

# Mesenchymal Stem Cells for the Treatment of Diabetes

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**T**he field of regenerative medicine is rapidly evolving, paving the way for novel therapeutic interventions through cellular therapies and tissue engineering approaches that are reshaping the biomedical field. The remarkable plasticity of different cell subsets obtained from human embryonic and adult tissues from disparate sources (including bone marrow, umbilical cord, amniotic fluid, placenta, and adipose tissue) has sparked research endeavors evaluating use of these cells for numerous conditions, including diabetes and its complications (1).

A readily accessible source for multipotent stem cells is the bone marrow, which comprises progenitors of hematopoietic, endothelial, and mesenchymal stem cells (MSCs). Unfractionated and fractionated bone marrow-derived stem cells have been used in experimental and clinical settings to improve diabetes and diabetes complications. Bone marrow-derived MSCs are stromal, nonhematopoietic cells generally obtained from iliac crest aspirates following enrichment based on their preferential adhesion on culture vessels in defined media. MSC characterization relies on expression of specific surface markers and on their ability to differentiate into fat, bone, and cartilage when exposed to appropriate culture conditions (2).

Recent clinical trials have demonstrated powerful immunomodulatory effects of the inoculum of MSCs to treat graft-versus-host disease (3,4), to improve allogeneic renal transplant outcomes using lower immunosuppressive regimens (5), and to reduce immune cell activation in patients with multiple sclerosis and amyotrophic lateral sclerosis (6). Autologous MSCs were shown to improve Crohn disease lesions refractory to other therapies (7,8) and were tested for treatment of ischemic hearts (9).

In the context of diabetes research, MSCs have been used to generate insulin-producing cells (10), counteract autoimmunity (11,12), enhance islet engraftment and survival (13,14), and to treat diabetic ulcers and limb ischemia (15). Also, MSC inoculum improved metabolic control in experimental models of type 2 diabetes (T2D) (16). Non-randomized, pilot trials in T2D suggest a positive impact of bone marrow-derived mononuclear cells on metabolic control (i.e., reduction of insulin requirements and of A1C values) in the absence of adverse events following intra-arterial injection by selective cannulation of the pancreas vasculature (17,18). Unfortunately, because these

studies are small and lack in-depth mechanistic analyses, it is yet unknown how MSCs exert their beneficial effects in T2D.

The interesting study by Si et al. (19) attempts to understand the effects of autologous MSC inoculum in a rat model of T2D (induced by high-fat diet for 2 weeks followed by a suboptimal dose of the  $\beta$ -cell toxin streptozotocin [STZ] to induce a hyperglycemic state). Autologous MSCs were administered either 1 or 3 weeks after STZ treatment. Improved metabolic control, measured by enhanced insulin secretion, amelioration of insulin sensitivity, and increased islet numbers in the pancreas, was observed in animals receiving MSCs particularly when MSCs were given early (7 days) after STZ treatment. Consistent with previous reports, the metabolic effects of MSC inoculum were short-lived (for a period of 4 weeks), and reinoculum provided an additional, comparable, and transient effect.

Clamp studies demonstrated significantly improved blood glucose metabolism and insulin sensitivity in animals receiving MSC therapy. A set of novel mechanistic data emerging from this study indicates that MSC therapy is associated with improved insulin sensitivity via increased signaling (insulin receptor substrate-1 [IRS-1] and Akt phosphorylation upon feeding, as well as translocation of GLUT-4 on cell membrane upon insulin administration) in the muscle, liver, and adipose tissue of animals receiving MSC inoculum, when compared with controls. Although many questions remain unanswered, these data shed new light on the effects of autologous MSC inoculum on insulin target tissues in this rodent model of T2D.

It is important to consider the potential confounding elements that can be introduced by the disease model used in this and other similar studies. In the model used by Si et al., it is prudent to be cautious because of the relatively short duration of diabetes before initiation of the intervention. This model may not fully reflect the physiopathology of the progressive development of human T2D.

Si et al. (19) present important data that highlight the importance of a cautious interpretation of the results of their T2D model. For instance, the positive impact of MSC treatment on metabolic function was more pronounced when administered early (7 days) than late (21 days) after induction of diabetes. STZ is a naturally occurring nitrosourea with various biological actions as well as induction of acute and chronic cellular injury on several tissues, including pancreatic  $\beta$ -cells, liver, and kidney. In the animals receiving labeled MSC inoculum "early" after STZ (but not in those in the "late" STZ group), MSCs accumulated in pancreatic islets and liver where they may have contributed to tissue repair or remodeling, thereby mitigating the injury induced by STZ and a high-fat diet and improving metabolic function. Preservation of  $\beta$ -cell mass was also observed in the "early" MSC group, an observation that did not appear to result from increased replication (assessed by Ki67 immunoreactivity), but rather from tissue repair and the cytoprotective properties of MSCs.

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MSCs offer new opportunities in the treatment of diabetes, but they also raise many scientific questions that need to be addressed, particularly those related to safety and efficacy. These issues have obvious implications for the clinical application of MSC and other innovative cellular therapies.

Further in-depth mechanistic studies are needed to understand how MSCs affect metabolic function in T2D and to help overcome the transient results that have been observed in several studies. It remains to be determined whether the diabetic microenvironment and/or comorbidities alter the quality or efficacy of MSCs isolated from and/or after inoculum in patients with diabetes (20). Identity, stability, potency, and safety of cellular products are of paramount importance in order to obtain reproducible results and prevent undesirable side effects.

The increasing body of evidence on the potential therapeutic properties of MSCs justifies cautious optimism concerning development of effective cellular therapies for treatment of diabetes in the future.

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