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The primary aim of *World Journal of Diabetes (WJD, World J Diabetes)* is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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Alternative therapeutic strategies in diabetes management

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Abstract

Diabetes is a heterogeneous metabolic disease characterized by elevated blood glucose levels resulting from the destruction or malfunction of pancreatic β cells, insulin resistance in peripheral tissues, or both, and results in a non-sufficient production of insulin. To adjust blood glucose levels, diabetic patients need exogenous insulin administration together with medical nutrition therapy and physical activity. With the aim of improving insulin availability in diabetic patients as well as ameliorating diabetes comorbidities, different strategies have been investigated. The first approaches included enhancing endogenous β cell activity or transplanting new islets. The protocol for this kind of intervention has recently been optimized, leading to standardized procedures. It is indicated for diabetic patients with severe hypoglycemia, complicated by impaired hypoglycemia awareness or exacerbated glycemic lability. Transplantation has been associated with improvement in all comorbidities associated with diabetes, quality of life, and survival. However, different trials are ongoing to further improve the beneficial effects of transplantation. Furthermore, to overcome some limitations associated with the availability of islets/pancreas, alternative therapeutic strategies are under evaluation, such as the use of mesenchymal stem cells (MSCs) or induced pluripotent stem cells for transplantation. The cotransplantation of MSCs with islets has been successful, thus providing protection against proinflammatory cytokines and hypoxia through different mechanisms, including exosome release. The use of induced pluripotent stem cells is recent and requires further investigation. The advantages of MSC implantation have also included the improvement of diabetes-related comorbidities, such as wound healing. Despite the number of advantages of the direct injection of MSCs, new strategies involving biomaterials and scaffolds have been developed to improve the efficacy of mesenchymal cell delivery with promising results. In conclusion, this paper offered an overview of new alternative strategies for diabetes management while highlighting some limitations that will need to be overcome by future approaches.

Key Words: Diabetes; Pancreas/islet transplantation; Mesenchymal stem cells; Induced pluripotent stem cells; Exosomes; Scaffolds

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Core Tip: Common management issues are associated with insulin administration for the treatment of diabetes, a heterogeneous metabolic disease characterized by elevated blood glucose levels resulting from the destruction or malfunction of pancreatic β cells. This review focused on alternative therapeutic strategies, such as islet/pancreas implantation and islet/mesenchymal stem cell and induced pluripotent stem cell transplantation. The use of these different approaches is also associated with amelioration of diabetes-related comorbidities.

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INTRODUCTION

Diabetes mellitus (DM) is a heterogeneous metabolic pathology characterized by elevated blood glucose levels resulting from destruction or malfunction of β cells, insulin resistance in peripheral tissues, or both, and results in an insufficient production of insulin[1]. Prolonged hyperglycemia in diabetes is linked to serious complications that affect the health of patients with DM and even lead to death. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia[2].

CLASSIFICATION OF DM

The etiopathology of diabetes, thus the mechanisms leading to the destruction of β cells in the endocrine pancreas, enables diabetes to be classified as type 1 (T1D) or type-2 (T2D)[3]. Himsworth was the first to classify diabetes into T1D and T2D in 1930[4-6]. Tattersall *et al*[5] expanded this classification to acknowledge the presence of diabetes subtypes inherited in an autosomal dominant manner.

T1D or juvenile diabetes is a chronic autoimmune disease where β cells in the Islets of Langerhans are progressively destroyed by immune cells. Subsequently insulin production is insufficient to control the homeostasis of glucose[7]. The T1D patient population is highly varied. Individuals within this group may experience the condition at different levels of severity. The origins of the disease can also differ, and individuals may possess diverse genetic backgrounds[8].

T2D features the non-response of peripheral tissue to insulin action, which reduces the ability of the tissue to uptake glucose[9]. T2D is influenced by genetic and lifestyle factors such as diet, physical activity (PA), environment, and pollution. These factors, unlike genetic predisposition, are modifiable, bringing significant benefits in complications of T2D [10].

In both T1D and T2D, inflammation plays a crucial role in the destruction of insulin-producing β cells. In T1D, damaged β cells release autoantigens, which are then presented to T helper cells by antigen-presenting cells. Activated T helper cells release cytokines that amplify inflammation, triggering the production of reactive oxygen species and Fas, ultimately leading to the apoptosis of β cells. Similarly, in T2D, adipose tissues release cytokines that intensify inflammation. This inflammatory environment affects insulin signaling in β cells by activating the JNK and NF- κ B pathways. This disruption in insulin signaling contributes to the deterioration of β cell function and survival in T2D[11-13].

Moreover, there are other types of diabetes, such as gestational diabetes, a condition in which women, who did not have diabetes prior to pregnancy, experience abnormal levels of blood glucose during their pregnancy. In a typical pregnancy, there is an increase in the number of pancreatic β cells due to the stimulation of human placental lactogen and prolactin. This leads to elevated levels of insulin[14].

EPIDEMIOLOGY OF DIABETES

It is expected that there will be 693 million DM patients worldwide by 2045, thus the increasing prevalence of DM is a significant focal point in public health, imposing unmanageable pressures on individuals, their professional pursuits, healthcare infrastructures, and broader society[15].

T2D represents the majority (> 85%) of the overall prevalence of diabetes. One of the reasons behind this trend can be found in the increasing incidence of obesity as well as unhealthy and sedentary lifestyles[16]. Another factor contributing to the rising prevalence is the improved survival of individuals with diabetes in certain populations. This is attributed to

early detection and enhanced diabetes management, leading to a consequent decrease in premature mortality. In recent years, the increase in the prevalence of T2D is linked to the growing number of cases of T2D observed in young individuals and their prolonged survival.

Both variants of diabetes can result in complications affecting multiple bodily systems, including bone disease[17-19], microvascular outcomes such as retinopathy, nephropathy, and neuropathy, as well as macrovascular outcomes such as ischemic heart disease, stroke, peripheral vascular disease, and impaired wound healing. The early onset of illness, increased mortality rates, diminished life expectancy, and the associated economic burdens of diabetes underscore its significance as a critical public health issue[16].

PATHOPHYSIOLOGY OF DIABETES

Diabetes is a complex metabolic disorder with a multifactorial etiology, involving both genetic and environmental factors. It is essential to understand that T1D and T2D each have a distinct pathophysiology[20,21]. It is important to note that while insulin resistance is a common feature in T2D. It can also be observed in certain conditions, including some cases of T1D. However, in the latter the immune system mistakenly attacks and destroys insulin-producing β cells in the pancreas, leading to a lack of insulin. In some cases though individuals with T1D may also develop insulin resistance over time [22]. Overall, the interplay of genetic and environmental factors contributes to the development of T2D. Lifestyle factors such as diet, PA, and obesity also play crucial roles in the manifestation of the disease. Understanding the genetic basis of T2D can aid in the development of personalized treatment approaches and preventive strategies[22,23].

The frequency of both types of diabetes is increasing globally at a rate that surpasses genetic variation, despite the hereditary roots of the disease, suggesting that environmental variables may play a significant role in both types of diabetes[24]. These environmental factors include diet, endocrine disruptors, various environmental pollutants, and the composition of the gut microbiota. Most of the heritability of T2D is likely attributed to a range of factors, such as the diversity in the disease, interactions between genes, and epigenetic influences.

DIABETES THERAPY

Current standard therapies

To adjust blood glucose levels, T1D patients need exogenous insulin administration in the form of subcutaneous injections. Over time, evidence has strongly supported the benefits of more intensive insulin replacement therapies, such as multiple daily injections or continuous subcutaneous infusion *via* an insulin pump, as they offer the optimal combination of effectiveness and safety for T1D patients[18]. The Diabetes Control and Complications Trial demonstrated that intensive therapy, including multiple daily injections or continuous subcutaneous insulin infusion not only reduced glycated hemoglobin (HbA1c) levels but also led to improved long-term outcomes[25-27].

The integration of continuous glucose monitors (CGMs) into clinical practice has significantly enhanced diabetes management for patients on insulin therapy[28]. CGM usage is now considered standard of care for T1D patients. Notably, the reduction of nocturnal hypoglycemia in patients using insulin pumps with CGM is further improved by the automatic suspension of insulin delivery at a predetermined glucose level[29-31].

The United States' Food and Drug Administration has approved several hybrid closed-loop pump systems. Literature data support the safety and efficacy of these hybrid closed-loop systems in T1D adolescents and adults[32,33]. Additionally, evidence suggests that closed-loop systems outperform sensor-augmented pump therapy in terms of glycemic control and reducing hypoglycemia, as demonstrated over a 3-month comparison period in both T1D children and adults [34]. In the International Diabetes Closed Loop trial, which spanned 6 months and involved T1D patients aged 14 years and older, the use of a closed-loop system was associated with lower mean glucose and HbA1c levels compared to the use of a sensor-augmented pump[35].

Injectable and oral drugs have been evaluated for their effectiveness in addition to insulin treatment in T1D patients. Pramlintide, an amylin analog, is approved for T1D adults. Clinical trials showed both modest HbA1c decrease and weight loss with pramlintide[36-39]. The trial with liraglutide, a glucagon-like peptide 1 receptor agonists, demonstrated modest HbA1c decrease, weight loss, and insulin dose reductions[40,41]. Likewise, clinical trials testing sodium-glucose cotransporter 2 inhibitors demonstrated HbA1c improvements and weight loss[42-44]. In T1D, sodium-glucose cotransporter 2 inhibitor administration has been associated with diabetic ketoacidosis.

These drugs are used for T2D management, and insulin becomes effective when other agents are not. They should be used in combination in cases of severe hyperglycemia, particularly if catabolic features (weight loss, hypertriglyceridemia, ketosis) are evident. It is common practice to start with insulin therapy for patients with blood glucose levels ≥ 300 mg/dL or HbA1c $> 10\%$ or if the patient has symptoms of hyperglycemia (*i.e.*, polyuria or polydipsia) or catabolism evidence. As the emergency resolves, the use of noninsulin agents is possible[28].

MEDICAL NUTRITION THERAPY, PHYSICAL ACTIVITY, AND LIFESTYLE INTERVENTIONS

It is a common practice before initiating pharmacotherapy in the management of diabetes to prioritize lifestyle interventions, such as medical nutrition therapy (MNT), weight loss, increased PA, and smoking cessation. It is recommended especially in patients with HbA1c near target levels (*i.e.*, 7.5%) for 3-6 months[8]. However, these lifestyle interventions have been combined with insulin therapy in T1D and T2D management, as described below.

MNT

Nutrition therapy has an essential role in diabetes management, and diabetes patients should be actively involved in self-management, education, and treatment planning with the health care team, leading to the development of an individualized eating plan[45,46]. All health care professionals should discuss individualized MNT provided by a specialized registered dietitian nutritionist at diagnosis and throughout treatment. MNT determines a HbA1c absolute decrease of 1.0%-1.9% for T1D patients and 0.3%-2.0% for T2D patients[47]. Due to the progressive characteristics of T2D, after medication is initiated, MNT should be modified in relation to disease evolution[45,46].

It has been reported that there is not an ideal calories percentage arising from carbohydrates, protein, and fat for diabetic patients. Consequently, macronutrient distribution should consider a personalized evaluation of preferences, current eating patterns, and metabolic goals. It is important to highlight non-starchy vegetables, minimize added sugars as well as refined grains, and select whole foods over highly processed foods. The Mediterranean, vegetarian, low-carbohydrate, and plant-based eating diets represent healthful eating patterns that have demonstrated positive results in T2D. In contrast, there is insufficient data to establish one eating diet over another for pediatric and adult T1D patients. In particular, the literature gap relates to the efficacy and long-term management implications of nutrition interventions for T1D children[48]. T2D patients not meeting glycemic control should reduce their carbohydrate intake with a low- or very-low-carbohydrate diet[49-51]. However, the recommended approach is to personalize meal plans with a macronutrient distribution that is more coherent with personal preference and usual intake to augment the probability for long-term maintenance. An important challenge of MNT is represented by weight management.

Weight management

Weight reduction and management is important for T1D, T2D, or prediabetic patients with overweight or obesity. To sustain these patients, MNT together with diabetes self-management education and support services should include a personalized eating plan characterized by an energy deficit associated with increased PA[45]. Lifestyle intervention programs should be intensive with frequent follow-up to realize a significant decrease in extra body weight and ameliorate clinical indicators. Consistently, it has been reported that weight loss can slow down the progression from prediabetes to T2D and is helpful for T2D management. In prediabetes, weight loss of 7%-10% has been shown to prevent the progression to T2D[52]. People with prediabetes at a healthy weight should also be considered for behavioral interventions to help establish routine aerobic and resistance exercise[52-54] and to establish healthy eating patterns.

T2D patients with overweight and obesity needed to achieve a 5% weight loss[55]. However, if the positive outcomes of weight loss are continuing and important (*i.e.*, 15%) the benefits may increase[56,57]. Overweight and obesity are also important in T1D patients. Sustaining weight loss can be difficult[55,58], although it has lasting benefits; interestingly weight loss is associated with HbA1C and lipid level improvements[59].

Different reports have shown that several eating plans, assorted in macronutrient composition, can be utilized successfully and safely over the short term (1-2 years) to accomplish weight loss in diabetic patients (*e.g.*, Mediterranean eating diet[60], structured low-calorie meal plans with meal replacements[57,59,61], and low-carbohydrate meal plans with additional support[62,63]). However, it is important to use meal plans containing nutrient-dense foods, including vegetables, legumes, fruits, dairy, lean sources of protein, seeds, nuts, and whole grains. Any approach to meal planning should be personalized, considering the health status, personal preferences, and ability of the patient to sustain the plan recommendations.

PA

PA, as defined by the World Health Organization, includes any movement involving the skeletal muscles that consumes energy. This includes activities undertaken during leisure, for transport to get to and from places, or as part of work. Both moderate and vigorous levels of PA are beneficial for health. During any type of PA, glucose levels increase in active muscles through insulin-independent pathways, whereas their circulating levels are maintained by hepatic glucose production and mobilization of free fatty acids, which may be impaired by insulin resistance or diabetes[64,65]. Moreover, regular PA enhances β cell function[66], insulin sensitivity[67], vascular function[68,69], and gut microbiota[70], all of which may lead to better diabetes management as well as comorbidities risk reduction.

Regular PA can help diabetes patients achieve a variety of aims including increased cardiorespiratory fitness and vigor, improved glycemic control, decreased insulin resistance, improved lipid profile, reduced blood pressure, maintenance of a healthy body mass after weight loss, less depression and anxiety, less medication use, and overall improved quality of life[71].

Although Bazargan-Hejazi *et al*[72] reported that less than 50% of the 871 individuals with T2D analyzed met the recommended threshold for exercise, specific suggestions and precautions can be modified based on the type of diabetes, age, activity, and presence of diabetes-related health complications. Females with preexisting familial history of diabetes and those with gestational diabetes should begin moderate PA during their pregnancies as tolerated[73].

In particular, the American Diabetes Association in "Standards of Care in Diabetes", published in 2023, emphasize that PA plays a key role in the prevention and management of diabetes especially in T2D[71,74]. Recommendations should be

personalized for each individual[73], thus according to American Diabetes Association guidelines T1D and T2D adults should perform[73]: (1) 150 min or more of moderate- to vigorous-intensity aerobic activity per week spread over at least 3 d/wk, with no more than 2 consecutive days without activity; (2) 2-3 d/wk of resistance exercise on non-consecutive days with each session consisting of at least one set of five or more different resistance exercises involving the large muscle groups[71]; (3) interrupt prolonged sitting every 30 min to gain blood glucose benefits; and (4) 2-3 times/week of flexibility and balance training.

However, PA in diabetic patients might cause hypoglycemia if the MNT does not contain the appropriate amount of carbohydrates for an exercise session. If glucose levels pretraining are less than 90 mg/dL, people need to eat additional carbohydrates according to their metabolism, intensity, and duration of PA[75]. In some patients, hypoglycemia following exercise may appear and persist for several hours due to heightened insulin sensitivity.

In individuals not treated with insulin or insulin secretagogues, hypoglycemia is less common, and routine preventive measures for hypoglycemia are typically not recommended in such cases. Intense activities may, in fact, elevate blood glucose levels instead of reducing them, particularly if pre-exercise glucose levels are elevated[75]. However, due to the variability in glycemic response to exercise sessions, individuals with diabetes should be instructed to monitor blood glucose levels before and after PA and be aware of potential prolonged effects based on intensity and duration.

Aerobic activities are linked with lower cardiovascular disease and overall mortality risks[76]. Moreover, this type of exercise training increases insulin sensitivity in individuals with diabetes and improved mitochondrial function in muscle fibers from vastus lateralis muscle[77]. Vigorous-intensity aerobic exercise training for 7 d may improve glycemia without reducing body weight through enhanced insulin-stimulated glucose clearance and inhibition of hepatic glucose production[67].

Meta-analyses and systematic reviews determined that regular aerobic exercise training improved glycemia in adults with diabetes including a 0.5%-0.7% reduction in HbA1c[78-83]. A meta-analysis published in 2019 examined the importance of resistance exercise in the management of diabetes and proposed that high-intensity training is more helpful than low-to-moderate-intensity training for overall glucose management and attenuation of insulin levels in diabetics patients. However, they noted that it is important to improve strength, balance, and the ability to engage in activities of daily living during the life span[84].

In 2010, a trial on T2D patients demonstrated that, combined aerobic and resistance training improved HbA1c levels compared with non-exercising controls, although neither resistance nor aerobic training alone resulted in significant changes[85]. Moreover, the patient group doing combined training lost more weight and improved aerobic fitness more so than controls[85].

Another important consideration is the significance of PA for diabetic children. They should perform at least 60 min of aerobic activity every day, with strength training 3 d/wk[86]. T1D children and adolescents benefit from physical activity [87] and thus may have better health outcomes and health-related quality of life[88,89].

Challenges in diabetes management

Although new technological devices are available and led to amelioration of metabolic control and life quality, challenges for T1D management are abundant. In detail, insulin administration remains a therapy and not a cure for DM. It requires compliance of the patients, which is particularly difficult for pediatric patients. Furthermore, the risk of severe hypoglycemia persists. Therefore, with the aim of improving insulin availability in T1D patients, different strategies have been employed, including enhancing endogenous β cell activity and transplanting new islets (Figure 1).

Plant extracts in diabetes management

A different approach can arise from the use of plant extracts that are rich of polyphenols, characterized by an anti-diabetic effects. Promising *in vitro* results have been obtained using extracts from *Coronopus didymus*[90], *Molineria capitulata*, *Trichosanthes tricuspidate*, *Amorphophallus campanulatus*[91], *Datura metel* L[92]. Furthermore, in alloxan induced diabetic rats the anti-hyperglycemic and anti-oxidant roles of the 1,3,4-oxadiazole derivative[93] was found, whereas extracts of *Centella asiatica* leaf[94] affected weight, insulin level, and antioxidant factors compared to the control group. Also, Mitra *et al*[95] investigated the biological effects of leaf extract of *Avicennia alba* in alloxan induced diabetic rats, the dosages of 200, 400, and 500 mg/kg reduced glucose levels of blood, increased body weight and have anti-inflammatory activity. However, some polyphenols needed to be included in nanoformulations to overcome pharmacokinetic barriers resulting in the improvement of their anti-diabetic activity[96]. Despite the positive restorative consequences of phytochemicals, inconsistent or contradictory data from clinical trials emerged, although beneficial effects can be observed from the combination of the classic therapy and phytochemicals[97].

Enhancement of endogenous β cell activity

The first strategy showing interesting results arose from preclinical models. In detail, in 2022, it was reported that prolonged blocking of the death receptor TMEM219 determined a strong β cell expansion simultaneously with the islet area and insulin levels in non-obese diabetic mice[98]. Furthermore, in 2007, 2019, and 2021, the use of rapamycin, an mTOR inhibitor, was linked to different results[99-101]. For example, in islet xenograft the simultaneous use of rapamycin and anti-CD154 mAb determined graft survival[99]. Whereas in a non-human primate study, rapamycin administration was linked to long-term islet allograft survival and the disappearance of alloantibodies[100]. It has also been reported that rapamycin affects autoimmune response, β cell proliferation, and survival[101]. Interestingly, in long-standing T1D a phase II trial in 2007 showed that rapamycin was not able to improve β cell activity[102]. In contrast, pancreas/islet transplantation has excellent results.

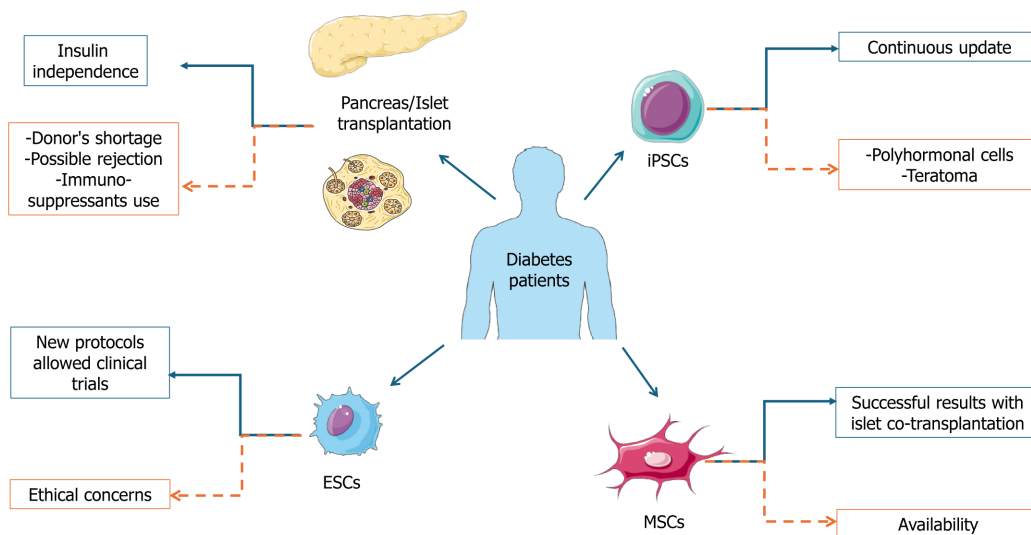


Figure 1 Diabetes therapy. Advantages (blue) and limitations (orange) of cellular diabetes therapy. ESC: Embryonic stem cell; iPSC: Induced pluripotent stem cell; MSC: Mesenchymal stem cell. Citation: The figure was generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license ([Supplementary material](#)).

Pancreas/islet transplantation

The protocol for this kind of intervention has been recently optimized, leading to standardized procedures. It is indicated for T1D patients with severe hypoglycemia, complicated by impaired hypoglycemia awareness or exacerbated glycemic lability, as defined by the current recommendation[103,104]. Islet/pancreas transplantation can always be associated with kidney transplant; however, the absence of cardiovascular disease is imperative in this case and is typical for patients aged up to 55-years-old. Pancreas transplantation has been associated with improvement of all comorbidities associated to diabetes, quality of life, and survival[105].

Allogenic islet transplantation is fundamental to restore the right levels of insulin, glucagon, and other hormones produced by these cells. Allogenic islets are isolated from the pancreas of a deceased donor, using a standard protocol requiring enzymatic and mechanical digestion, followed by density gradient purification[106]. It is possible to continue with transplantation only if more than 200000 viable pure sterile islets are obtained[103]. Only a few institutions routinely carry out this kind of transplantation due to the complexity of the intervention. Consistently, it requires an islet-isolation team available 24 h/d and 7 d/wk, and there are often difficulties due to the transplantation itself. Islets can be infused through the portal vein for delivery to the liver under immunosuppression. Islets can either be transplanted fresh or after culture that can cover a period of 12-72 h after immunosuppression induction. Normally, two/three islet preparations need to be injected to achieve the right insulin level. Immunosuppression is also fundamental in this case, and it includes an induction phase at each islet infusion, followed by a maintenance period during islet transplantation.

The best-known successful protocol for the transplantation of islets is the Edmonton protocol, which requires an anti-IL2 receptor infusion before each islet administration combined with an mTOR inhibitor (sirolimus)[107]. However, alternative protocols have been used with different immunosuppressive approaches including T-cell depleting agents, steroids, anti-TNF α , or anti-IL1 β antibody. A maintenance therapy is also required[108-112].

The CIT Consortium Protocol 07 (CIT-07) trial showed islet transplantation to be an effective treatment for subjects with impaired awareness of hypoglycemia and intractable severe hypoglycemic events[113]. This was a multicenter phase 3 study published in 2016 involving 48 T1D adults with successful results 1 year after transplantation. In 2018, an additional study on the same patients reported that 87.5% of patients reached the first endpoint of freedom from severe hypoglycemic events together with attainment of glycemic control 1 year following islet transplantation and amelioration of health-related quality of life[114].

In 2023, primary graft function was evaluated as an independent predictor of 5-year clinical islet transplantation outcomes[115]. In detail, the authors referred to the Collaborative Islet Transplant Registry, which is a comprehensive global registry that reports all data from most islet transplant programs in North America, Eurasia, and Australia. They demonstrated an inverse, independent, and linear relationship between primary graft function evaluated 28 d after the last islet infusion together with the cumulative 5-year incidence of unfavorable events after islet transplantation such as unsuccessful islet transplantation, graft exhaustion, insufficient glucose control, and the need for exogenous insulin treatment.

Researchers also investigated the omentum as another potential site for islet injection. Its great surface area, vascularity, and portal venous drainage system led to its identification as an opportune transplant site[116]. Consistently, a 2021 clinical trial (NCT02213003) is ongoing in Miami with transplantation of islets onto the omentum in T1D patients. This is performed laparoscopically, and the islets are mixed with human thrombin to generate a biological mesh that adheres to the omentum (ClinicalTrials.gov. Allogeneic Islet Cells Transplanted onto the Omentum. Available online: <https://classic.clinicaltrials.gov/ct2/show/NCT02213003>).

In 2017, a preliminary case report described the case of a 43-year-old female patient with a 25-year history of diabetes who had 600000 islet equivalents laparoscopically transplanted onto her omentum. She discontinued insulin infusion after the transplant and maintained insulin independence 12 months after her procedure with stable glycemic control [117]. A partner study is ongoing at the University of Alberta (NCT02821026), in collaboration with the University of Miami, with the same method of omental transplantation and immunosuppression (ClinicalTrials.gov. Omental Islet Transplant. Available online: <https://classic.clinicaltrials.gov/ct2/show/NCT02821026>). Recruitment is ongoing and updates are required.

Despite the beneficial effects of islet/pancreas transplantation, some limitations occur that limit its application on a large scale. In detail, the supply of donor tissues is limited, thus the transplantation can be restricted to only a few patients. Consistently, data from the Eurotransplant foundation showed that in 2020 in North Europe only 163 donors were available for a waiting list of 385 patients and an estimated mean of 50000 T1D patients (Monthly statistics. Eurotransplant. <https://www.eurotransplant.org/statistics/monthly-statistics/>).

Furthermore, up to 80% of the transplanted islets were lost before becoming included into tissue due to acute inflammatory responses and release of the proinflammatory cytokines IL-1 β , TNF α , and IFN γ [118-123]. One year after implantation some β cells were lost due to problems during the engraftment, the always active autoimmunity, and inflammation. All these limitations led to the identification of alternative therapeutic strategies, involving mesenchymal stem cells (MSCs).

MSC THERAPEUTIC STRATEGIES

MSCs

MSCs represent a varied group of multipotent precursor cells found in the supportive tissues of numerous adult tissues. The distinctive features of MSCs, including their ability to renew themselves, their capacity to differentiate into multiple cell types, and their ready availability, coupled with their immunomodulatory properties and minimal ethical concerns, underscore their significance in the field of regenerative medicine. The characteristic of multipotency is defined as the ability to differentiate into different cytotypes under *in vivo* and *in vitro* conditions[124,125].

Dominici *et al*[126] proposed three criteria to define MSCs: Adherence to plastic of the dish in standard types of culture; specific surface antigen expression (CD105, CD73, and CD90); and multipotent differentiation in osteoblasts, adipocytes, and chondroblasts. Furthermore, MSCs do not have expression of hematopoietic markers CD45, CD34, CD14, or CD11b, CD79a or CD19, HLA-DR[127], and endothelial marker CD31. Likewise, *in vitro* MSCs can function as alloantigen presenting cells (antigen-presenting cells). In fact, these cells suppress lymphocyte T proliferation and activation.

Consistently, MSCs have unique immunomodulating properties, which is very important during the procedure of transplantation[128]. MSCs are found in both embryonal, fetal tissues and numerous adult tissues with some exceptions. Embryonic stem cells (ESCs), derived from the inner cell mass of blastocyst-stage human embryos, are a potentially unlimited renewable source for cell transplantation aimed at treating numerous diseases[129]. Well-organized populations of MSCs have been isolated from bone marrow[130]. Furthermore, cells showing MSC properties have been isolated from adipose tissue[131], dental pulps[132], endometrium[133], peripheral blood[134], skin[135], placenta[136], umbilical cord[137], and synovial fluid[138]. It has been proposed that the functions of MSCs may vary depending on the specific tissue they are in, with their adaptability influenced by the surrounding microenvironment[139]. Among the different applications, stem cell therapy is currently the most investigated modality to treat DM[140].

MSC strategies

One interesting promising strategy is the cotransplantation of MSCs with islets, thus providing protection against proinflammatory cytokines and hypoxia[141]. In 2021, a pilot study demonstrated that autologous MSCs and islet cotransplantation was safe and increased islet engraftment in patients with chronic pancreatitis[142]. A different approach has been realized by using MSCs as a potential source of β cells, even if the results are not as excellent as expected. Different studies have been performed starting in 2005. D'Amour *et al*[143] differentiated ESCs toward pancreatic progenitors using different growth factors. They obtained functional multihormonal cells, but following transplantation they became unresponsive to glucose and producing insulin. Kroon *et al*[144], generated glucose responsive endocrine cells from human ESCs that following transplantation in diabetic mice differentiated into active β cells with the right balance between glucose and insulin levels. Pagliuca *et al*[145] obtained active β cells *in vitro* from ESCs.

Other authors have tried to ameliorate the protocol working on the activation of specific pathways (WNT, FGF, BMPs, and Notch) and using suspension cultures leading to the decrease in multihormonal cells and the increase in glucose sensitive cells[146]. All these findings led to the development of two clinical trials by Vertex and ViaCyte (both, Vertex Pharmaceuticals, Boston, MA, United States)[147].

In 2022, Vertex announced the findings of the first trial on a T1D patient receiving an intraportal infusion of ESC-derived islets. They reported an augment in both fasting and post-prandial C-peptide levels. Overall, they reported that the patient reached complete independence from insulin injection (Vertex Pharmaceuticals Incorporated. Vertex Announces Positive Day 90 Data for the First Patient in the Phase 1/2 Clinical Trial DosedWith VX-880, a Novel Investigational Stem Cell-Derived Therapy for the Treatment of Type 1 Diabetes. BusinessWire, 18 October 2021). However, a high chronic dose of immunosuppressant was required to avoid cell rejection.

To overcome the problem of immunosuppressor use, ViaCyte encapsulated ESC-derived pancreatic cells in a biological membrane that was subcutaneously implanted. The device is known as PEC-Encap. The implanted cells further differentiated into active β cells. This first approach was superseded by the same ViaCyte using more mature and functional cells, and preliminary results arising from 17 T1D patients showed that implanted ESCs created a renewable source of islet cells [148].

Encapsulation can be differentiated into two groups: microencapsulation and macroencapsulation. In the former, system islets were coated in a thin natural polymer [149]. The preferred polymers are alginate hydrogels, as they can be adjusted for permeability and firmness. The mix of islet and alginate led to the formation of a fibrin gel that appears as a porous nest for the islets [150]. The major limit associated with microencapsulation is the inflammatory response against the polymer. Researchers moved on to develop macroencapsulation techniques, implanting devices over 1 mm in size, which are easily implantable, monitored, and removed if necessary [149].

Induce pluripotent stem cells

Although further improvements have been obtained in β cell differentiation [151], stem cell-derived β cells are not completely like pancreatic β cells, thus they do not reach optimal glucose control. This has prompted different researchers to use induced pluripotent stem cells (iPSCs). This approach overcomes some limitations associated to the use of ESCs, such as the alloimmune response but led to other complications such as polyhormonal cells and teratomas [152]. Recently, the improvement of the protocol for using iPSCs with specific growth factors and a planar technology cultivation for long periods seems to offer good prospectives [153]. Islet-like aggregates have also been created with iPSCs using different biomaterials (*e.g.*, fibronectin, matrigel, decellularized scaffolds) transplanted into diabetic mice as organoids with interesting but still limited results. However, all other protocols based on the use of iPSCs as a source of β cells led to rejection and prolonged immunosuppression. Therefore, the evaluation of the long-term therapeutic effects is difficult and further investigation is required [154].

Additional limitations include low reprogramming efficiency, tumorigenesis, low survival and engraftment, cell phenotype loss following transplantation, and genetic and epigenetic instability. Very recently, a clinical case has been described. A T1D patient developed a teratoma after iPSC-derived β cell transplantation. It is important to underline that in this patient the β cells arose from autologous iPSCs. They were injected into the deltoid and developed a mass there 2 months following implantation. The tumor showed high growth and metastasis to the lymph node and was chemotherapy resistant [155].

DIABETES COMORBIDITIES

MSC-derived exosomes for the treatment of diabetes comorbidities

Several studies have investigated the role of the complex secretome released from MSCs [156-162]. In recent years, interest has increasingly been directed toward the study of small extracellular vesicles, called exosomes [163-169]. The interest in these small 30-100 nm vesicles comes from their role in cellular physiology. Indeed, exosomes not only modify the cells from which they originate but also those with which they interact, the target cells [170-172]. Exosomes are studied for their ability to act on intercellular communication, carrying proteins, RNA (mRNA, miRNA, and non-coding RNA), and DNA sequences. Moreover, exosomes interact with target cells, binding receptors, and surface enzymes, activating them for triggering of intracellular signaling [173].

Exosome interaction with the target cells causes the activation of signal transduction mechanisms and consequently gene expression through specific enzymes, transcription factors, and proteins [173,174]. The therapeutic potential of MSC-derived exosomes in different disease including T1D and T2D is of great interest [175,176].

In diabetes patients, neovasculogenesis, certainly one of the most important factors influencing wound repair, is compromised, and this leads to a delay in wound healing [177]. Yu *et al* [178] investigated the role of MSC-derived exosomes in enhancing angiogenesis during wound repair after making full-thickness skin defects in streptozotocin-induced diabetic rats. In that study, exosomes were isolated from human bone marrow MSCs and treated or not treated with atorvastatin (ATV). A 2-cm diabetic rat lesion was treated with phosphate-buffered saline, exosomes, or ATV-pretreated exosomes. Treatment with exosomes and ATV-treated exosomes accelerated wound closure compared with the control group. Moreover, wounds treated with exosomes and ATV-exosomes had significantly more blood vessels compared to the control group, which was highlighted by immunohistochemistry assays for CD31 and immunofluorescence for CD31 and α -SMA. To establish the mechanism underlying ATV-exosome action in diabetic rats, the AKT/eNOS pathway and 10 candidate microRNAs (miRNAs) were selected for investigation because of their ability to enhance angiogenesis. Among the 19 candidate miRNAs, miR-221-3p levels were upregulated in ATV-exosomes. The authors hypothesized that ATV-exosomes may promote angiogenesis processes through miR-221-3p release and *via* AKT/eNOS pathway activation [178].

More recently, Tang *et al* [179] published a study showing the ability of MSC-derived exosomes to increase skin wound healing in diabetic mice through the release of circ-Snhg11. Specifically, by luciferase assay, the involvement of SLC7A11 and miR-144-3p, downstream targets of circ-Snhg11, was confirmed.

Another noteworthy diabetes health complication is diabetic peripheral neuropathy (DPN) [180]. DPN affects the peripheral nervous system and is characterized by sensory axonal loss. DPN begins in the lower extremities and is characterized by pain and morbidity. Hyperglycemia is the main cause of DPN in T1D, while dyslipidemia is a contributory factor in etiopathogenesis of DPN in T2D [181-183].

Fan *et al*[184] used 20-wk diabetic mice as a DPN model, and MSC-derived exosomes were injected weekly into the tail vein for 8 wk. Neurophysiological, thermal, and mechanical sensitivity measurements were examined. Moreover, toluidine blue-staining and immunohistochemistry for protein gene product 9.5, myelin basic protein, and hypophosphorylated neurofilament H were performed on sciatic nerves of the diabetic mice. MSC-exosome treatment significantly increased motor nerve conduction velocity and sensory nerve conduction velocity at weeks 4 and 8 post-injection in the diabetic mice. In addition, exosome treatment decreased the mechanical response threshold and thermal response time latency at weeks 4, 6, and 8. Moreover, morphological analysis revealed that MSC-derived exosomes significantly improved myelination as well as nerve fiber density and diameter of diabetic mice. MiRNA profiling within exosomes derived from MSCs was examined, and a total of 215 miRNAs were detected. Let-7a, miR-23a, and miR-125b miRNAs, which synergically target the TLR4/NF- κ B signaling pathway, were upregulated. Notably, there is some evidence for involvement of the TLR/NF- κ B signaling pathway in DPN disease[184].

Notably, Fan *et al*[185] performed a study to evaluate the therapeutic effects of engineered MSC-derived exosomes with miR-146a (exo-146a) on DPN of diabetic mice. Two-week treatment with exo-146a in diabetic mice compared with non-engineered exosomes significantly increased nerve conduction velocity and decreased the threshold of thermal and mechanical stimuli. In addition, exo-146a significantly reduced inflammatory peripheral blood monocytes and endothelial cell activation targeting the TLR-4/NF- κ B signaling pathway.

The role of treatment with MSC-derived exosomes has also been investigated in erectile dysfunction arising in 50% of diabetic men because of corpus cavernosum smooth muscle cell dysfunction[186-188]. Having established that MSC-derived exosomes could improve erectile function, Huo *et al*[188] investigated the ability of exosomes to communicate intercellularly with corpus cavernosum smooth muscle cells through miR-21-5p release in a rat model of DM-induced erectile dysfunction. The authors hypothesized that miR-21-5p could be released from exosomes in corpus cavernosum smooth muscle cells, enhancing proliferation and inhibiting smooth muscle cell apoptosis, in turn alleviating erectile dysfunction in DM rats[188]. It has been demonstrated that miRNA-21 enhances pulmonary artery smooth muscle cell proliferation and migration and prevents T1D, caused by pancreatic β cell apoptosis through blocking programmed cell death 4 protein production[189,190].

Recently, in 2024, the therapeutic role of MSC-derived exosomes, administered by intracavernous injection, was investigated in erectile dysfunction in a cavernous nerve injury rat model[191]. To examine the beneficial effect of exosomes in erectile dysfunction, intracavernosal pressure/mean arterial pressure ratio, immunohistochemical assay and molecular analysis were performed. Erectile dysfunction, evaluated by intracavernosal pressure/mean arterial pressure ratio, was ameliorated in the exosome group. Moreover, the smooth muscle/collagen ratio was increased after exosome-repeat injection, inhibiting corpus cavernosum fibrosis and atrophy. Molecular analysis identified three genes, significantly expressed in the exosome-treated group, including Ras homolog family member B, which can enhance cell proliferation and angiogenesis of HUVECs[191].

Wound healing

The advantages of MSC implantation are seemingly not restricted to the restoration of pancreatic functionality. An MSC implant has also been shown to be a potential new and valid approach in the treatment of diabetic wound healing through the modulation of fibrosis, tissue regeneration, immune suppression[119,192], and re-epithelization[193]. One common complication of diabetes is impaired wound healing, which leads to prolonged periods of tissue repair and deposition of scars with elevated collagen density and decreased tensile strength[194,195]. In the absence of healthy scarring, diabetic patients present increased risks for infections, sepsis, surgery, and reoperation[195], as well as developing diabetic foot ulcers, a serious and potentially debilitating condition expected to occur in 25% of people diagnosed with diabetes in their lifetime[193].

There currently exists no successful clinical strategies for repairing damaged blood vessels and nerves[193] or enhancing the healing process, apart from amputation for the treatment of the diabetic foot ulcers[196] or conventional treatments that ameliorate the symptoms (*e.g.*, by reducing the risk of infections or keeping the wound bed moist[197]). This lack of approach options emphasizes the importance of proper diabetes management to prevent and mitigate these issues.

Strategies and scaffolds for MSC delivery in the treatment of diabetic wound healing

MSCs have been successfully tested and administered by local and systemic delivery for the treatment of cutaneous wound healing and diabetic foot ulcers[193,198,199]. For local delivery, nonvascular injections into tissue are reported to be the most widely used route of administration, followed by topical administrations[198]. For systemic cell delivery, it has been performed as an endovascular injection *via* the intraarterial femoral route in clinical studies, and the intravenous tail vein route in preclinical studies[198]. Despite the number of advantages in the direct injection of MSCs, several limitations to its therapeutical potential have been revealed for this administration route, including reduced cell viability, impaired localization of cells at the bed of diabetic wounds[200], and higher infection risks[198]. For these reasons, new strategies involving biomaterials and scaffold have been developed to improve the efficacy of mesenchymal cell delivery [200].

Hydrogel scaffolds

Hydrogel scaffolds are mesh-like networks of polymer chains that can be either naturally derived or synthetic[201]. Despite reduced water retention capacity, limited biomechanical features, and higher variability in properties between natural hydrogel batches, they both possess the ability to preserve cell viability for resident and engrafted cells at the wound site[201], thus overcoming one of the major issues related with MSC injection.

The advantages of employing hydrogel-based scaffolds also rely on their ability of being functionalized with customizable properties. Hydrogels can be tailored by incorporating specific crosslinkers, such as the RGD-like motif[202], utilizing multiple components (*i.e.*, sodium alginate/gelatin[203]), or adjusting their size, shape, and biodegradability [201]. This customization imparts mechanical and biological cues that not only enhance engraftment adhesion but also restore other physiological functions, including epidermal regeneration, angiogenesis, and collagen recovery[203]. Additionally, hydrogels exhibit great cytocompatibility and antibacterial properties[201], which collectively establish these matrices as suitable and valuable options in the field of regenerative medicine.

Recent advancements in tissue engineering have expanded the application of matrices beyond their traditional use as bulks. They are now utilized in various forms and geometries, including hydrogel sheets, *in situ* forming hydrogels, and hydrogel microspheres, enhancing their versatility in the field[204,205].

Several types of films or sheets of hydrogels have been successfully developed for treating various types of ulcers and wounds in different pathophysiological contexts[206-208]. The surface of diabetic ulcer wounds, however, typically exhibits a complex and uneven topography, making the hydrogel dressing more prone to detachment due to weak adhesion to the wound surface, and is susceptible to bacterial infections[209]. Therefore, thin hydrogel nanosheets that display low risk of trauma to the wound bed, greater antibacterial performance[210], and inhibition of chronic inflammation[202] are of particular interest in diabetic bacterially-infected tissue damage.

A full list of preclinical and clinical studies of hydrogels combined with different MSCs lines tested for the treatment of diabetic wound healing is available in the paper by Li *et al*[211].

Sponge scaffolds

Sponge scaffolds retain a low percentage of water in their process, which requires longer manufacturing times and additional surface and structural modifications (*i.e.*, pore size network) depending on the type of cells to be delivered[201] compared to non-porous scaffolds.

Sponges have proven to be effective devices in tissue regeneration of diabetic wounds. On one hand, due to their ability in retaining fluids, they are useful in absorbing exudates from the wound, thus creating a conducive environment for cell proliferation and migration[201]. On the other hand, they can be embedded with media enriched with growth factors that can be released once implanted in the wound bed and effectively promote skin regeneration and wound healing[212]. Due to their caveolar structure, sponge-like scaffolds (SLS) are exceptionally suitable for hosting MSC cells, whose adhesion and numerosity can be augmented in functionalized SLS (*i.e.*, soy protein and β -chitin[213], platelet-rich plasma[214]).

Collagen and chitosan-based sponges are the most commonly used scaffolds for MSC delivery[200]. As for the usage of SLS in diabetic wound treatment, collagen scaffold derived from bovine skin has been shown to result in improved biocompatibility, re-epithelization, anti-inflammatory effects, and neovascularization of chronic wounds in diabetic mice [215,216]. Studies performed on MSCs and exosomes have further showed that the combination of gingival MSC-derived exosomes and hydrogel sponges accelerates skin wound healing and the re-epithelization process[217].

Nanofibrous scaffolds

Nanofibrous scaffolds are produced from natural or synthetic polymers[218]. The nano-geometry and three-dimensional structures of fibers represent a critical factor in tissue regeneration including elevated pore size together with the higher ratio between pore and cell size, which are reported to be associated with enhanced cell migration and invasion[219] as well as the alignment of nanofibers in multiple directions (*i.e.*, radial, vertical) that confers mechanical resistance to compressive force[220]. Nanofibrous scaffolds exhibit greater potential in the context of wound healing of diabetic ulcers compared to other conventional scaffold matrices. They not only greatly support cell adhesion and proliferation due to their high surface-to-volume ratio but also safeguard the wounded region against dehydration, impede the infiltration and proliferation of microorganisms, and topically deliver drugs and therapeutics that can be incorporated in the matrix design[218].

Sprays and drops

A relatively fast and safe scaffold technology in wound repair is represented by the spray delivery of stem cells embedded in a liquid matrix[221]. It was introduced as a standardized clinical practice more than 15 years ago (Avita Medical Europe Ltd., Melbourne, Australia). Since sprays require an uncultured mixture of cells in suspension, the main advantages include faster culture time and the elimination of the need for specialized personnel to handle the cells[221]. Due to their sealing properties, the most common sprays are fibrin-based, reported to efficiently facilitate the topical adhesion of suspended cells to the wound bed and accelerate healing[221,222]. Despite the benefits of such techniques, little research has been conducted on the optimization of spray-delivery technology in the context of the treatment of diabetic wound healing[222], and further investigations are required.

CONCLUSION

Currently, no cure is available for DM, and it can be managed using available medication (primarily insulin) together with MNT, PA, weight loss, and smoking cessation. Consistently, MNT and PA represent the first approach for prediabetes management leading to a retardation of the disease manifestation. However, it is important to consider that the therapeutic approach together with MNT and PA could lead to side effects, such as hypoglycemia and glycemic instability. Furthermore, diabetes can aggravate over time with the consequent development of common comorbidity,

such as bone disease, neuropathy, retinopathy, nephropathy, and cardiovascular disease, with consequent augment of mortality and morbidity. A beneficial effect was demonstrated from the use in combination of standard therapy with polyphenols arising from plant extracts. In addition, the alternative pharmacological approach for DM management can manifest adverse effects, leading to an unmet need to develop novel and safe anti-diabetic drugs. Different approaches focused on improvement of β cell/pancreas activity were developed; thus crucial advantages are associated with transplantation. In detail, the major advantage of β cell transplantation is that it leads to normalized glucose levels. Transplantation patients become insulin-independent for long periods. At present, however some issues remain to be resolved including the major availability of β cells/islets from donors to allow transplantation in all patients. However, the possibility of supporting the differentiation of ESCs and iPSCs could represent an alternative in cases of organ shortage. All the engineering approaches associated with the use of these cells are promising for the development of active β cells without the simultaneous use of immunosuppressants. Thus, these hopeful new approaches together with the commitment of the scientific community will lead to further amelioration resulting in the improvement of diabetes management.

FOOTNOTES

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