

Diabetes duration and obesity matter in autologous mesenchymal stem/stromal cell transplantation in type 2 diabetes patients

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Type 2 diabetes develops as a result of functional β -cell loss after insulin resistance. Sustained increased insulin demand compels β -cells into apoptosis and dedifferentiation resulting in decreased β -cell mass. In adults, β -cell regeneration (proliferation, neogenesis or transdifferentiation) rarely occurs in a physiological condition. Because of this stagnant nature of β -cells, β -cell mass is not sufficiently recovered once their numbers are severely decreased. Constant efforts have been made to replenish the decreased β -cell mass in diabetes patients by islet or pancreas transplantation^{1,2}. However, donor shortage and constant immunosuppressant use remain as critical hurdles to clinical application of these allogenic β -cell transplantations. To overcome these hurdles, embryonic/induced pluripotent stem cell-derived β -cell transplantation, xenotransplantation or mesenchymal stem cell transplantation have been extensively studied.

Bone marrow is an attractive source of stem cells in future regenerative medicine. Because of its accessibility and immune tolerance when autologously transplanted, bone marrow-derived stem cells can be an ideal source of β -cells for insulinopenic diabetes patients. Indeed, bone marrow-derived stem cells can be differentiated into insulin-producing cells *in vitro*³. Importantly, Hess *et al.*⁴ showed that autologous bone marrow-derived stem cell transplantation can ameliorate hyperglycemia in diabetic mouse models. In that study, the authors showed that intravenously injected bone marrow-derived stem cells engraft to the damaged islet or ductal structures in the pancreas and differentiate into insulin-producing cells in diabetic mice. This scientific evidence encouraged clinical research that supported the human relevance of autologous bone marrow-derived stem cell treatment in diabetes patients⁵⁻⁷. In these clinical studies, human diabetes patients were safely treated with bone marrow-derived mononuclear or mesenchymal stem

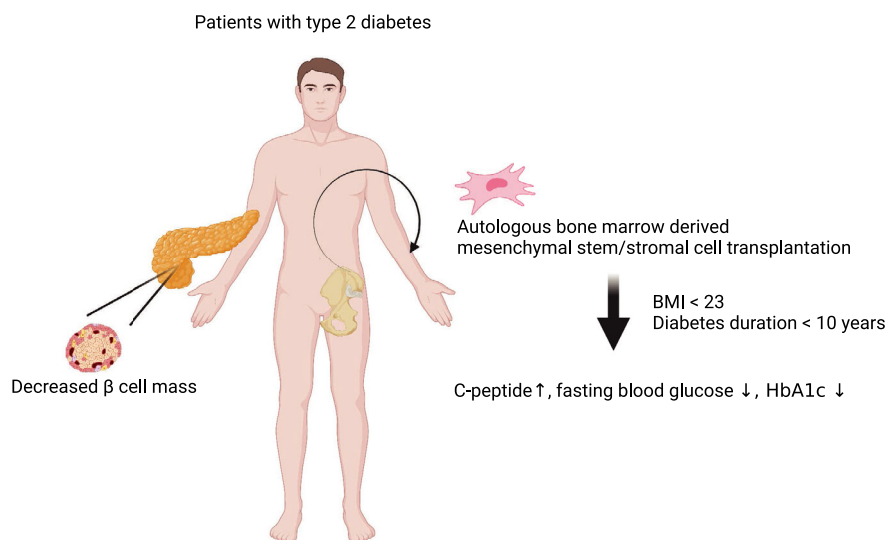


Figure 1 | Autologous bone marrow-derived mesenchymal/stromal stem cell transplantation can safely ameliorate hyperglycemia and restore C-peptide levels in patients with type 2 diabetes. The autologous stem cell transplantation was more effective in patients whose body mass index (BMI) was <23 and diabetes duration was <10 years. HbA1c, glycated hemoglobin.

cells^{5,6}. However, the degree and duration of the glucose-lowering effect by autologous transplantation of bone marrow-derived mesenchymal stem cells (BM-MSC) in type 2 diabetes patients varied between studies^{8–11}. These conflicting results suggest that some subpopulations of type 2 diabetes patients might benefit more from autologous BM-MSC transplantation. However, how the patient characteristics affect the efficacy of autologous BM-MSC transplantation has been poorly understood.

Recently, Nguyen *et al.*¹² published an interesting study that evaluated the safety and efficacy of autologous transplantation in type 2 diabetes patients. In that study, the authors enrolled 30 type 2 diabetes patients and randomly assigned them to two groups differing by the stem/stromal cell delivery route (intravenous, dorsal pancreatic artery), and assessed the safety and efficacy for 12 months. The safety and efficacy of autologous stem/stromal cell transplantation were comparable in both groups. Hyperglycemia ($n = 3$), hypoglycemia ($n = 1$), abdominal pain ($n = 3$), splenomegaly ($n = 1$), insomnia ($n = 1$), vomiting ($n = 1$), headache ($n = 1$) and hypertension ($n = 1$) were the most significant side-effects. No severe adverse event was observed. Although the clinical outcome did not differ by the delivery route, the patient characteristics significantly affected the efficacy of autologous stem/stromal cell transplantation. Importantly, patients with diabetes duration <10 years and body mass index (BMI) <23 showed a better clinical outcome after autologous bone marrow-derived stem cell transplantation than the other subgroup of diabetes patients (Figure 1). The duration of efficacy ranged from 3 to 6 months. To explain the mechanism of different clinical outcomes depending on the patient characteristics, the authors analyzed the BM-MSC from a different subpopulation of type 2 diabetes patients. The authors showed that BM-MSC from a longer duration of diabetes had some comparable stem cell characteristics, but decreased proliferative capacity. From these results, the authors suggest that autologous BM-MSC transplantation in type 2 diabetes patients is safe and that it should be carried out in patients with BMI <23 and diabetes duration <10 years.

This study is interesting in the sense that it provides a reasonable answer to the previous conflicting results regarding the efficacy of autologous BM-MSC transplantation. The altered proliferative capacity of BM-MSC depending on the patient's characteristics is valuable information for future diabetes research.

This study also provides a novel insight regarding the timing of intervention for β -cell regenerative therapy. Conventionally, β -cell replenishment therapy has been regarded as a therapy for those whose β -cell function is severely decreased. In diabetes treatment, early intervention (early intensive insulin therapy, early combination therapy) has shown benefits to achieve long-term stable glycemic control^{13,14}. Likewise, this research suggests that type 2 diabetes patients might benefit from early β -cell replenishment therapy. However, as not all diabetes

patients require β -cell replenishment therapy, a careful selection of diabetes patients who can benefit from early β -cell replenishment therapy should be of future interest.

In this article, the authors have well characterized the altered characteristics of BM-MSC by the diabetes duration. However, the impaired proliferative capacity of BM-MSC might not fully explain the different efficacy of autologous BM-MSC by the patient's characteristics. Studies evaluating how diabetes duration or BMI affect the differentiation capacity of BM-MSC into insulin-producing cells or efficiency of engraftment will be of interest in future research. Functional β -cell mass declines as diabetes progresses and BMI correlates to insulin resistance. For this reason, future studies evaluating how remnant β -cell mass (partial pancreatectomy, rat insulin promoter specific diphtheria toxin receptor expressing mouse) or insulin resistance (high fat diet, insulin receptor antagonist) affect the efficacy of autologous BM-MSC transplantation should be followed.

Of note, the BM-MSC-induced glucose-lowering effect was marginal, and the duration of efficacy was relatively short (3–6 months). High efficacy *ex vivo* differentiation of BM-MSC before autologous transplantation or *in vivo* medical intervention to enhance the BM-MSC engraftment or BM-MSC differentiation to β -like cells should be studied in the future.

In conclusion, this study provides valuable information regarding the efficacy and safety of autologous BM-MSC transplantation in type 2 diabetes patients. This study also leaves many important questions for future research. A carefully designed translational study should be carried out. The path to future regenerative medicine for diabetes still seems challenging, yet promising.

DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: N/A.

Informed consent: N/A.

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Animal Studies: N/A.

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