GI surgery	vs. RYGB followed by low-calorie	β-cell function and insulin sensitivity	
	C-peptide response to mixed meal ≥ 0.6 ng/ml	Significant cardiovascular, renal,	diet (LCD) for 8 weeks, followed	compared to intensive medical therapy	
	Age 20–60 years	or hepatic disease	by 52 weeks of weight maintenance		
		Significant psychiatric or			
		neurologic disorders			
		Pregnancy or planning to become			
		pregnant within 2 years			
Trial	**Intervention**	**Outcome**			**Ref.**
STAMPEDE Trial	Medical therapy vs. bariatric surgery	Bariatric surgery combined with medical therapy resulted in superior glycemic control compared to medical therapy alone.			[92]
		The surgery group showed a significantly higher proportion of patients achieving HbA1c levels of less than 6 % at 5 years (36 % vs. 5 %).			
Swedish Obese Subjects Study	Gastric bypass vs. banding	T2D remission rates were significantly higher in the surgical groups compared to conventional treatment (gastric bypass: 72.3 % vs. 16.4 %).			[93]
		The surgical groups exhibited sustained improvements in HbA1c levels.			
Cleveland Clinic Study	Bariatric surgery	Bariatric surgery improved β-cell function and insulin secretion, leading to enhanced glycemic control and reduced insulin requirements.			[94]
		Preservation of β-cell function was observed even in patients without complete diabetes remission.			
Observational Studies	Bariatric surgery	Significant improvements in β-cell function and insulin sensitivity were reported post-surgery.			
		Studies consistently demonstrated reductions in HbA1c levels and decreased insulin resistance.			
		Surgery's metabolic effects go beyond weight loss, involving changes in gut hormones and bile acid metabolism.			

particularly those with T2D. Intriguingly, while weight loss-induced remission of T2D has been observed in obese individuals (> 27 kg/m²) [89, 90], it remained uncertain if this phenomenon extended to those with a BMI (< 27 kg/m²). Recently, the ReTUNE study investigated whether individuals with a BMI could achieve remission through induced 5 % weight loss cycles using tailored dietary plans

▶ **Table 3** Effect of antidiabetic medications on β-cells.

Medication	Mechanism of action	Role in preserving β-cells
Metformin	Reduces hepatic glucose production	Reduces demand on β-cells to produce excessive insulin
	Enhances insulin sensitivity in peripheral tissues	Improves insulin sensitivity, reducing strain on β-cells
	Inhibits intestinal glucose absorption	
Sulfonylureas and Meglitinides	Stimulate insulin secretion from β-cells	Overcome impaired insulin secretion in T2D
		Long-term use may lead to β-cell exhaustion and reduced responsiveness
Incretin-based therapies	GLP-1 receptor agonists stimulate insulin secretion, inhibit glucagon release, delay gastric emptying, and promote satiety	Preserve β-cell function
	DPP-4 inhibitors enhance the action of endogenous GLP-1	Promote glucose-dependent insulin secretion
Sodium-glucose cotransporter-2	Reduces renal glucose reabsorption, leading to increased urinary glucose excretion	Indirectly relieve the workload on β-cells
	Lower blood pressure and body weight	Improve glucose regulation and reduce the burden on β-cells
Thiazolidinediones (TZDs)	Activate PPAR-γ receptors, improving insulin sensitivity	Reduce demand on β-cells to produce excessive insulin
		Preserve β-cell function



▶ **Fig. 1** Strategies of β-cell preservation in diabetes mellitus. Different strategies can be adopted to preserve the mass and function of β-cells in type 1 and type 2 diabetes mellitus. In T1D, the main strategies included immunosuppressive therapy, islet transplantation in addition to different methods of β-cell regeneration. In T2D, the main focus is on modification of lifestyle and medications, in addition to the significant multifaceted role and consequences of bariatric surgery in patients with obesity. (Created with BioRender.com) [rerif].

[91]. Interestingly, for the first time, the ReTUNE study showed that non-obese diabetic patients can achieve remission through a structured low-calorie diet program. Crucially, the study underscores the pivotal role of shedding detrimental fat from the liver and pancreas in achieving this remission [92]. ▶ **Table 2** presents examples of bariatric surgery studies and their outcomes [89–95].

Anti-diabetic medications with favorable effect on β-cell survival and function

It is important to note that medications alone cannot substitute for lifestyle modifications, which should be an integral part of T2D management. Combining medication therapy with a healthy lifestyle, including diet and exercise, is critical for optimizing glycemic control, preserving β- cell function, and managing T2D effectively. The choice of medication and treatment strategy should be individualized based on disease progression, comorbidities, and patient preferences. ▶ **Table 3** shows the role of various antidiabetic medications in preserving β-cells.

Conclusion

This review highlights the critical importance of β-cell preservation in diabetic patients, shedding light on insights and advances gained over the past decades. The studies examined in this review emphasize the significance of novel therapeutic approaches to safeguard β-cell mass and function. While significant progress has been made in understanding the underlying mechanisms of β-cell mass decline and exploring innovative interventions, further research is warranted to refine current strategies and develop new ones. Strategies of β-cell preservation in diabetes mellitus is formally presented in ▶ **Fig. 1**.

As we continue to strive for improved diabetes management and outcomes, a collaborative effort among researchers, clinicians, and industry stakeholders is crucial by integrating the latest scientific findings and technologies into clinical practice. Finally, enhancing β-cell preservation is a promising strategic approach in diabetes management.

Conflict of Interest

The authors declare that they have no conflict of interest.

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