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# Mesenchymal Stem Cell Therapy in Type 1 Diabetes Mellitus and Its Main Complications: From Experimental Findings to Clinical Practice

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## Abstract

Type 1 diabetes mellitus (T1DM) is a complex multifactorial disorder which involves a loss of self-tolerance leading to the autoimmune destruction of pancreatic β−cells. Exogenous insulin administration cannot mimic precise pancreatic β-cell regulation of glucose homeostasis, thereby leading to severe long-term complications. Pancreas or islet transplant only provides partial exogenous insulin independence and induces several adverse effects, including increased morbidity and mortality. The scientific community and diabetic patients are thus, still waiting for an effective therapy which could preserve the remaining β-cells, replenish islet mass and protect newly-generated β-cells from autoimmune destruction.

Mesenchymal stem cells (MSCs) have been envisioned as a promising tool for T1DM treatment over the past few years, since they could differentiate into glucose-responsive insulin-producing cells. Their immunomodulatory and pro-angiogenic roles can be used to help arrest β-cell destruction, preserve residual β-cell mass, facilitate endogenous β-cell regeneration and prevent disease recurrence, thereby making them ideal candidates for the comprehensive treatment of diabetic patients.

This review focuses on recent pre-clinical data supporting MSC use in regenerating β-cell mass and also in treating several T1DM-associated complications. Clinical trial results and the ongoing obstacles which must be addressed regarding the widespread use of such therapy are also discussed.

**Keywords:** Mesenchymal stem cells; Type 1 diabetes mellitus; Diabetic complications; Clinical practice; Therapy

## Introduction

Type 1 diabetes mellitus (T1DM) is a devastating chronic metabolic disease whose incidence has been rising at alarming rates during the last decade [1]. T1DM pathophysiology has been clearly related to an innate immune system defect resulting in a loss of self-tolerance, leading to the destruction of pancreatic β-cells by self-reactive-T-lymphocytes [2]. Standard T1DM patients' care strategies are based on the ongoing monitoring of food intake and continuous insulin prophylaxis. Nevertheless, endogenous insulin production and secretion are highly sensitive to minute-by-minute changes in blood glucose levels. Exogenous insulin injections thus do not represent a definitive cure for T1DM since they cannot mimic precise β-cell glucose homeostasis regulation. It must be stated that, even when being treated, T1DM patients develop severe long-term complications which clearly reduce their life-expectancy [3,4].

Around 1,300 T1DM patients receive pancreas or β-pancreatic islet transplants from cadaveric donors each year in the USA as an alternative to insulin administration [5]. Around 80% of transplant recipients can become insulin injection free for a five-year period [6,7], thereby indicating that a cure for T1DM is possible through β-cell mass replenishment; however, the demand for organs exceeds their availability [8]. Transplanted patients have to undergo life-long nonspecific immunosuppressive regimens to avoid transplanted organs becoming rejected and thus hindering this therapy's widespread use [9]. Such difficulties have led researchers to search for other sources of glucose-responsive insulin-producing cells; strategies based on different types of stem cell seem to be the most promising ones to date [10].

## Mesenchymal Stem Cells for Regenerating Pancreatic β-Cell Mass

The main challenge for successful stem cell therapy to treat T1DM lies in producing functional β-cells and overcoming the autoimmune response. In theory, β-cell mass and function could be preserved and/or restored in at least three different ways: replacing damaged β-cells by direct stem cell differentiation, modifying the pancreatic microenvironment allowing endogenous β-cell regeneration and abrogating the autoimmune response to β-cells. Multipotent mesenchymal stromal cells (also referred to as mesenchymal stem cells -MSCs), a heterogeneous adult stem cell population, seems to represent an ideal tool, since they can be easily isolated from bone-marrow and other mesenchymal tissue, like adipose tissue, dental pulp, placenta, Wharton's jelly and umbilical cord, and rapidly expanded *ex vivo* [11,12]. MSCs are hypo-immunogenic, allowing allogeneic transplant without histocompatibility or recipient conditioning being required [13]. When MSCs are systemically administered they can selectively migrate and engraft in damaged tissue [14] and differentiate into insulin-producing cells [15,16]. As immunomodulatory cells, MSCs can limit inflammation in damaged tissue [17], produce a broad range of trophic factors protecting parenchymal cells from dying by apoptosis and promote the proliferation and differentiation of endogenous precursors [18]. MSCs have been transplanted into over 1,000 human

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patients suffering different diseases, providing beneficial effects without inducing major toxicity [19-21].

## Replacing pancreatic β-cells by direct differentiation

One approach to produce more β-cells has involved differentiating MSCs into functional β-cells. Hisanaga et al., have shown that a simple protocol can induce murine bone marrow-derived MSC differentiation into insulin-secreting cells [22]; the differentiated cells contained insulin-secretory granules and secreted mature insulin after glucose stimulation. Such cells reduced blood glucose levels when they were transplanted into diabetic mice [22]. Zhang et al., have demonstrated that human bone marrow-derived MSCs could differentiate into pancreatic islet-like cell clusters when following a more complex four-step induction protocol [23]. Differentiated cells have expressed a broad pancreatic β-cell genetic profile, released high levels of insulin in response to glucose stimulation *in vitro* and reduced blood glucose levels when transplanted to streptozotocin (STZ)-induced diabetic mice [23].

Other studies have proved that human adipose-derived MSCs have been able to adopt a pancreatic endocrine cell phenotype *in vitro* [24,25]; differentiated cells co-expressing insulin, glucagon and somatostatin reduced blood glucose levels within two weeks when they were transplanted into STZ-induced diabetic mice [24,25]. Similar results have been obtained with MSCs isolated from dental pulp [26], placenta [27], Wharton's jelly [28] and umbilical cord [29], suggesting that such therapeutic effect could be a common property for any type of MSCs.

Some other reports have suggested that MSC differentiation into insulin-secreting cells could also be achieved *in vivo* [15,30,31]; transplanting undifferentiated bone marrow-derived MSCs into diabetic mice in these studies increased insulin levels and reduced hyperglycaemia. The authors found that some transplanted cells homed to pancreatic injury sites when analysing receptor mouse pancreatic tissue and that they differentiated into insulin-positive cells [15,30,31]. However, such cell lineage switch has still to be confirmed, since several other laboratories have reported that MSCs infused into diabetic mice lowered blood glucose level and increased β-cell mass but they could not differentiate into β-cells [32-34].

Furthermore, while proof of concept has demonstrated that MSCs can differentiate into insulin-secreting cells (at least *in vitro*), such an approach is limited by an inability to achieve a fully-differentiated β-cell phenotype, the relatively low amount of insulin secreted *in vivo* and inefficacy in rapidly adapting to day-to-day physiological requirements. The scientific community is thus still searching for a well-defined and reproducible condition enabling this target to be achieved (i.e. to provide a clinically-relevant β-cell mass compatible with transplants in humans).

## Modifying the pancreatic microenvironment to allow endogenous regeneration of pancreatic β-cells

It is well-known that β-cell mass increases markedly during development and can also proliferate postnatally in response to situations involving increased metabolic demand, such as obesity and pregnancy [35]. Significant regeneration of pancreatic tissue, including β-cells, has also been shown in adult mice and rats following 70% pancreatectomy [36,37].

Several studies have shown that existing β-cells' self-duplication and pancreatic ductal cell differentiation are the main mechanisms by which pancreatic β-cells could be replenished in rodents and humans [36,38,39]. Thus, stimulating β-cell replication or local precursor differentiation could provide a promising alternative by which diabetic patients' β-cell mass could become restored.

It is well-known that MSCs secrete a broad range of bioactive growth factors in their vicinity (i.e. VEGF, bFGF, IGF, HGF and EGF) [18]. Therefore, MSCs could provide trophic support for injured tissue by modifying the microenvironment to induce local precursor proliferation and differentiation, improve damaged tissue irrigation and prevent parenchymal cell apoptosis [18,40]. Hess et al., have shown that transplantation of bone marrow-derived cells has increased insulin levels in diabetic mice and reduced their hyperglycaemia [41]. A careful histological analysis of these animals' pancreases has shown that transplanted cells homed to the pancreatic injury site and promoted endogenous pancreatic regeneration, probably by secreting trophic factors [41]. These results have also been replicated in another study showing that newly-produced β-cells were in close vicinity to donor MSCs, suggesting that the cells so administered were involved in pancreatic progenitor cell proliferation and differentiation [42].

Our group has recently reported that intravenous injection of bone marrow-derived MSCs into diabetic mice has increased EGF plasmatic and pancreatic levels [33]. It has been reported that transgenic expression of EGF in the pancreas enhances β-cell proliferation and differentiation [43] and combined EGF and gastrin treatment has increased β-cell mass in diabetic rodents due to neogenesis from pancreatic duct cells [44,45].

Adipose-derived MSCs represent a very promising approach to diabetes since they are endowed with a large number of bioactive mediators, such as leptin, adiponectin and visfastin, which are known to regulate glucose homeostasis [46]. The secretion of the aforementioned growth factors could thus create a tissue microenvironment assisting endogenous β-cell regeneration and damaged islet revascularisation. However, most work to date has been carried out on rodents and islet architecture and niches are highly variable among different species [47]; thus, whether this could happen in humans remains unknown.

β-cell regeneration in humans has been suggested by observing residual β-cells in T1DM patients after onset [48] or even many years after diagnosis [49]; nevertheless, it remains unclear whether residual β-cells or the remaining endogenous precursors could be stimulated to a mass great enough to control glycaemia.

## Abrogating autoimmunity to pancreatic β-cells

Although the circumstances initiating T1DM have not been fully understood, growing evidence has shown the deregulation of innate and adaptive immune system components [50]. It has been shown that diabetes develops by dendritic cell and macrophage invasion of the pancreas, followed by CD4 and CD8 T-lymphocyte, natural killer (NK) cell and B-lymphocyte infiltration [50]. β-cell death during the course of inflammation is probably mediated by direct contact with activated macrophages and self-reactive T-lymphocytes and by exposure to soluble mediators secreted by these cells, including pro-inflammatory cytokines, nitric oxide and oxygen free radicals [51].

Following the identification of the disease's autoimmune aetiology, several immunosuppressive agents have been evaluated for preventing and/or reverting pancreatic β-cell destruction (reviewed by Waldron-Lynch et al. [52]). Such studies have shown that some patients experienced short periods of normoglycaemia without insulin treatment [52]; nevertheless, immunosuppressive drugs' chronic toxicity, a loss of

metabolic benefit after the withdrawal of immunosuppressive agents and a failure to induce a tolerant state have limited such therapies' routine use [53].

MSCs may thus prove to be useful in treating autoimmune diseases, such as T1DM, owing to their immunosuppressive and anti-inflammatory properties which could promote immunological tolerance [33,54]. MSCs have a wide range of immunomodulatory features as they can secrete anti-inflammatory cytokines and form cell-to-cell inhibitory interactions [54,55]; they can also affect dendritic cell function by inhibiting monocyte precursor differentiation [56]. MSCs thus indirectly limit NK and T-cell expansion and cytotoxic activity and also promote the appearance of regulatory T-lymphocytes, inducing antigen-specific tolerance [57].

Some studies have shown that injecting MSCs into diabetic rodents has successfully returned plasma glucose values to normal levels and increased β-cell mass [33,58-61]; they have also shown that MSCs have significantly suppressed β-cell specific T-cell proliferation in the pancreas and increased pancreatic regulatory T-cell levels. Endogenous β-cell regeneration may thus be attributable to MSC immunomodulatory properties, which could protect newly-formed β-cells from destruction by T-lymphocytes, thereby re-establishing peripheral tolerance toward β-cells.

Regarding MSC ability to migrate to damaged tissue [62], Sordi et al., have reported that the release of several chemokines by damaged pancreatic islets attracted human MSCs expressing several chemokine receptors [63]; once MSCs have been transplanted, they migrate to pancreatic islets where they can be detected for up to several weeks later [63]. Interestingly, both Fiorina et al., and our group have shown murine MSC preferential migration to secondary lymphoid organs, including pancreatic lymphoid nodes, thereby suggesting that such homing ability could be crucial in modulating an immune response [33,58]. Nevertheless, MSCs could also modulate autoimmunity from distant sites because it has been reported that MSCs embolised in the lungs improve myocardial infarction by releasing anti-inflammatory factors [64].

## MSC Administration in Treating Diabetic Complications

Chronic hyperglycaemia in diabetic patients leads to various metabolic alterations, inducing several secondary complications which are responsible for major morbidity and mortality [3]. This has prompted investigators to analyse the effect of using MSCs on glycaemic control and to evaluate its therapeutic effects regarding to secondary complications such as microvascular complications, including nephropathy, retinopathy, and neuropathy and wound healing which have been the main targets for several types of therapy involving MSCs.

### MSC-related therapy for diabetic nephropathy

Diabetic nephropathy (DN) is now the most common cause of end-stage renal failure in Western countries and the major cause of mortality in T1DM patients [65,66]. It is a multifactorial and multistage disease which is characterised by a progressive increase in albuminuria, hypertension and a decline in glomerular filtration rate [67]. It has been proposed that pathophysiological mechanisms act jointly in all renal compartments (tubulointerstitium, glomeruli and vessels), thereby leading to characteristic histological abnormalities, including mesangial cell proliferation and hypertrophy, thickening of glomerular basement membrane, podocyte loss and interstitial inflammation with fibrosis [68].

Different cells interact together to enable the kidneys to fulfil their physiological role; MSCs can differentiate, regenerate and/or protect mesangial cells [69], tubular epithelial cells [70,71], endothelial cells [72,73] and podocytes [74,75]. However, the diabetic microenvironment negatively influences MSC differentiation, proliferation, survival and homing, essentially through the effect of AGE accumulation and inflammatory mediators [76,77]. Although MSCs have been described as being renotrophic [78], engraftment frequency is scarce, suggesting that transplanted cells secrete paracrine molecules which could mediate kidney recovery [79,80].

Several pre-clinical studies using immune compromised NOD/SCID mice or STZ-induced T1DM models have shown that injecting MSCs has reduced DN progression, shown by reduced albuminuria (functional marker) and improved renal histology (structural marker) [59,81-85]. Renoprotection has been achieved without hyperglycaemia normalisation in some of these studies, thereby inferring that the therapeutic effect involved the direct MSCs action on the kidneys [81,84]. Recent studies have tried to highlight the intrinsic mechanisms involved in MSC renoprotective potential; research to date has shown that these cells essentially act through regulating oxidative stress [86], protecting podocytes from injury [83,87] and reducing inflammation and fibrosis [84,88].

The available animal models' major limitation is that they only mimic the earlier stages of DN; the impact of MSC administration on diabetic individuals exhibiting advanced signs of diabetic kidney disease thus remains unproven.

### MSC-related therapy for diabetic retinopathy

Diabetic retinopathy (DR) is the leading cause of irreversible vision loss in developed countries [89]. DR prevalence in T1DM patients in the Western world is around 28% [90] and increases dramatically with DM progression; hence, almost all T1DM patients will have a degree of DR after 20 years of DM evolution [91]. The earliest morphological change observed during the initial stages of DR is a reduced amount of pericytes in retinal capillaries [92]; this is followed by the formation of acellular-occluded capillaries, occasional micro-aneurysms, increased leukostasis and the thickening of the vascular basement membrane [93]. Such alterations progressively affect retinal microvessel integrity leading to increased vascular permeability and swelling (non-proliferative retinopathy). Further vessel deterioration during advanced stages of the disease results in poor blood flow and ischaemia, leading to the formation of new abnormal blood vessels, widespread haemorrhage and loss of vision (proliferative retinopathy) [94]. It has been well-documented that a hyperglycaemic state also affects the entire neurosensory retina, accelerates neuronal apoptosis and activates glial supporting cells, leading to reduced colour and contrast sensitivity during the early stages of the disease [95].

There is growing evidence that local inflammation and oxidative stress play pivotal roles during early and late stages of DR [96,97], thereby inducing pericyte and neuronal degeneration. MSCs could thus have a great impact on DR treatment since they can act as immunomodulatory agents and reactive oxygen species (ROS) scavengers [98]. Furthermore, due to striking similarities between MSCs and pericytes, MSCs might replace the latter, thereby compensating for pericyte loss [99]; Mendel et al., and Rajashekhar et al., have shown that adipose-derived MSCs intravitreally injected into diabetic mice were able to migrate and integrate into the retinal vasculature, leading to microvascular stabilisation and a marked reduction in capillary dropout [100,101].

Another study has shown that intravenous injection of human

adipose-derived MSCs into rats having established DR has led to improved blood retinal barrier integrity [102]; some donor cells differentiated into photoreceptor or astrocyte-like cells inside the retina of these rats [102]. A single intravitreal injection of placental-derived MSCs into diabetic rats has also resulted in a significant decrease in retinal cell apoptosis, such effect being related to increased intravitreal concentration of several neuroprotective growth factors [103].

The major limitation of available DN animal models is that they only mimic the earlier stages of DR (non-proliferative retinopathy) due to their reduced lifespan [104]; the impact of injecting MSCs into individuals exhibiting advanced signs of DR thus remains unverified.

### MSC-related therapy for diabetic polyneuropathy

Diabetic polyneuropathy (DPN) is a peripheral nervous system disorder affecting up to 60% of long-standing T1DM patients [105]; DPN patients have decreased quality of life due to chronic pain, loss of sensation in different parts of the body and chronic wounds leading to amputation [105]. The most relevant pathological findings concerning diabetic patients have included axonal atrophy, demyelination, and nerve fibre loss, reduced nerve blood flow and impaired nerve regeneration [106]. Several mechanisms have currently been proposed for linking chronic hyperglycaemia to DPN [107]; one of the main factors is the production of oxidative stress due to altered glucose metabolism. ROS accumulation increases lipid peroxidation, induces DNA and protein damage, induces cellular apoptosis and reduces nerve blood flow [108]; ROS accumulation also leads to increased expression of several genes involved in inflammatory reactions and neuronal dysfunction [109]. MSCs could thus represent an excellent therapeutic option due to their ability to act as ROS scavenger and secrete several anti-inflammatory, neurotrophic and vasculogenic factors which could promote neuron survival and the repair of damaged nerves [18,110].

Two recent studies have shown that the injection of bone marrow-derived MSCs into diabetic mice's hind limb muscles has increased several neurotrophic factor expression levels and ameliorated nerve conduction deficit [111,112]. Transplanted cells were located around the vasa nervorum in these studies and improved its vascularity. Shibata et al., have shown that intramuscular MSC injection into diabetic mice has led to the production of pro-angiogenic factors (bFGF and VEGF) and this was associated with an increased ratio between capillaries and muscular fibres, followed by increased blood flow to the nerves, improved motor nerve conduction speed and reduced hyperalgesia [113]. To our knowledge, there have been no reports showing MSC differentiation into neural cells in diabetic mice, suggesting the secretion of neurotrophic and pro-angiogenic factors as the main mechanisms associated with such potential therapeutic effect.

### MSC-related therapy for diabetic wounds

Chronic skin ulcers represent one of the most serious pathological consequences of diabetes; they are characterised by a loss of epidermal and dermal tissue [114]. About 10% to 25% of T1DM patients develop diabetic foot ulcers during their lifetime, representing a major factor contributing to amputation in these patients [115].

Around 50% of diabetic wounds are resistant to current therapies, even including the best available treatment involving chemicals, dressings and skin grafts [116]. Diabetic wound healing deficiency can be attributed to critical factors such as reduced peripheral blood flow and impaired growth factors and cytokine release by local fibroblasts and inflammatory cells, leading to a reduction in angiogenesis [117].

MSCs have been used to date in treating different skin disorders [20,118,119]; several groups have reported successful wound healing in pre-clinical models of diabetic wounds after the administration of autologous or allogeneic MSCs from different sources [120-123]. Wounds treated with MSCs in these reports have shown a qualitative improvement regarding histological characteristics, such as superior rete ridge architecture, multi-layered structure, improved dermal-epidermal junction and the formation of new skin appendage structures, such as hair follicles and sebaceous glands [120-123].

Although the mechanisms by which MSCs ameliorate skin damage have been the subject of debate for years, two theories currently offer explanations for these cells' therapeutic effects: bioactive soluble factor production (growth factors, cytokines and specific proteins) or their differentiation into dermal and epidermal cells [124,125]. Nevertheless, most studies agree that although MSCs can migrate to injury sites in response to chemotactic signals *in vivo* [126,127], only a small percentage of engrafted MSCs actually become incorporated and survive within damaged tissue [128]. On the other hand, other studies have revealed that transplanted MSCs do not necessarily have to be in close proximity to damaged tissue to promote wound repair and functional recovery, thereby suggesting that paracrine factor secretion is the main MSC therapeutic action concerned in repairing skin disorders [129,130]. This theory has been further reinforced by recent studies which have shown that allogeneic MSCs-conditioned medium has enhanced healing when administered locally into wounds [121,122,131-134].

Antibody-based protein array assays have shown that MSCs-conditioned medium contains most of the 79 human cytokines. Successful wound healing is particularly related to the secretion of trophic factors, such as VEGF, IGF-1, bFGF, PDGF-BB, Ang-1, SDF-1, EGF, KGF and MMP9, or cytokines, such as TGF-β, IL6 and IL8. These could contribute towards wound repair and skin regeneration by suppressing inflammation, angiogenesis and stimulating skin stem cell proliferation and differentiation into new keratinocytes [123,131,135-138].

## Mscs: From Preclinical Data to Clinical Practice

Despite the large amount of preclinical data supporting a therapeutic role for MSCs in β-cell mass regeneration and treating diabetic complications, few clinical trials have involved using MSCs in T1DM patients. In one such trial, Haller et al. studied the safety and efficacy of MSC-containing autologous cord blood infusion concerning DM in children. This trial recruited T1DM patients shortly after the onset of disease whose autologous cord blood was stored in private banks. There were no significant adverse effects, suggesting that cord blood infusion was feasible and safe in the aforementioned conditions [139]. The patients treated had increased peripheral regulatory T-cell level and reduced insulin requirement six months after cord blood infusion, compared to children who just received insulin therapy [139]. Nevertheless, the therapeutic effect disappeared two years after cell infusion; no patient thus achieve long-term preservation of the remaining β-cell mass [140].

The concept of immunomodulation by cord blood-derived MSCs was recently taken up by Zhao et al., who developed a novel process for re-educating patients' lymphocytes through co-culturing with allogeneic MSCs [141]. This device consisted of a stack of Petri dishes containing cord blood-derived MSCs functioning as part of a closed-loop system that circulates the patient's blood through a blood cell separator, briefly co-cultured a patient's lymphocytes with MSCs

*in vitro* and returned the lymphocytes to the patient's circulation. In this setting, through secreted and cell-surface signalling molecules, the MSCs educated the lymphocytes passing through the device. Results from this trial highlighted the fact that such treatment led to a clinically-relevant improvement in T1DM patient's metabolic control (increased C peptide levels and reduced daily insulin requirement in T1DM patients having or lacking residual β-cell mass), which lasted for months following a single treatment [141]. However, post-treatment observations regarding a larger number of patients covering a longer period of time are needed for evaluating whether the aforementioned therapeutic effects could be maintained for a longer period than that involved in the aforementioned study.

Hu et al. reported the results of a randomised controlled trial in another study aiming to evaluate the long-term effects of injecting Wharton's jelly-derived MSCs for new-onset T1DM patients. Treated T1DM patients had better glycaemic control and increased C peptide levels after two years' follow-up compared to individuals having the same age, diabetes' duration and receiving intensive insulin therapy [142]. A few more trials involving the administration of MSCs to T1DM patients to induce β-cell mass regeneration are ongoing. One of them has involved the use of allogeneic bone marrow-derived MSCs (Prochymal, a commercial formulation consisting of human MSCs harvested from healthy volunteer donors) for determining whether MSCs could halt autoimmunity progression and restore glycaemic control in newly-diagnosed T1DM patients (NCT00690066) whilst other studies have involved recruiting T1DM patients for evaluating the efficacy of transplanting autologous bone marrow-derived MSCs (NCT01157403 and NCT02057211) or autologous adipose-derived MSCs (NCT00703599). Regarding diabetic complications, one recruiting clinical trial is actively investigating MSC safety and efficacy in diabetic nephropathy (IRCT201111291414N28) and, concerning diabetic wounds, two studies have been completed with bone marrow-derived MSCs regarding ulcers in diabetic patients suffering critical limb ischemia (NCT00955669 and NCT01065337) whilst other is ongoing regarding umbilical cord-derived MSCs for diabetic foot (NCT01216865).

Our group considers that the paucity of clinical trials carried out to date has been related to remaining concerns regarding cell

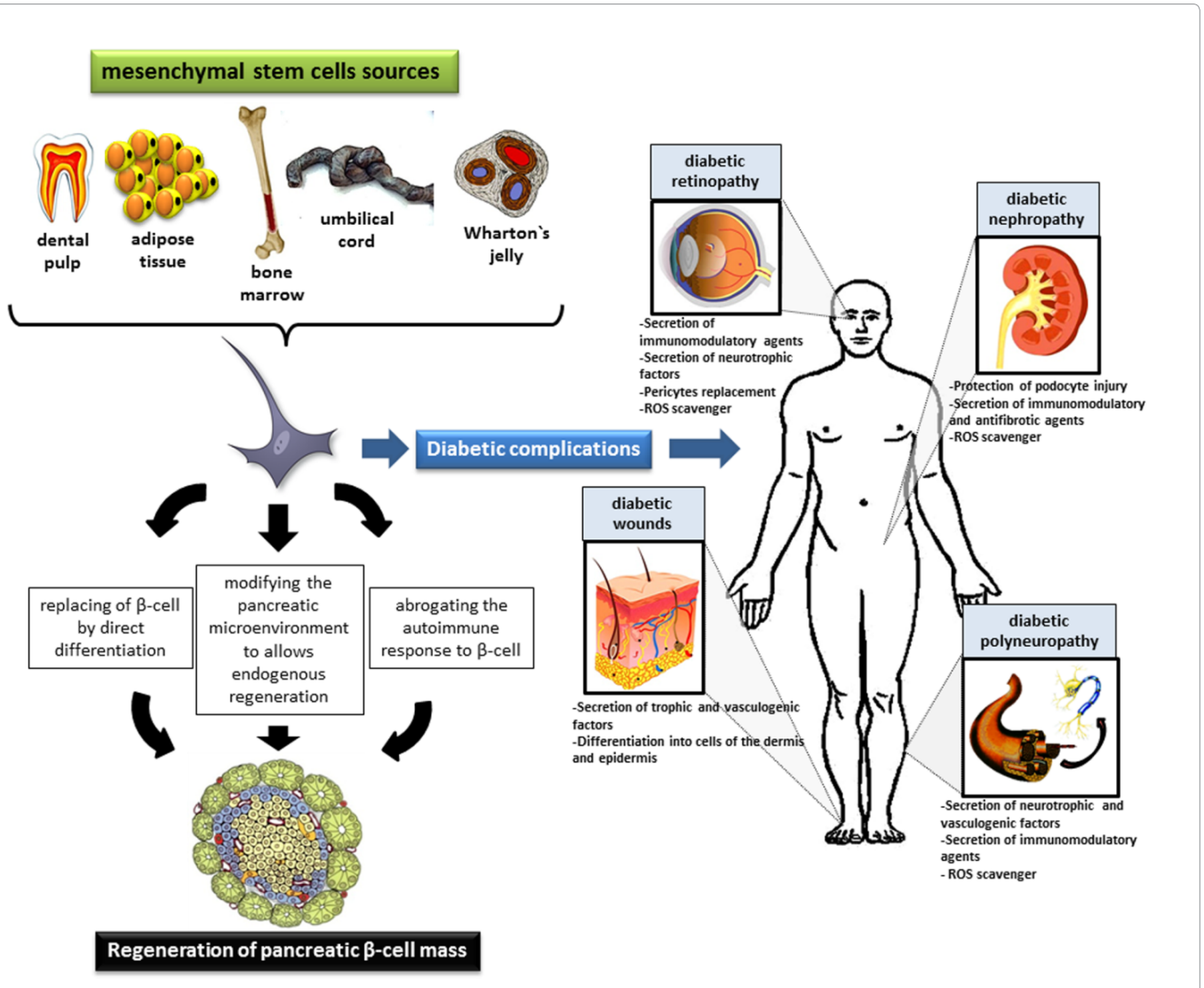


**Figure 1:** Potential role of MSCs in the regeneration of pancreatic β-cell mass and in controlling diabetic microvascular complications.

therapy strategies which still need to be addressed. The effectiveness of a patient's own cells needs to be evaluated, considering that MSCs derived from diabetic subjects may have reduced therapeutic potential [77]; experiments involving the use of autologous cells are necessary for addressing this concern. Cell therapy's long-term effects must be tested; given that T1DM and diabetic complications progress over a long period of time, a single administration of MSCs may not be enough to maintain any therapeutic effect over a long period of time. Furthermore, since stem cells are being used on human patients, safety is an especially relevant concern regarding tumour induction through spontaneous malignant transformation of MSCs or by promoting tumour development and growth. Compared to other types of stem cell (embryonic stem cells or induced pluripotent stem cells), MSCs have a better biosafety profile and lower risk of tumorigenicity [143]. Cultured MSCs have usually shown progressive senescence and growth arrest without tumour formation [144]; however, such cells may still acquire genetic abnormalities and become tumorigenic *in vivo* due to the many rounds of replication which they undergo before being transplanted into patients [145]. In this sense, Jeong et al. found that the transplantation of bone marrow-derived MSCs into STZ-induced diabetic mice frequently induced tumour formation at the injection site [146]. One way of circumventing this problem has been to encapsulate cells within a barrier allowing the diffusion of nutrients but not larger molecules, antibodies or cells; encapsulation can be configured using many different polymers, methods and sizes [147] and has the theoretical advantage of protecting cells from an immune attack but also avoiding the dissemination of potentially-oncogenic derivatives.

A better understanding of therapeutic mechanisms and careful assessment of the efficacy of clinical trials are also needed.

## Conclusion

MSCs have been shown to have the potential for revolutionising the treatment of many chronic diseases, including T1DM and its main complications. Progress made to date in understanding normal pancreas development has been crucial in formulating protocols aimed at directing MSC differentiation into insulin-producing cells *in vitro*. However, the feasibility and scalability of such attempts for achieving the final goal of large-scale β-cell replacement are still questionable; even with an abundant supply of MSCs-derived β-cells these will likely be targets for persistent autoimmune response in T1DM patients. Any efforts at replacing β-cells will thus require an additional approach for dealing with recurrent autoimmunity. MSC immunomodulatory properties are thus very useful since they could reduce self-reactive lymphocytes causing inflammatory damage to newly-formed β-cells. MSC ability to secrete trophic and angiogenic factors may also restrict islet damage by establishing a microenvironment which stimulates β-cell growth, survival and differentiation (Figure 1).

MSCs' beneficial roles could also be very useful in treating the main T1DM-associated complications where the reduction of parenchymal cells, inflammation and changes in the microenvironment are the main effectors concerning tissue damage, thereby making MSCs an effective tool for the comprehensive treatment of diabetic patients (Figure 1).

T1DM is undoubtedly a terrible, lifelong disease, involving substantial short-term and long-term complications. Insulin is fairly effective in combating it, albeit a cumbersome and imperfect therapy. Ongoing discussion thus concerns the level of risk doctors and patients are willing to accept in order to achieve a potential cure; it is expected that any new therapeutic approach (including cell therapy) must be associated with a low-risk profile, especially when being considered for use in children. Regarding such decision, further clinical trials will be critical for evaluating whether clinical benefits motivate the risk of assuming adverse effects and which patients would be most suitable for this kind of therapy.

Even though considerable challenges lie ahead, ongoing advances in the field make an effective MSC-therapy for T1DM and its main complications a realistic goal for the near future.

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