

Mesenchymal stem cells transplantation reduces diabetic nephropathy

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ABSTRACT

Diabetes mellitus is a metabolic disease in which the pancreas is unable to produce enough insulin due to the destruction of β -cells or the body does not utilize insulin properly. Continuous fluctuation of blood glucose levels is responsible for prolonged complications such as diabetic nephropathy (DN), diabetic retinopathy, or diabetic cardiomyopathy. Approximately, 20-30% of all diabetic patients face DN, which causes the formation of diabetic glomerular lesions and reduced glomerular filtration rate. In the case of renal failure, kidney transplantation is the only available therapy, however, it is expensive and almost unattainable due to unavailability of donors and host immune rejection. Stem cells are an alternative and attractive source of therapy because of their proliferative nature and the ability to produce distinct specialized cells. Mesenchymal stem cells (MSCs), which are derived from bone marrow, possess an anti-inflammatory property and the ability of self-renewal and differentiation into a variety of specialized cells. MSCs are widely used to treat different diseases including DN and they have shown encouraging outcomes. This review provides details about the regenerative efficiency of using MSCs in treating diabetic nephropathy.

Key words: Diabetes mellitus, Diabetic Nephropathy, Stem cells, Regeneration, Mesenchymal stem cells

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INTRODUCTION

Diabetes mellitus is a metabolic/ autoimmune/ hormonal/ endocrine disease consisting of elevated blood glucose levels. It is considered as an outbreak with a constant increase both in ratio and frequency around the globe¹. The number of patients with diabetes in 1980 was 108 million, which rose up to 415 million in 2015, and is estimated to reach 642 million by 2040². In 2012, 1.5 million deaths were reported from all over the world due to diabetes. Globally, diabetes was the eighth foremost cause of death among both males and females and was the fifth leading cause of death in women in 2012³. There are two types of diabetes mellitus, type 1 (T1D) and type 2 (T2D). T2D is the most common form of diabetes and 90-95% of people are affected with T2D. It is usually developed due to the permutaion of auxiliary insulin opposition which progressively damages pancreatic β -cells and leads to complete failure of endogenous insulin secretory cells. Chronic high blood glucose leads to complications including macroangiopathy and microangiopathy, retinopathy, chronic nephropathy, peripheral and central neuropathy, and cardiomyopathy⁴. At the starting phase of T2D, insulin opposition can be a coup but it ultimately requires exogenous insulin against functional β -cells exhaustion. 5-10% of people are affected by T1D at a younger age and require

acute exogenous insulin therapy. Regrettably, though exogenous insulin therapy may hold up disease progression, it does not eliminate the risk of the disease's chronic convolution⁵.

In pharmacologic therapy, different drugs are developed to control blood glucose levels, blood pressure and obstruction of the renin-angiotensin-aldosterone system (RAAS), however, these strategies only slow the progression of renal damage⁶.

Podocytes show a high level of constitutive autophagy, a passageway in which altered proteins, as well as organelles, are transported to lysosomes that represent a defensive system against podocyte aging and glomerular damages⁷. Therefore, modulating autophagy represents a useful therapeutic way to slow the succession of DN.

All these strategies can only delay the progression of renal damage but cannot stop or reverse renal damage due to diabetes. Stem cells (SCs) based therapies are expected to bring significant advantages to patients suffering a broad range of diseases and injuries. Various types of stem cells are found in the body and can be utilized for the treatment of numerous diseases (Figure 1).

Stem cells are widely used for the regeneration of cells/tissues damaged due to chronic diseases because of their unique properties:

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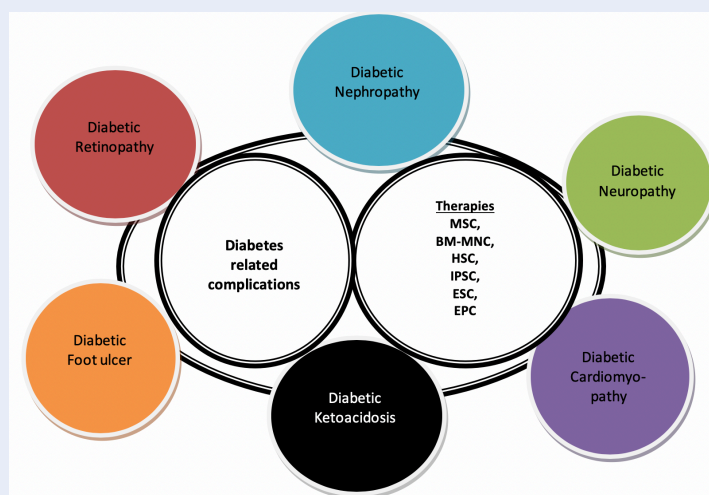


Figure 1: Therapeutic options for vascular complications in diabetes by Stem Cells Mesenchymal stem cell (MSC); Bone marrow-derived mononuclear cell (BM-MNC); Hematopoietic stem cell (HSC); Induced pluripotent stem cell (iPSC); Embryonic stem cell (ESC); Endothelial progenitor cell (EPC).

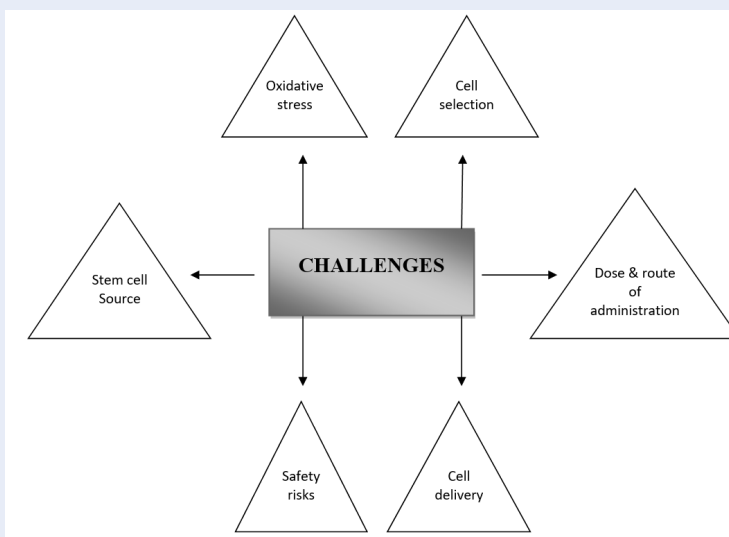


Figure 2: Challenges during stem cell therapy.

(i) self-renewal (capability to generate symmetric daughter cells),
 (ii) long-term viability and
 (iii) potentiality to produce distinct specialized cells⁸.
 However, the selection of stem cell types, techniques of cell isolation, culturing and injection into a patient are delicate and require expertise. Challenges faced during stem cell therapy are mentioned in **Figure 2**.

Table 1: Biomarkers used for monitoring MSC in Diabetic Nephropathy

Animal model used	MSC isolation	Number of cells injected	Biomarkers	Results	References
Sprague-Dawley rats	BM-MSCs	2×10^6	Nephrin and podocin, podocyte survival factors (VEGF and BMP-7)	↓ blood glucose levels and albuminuria Improvement in renal mass indication	9
BALB/C mice	BM-MSCs	2×10^9	nephrin, CD2AP, synap-topodin, TRPC6	↓ Urine protein excretion and foot process fusion, protect podocytes from PAN damage	10
C57BL/6 mice, male Sprague-Dawley rats, OLETF rats, and LETO rats	BM-MSCs	1×10^4	Igf-1, Ifn- γ , IL-1 β , IL-2, Rantes, and α -Sma	Umbilical cord extract ↑ therapeutic effect of BM-MSC and reduces renal damage	11
Wistar rats	BM-MSCs	2×10^6	IL-1 β , IL-6, TNF α , and hepatocyte growth factor (HGF)	Inhibition of MCP-1 expression by secreting HGF, ↓ macrophages infiltration, down-regulating IL-1 β , IL-6, TNF α expression in renal tissue	12
Sprague Dawley rats	BM-MSCs	2×10^6	Expressions of PAI-1, TGF- β 1 and Smad3 were detected	↓ the expression of PAI-1 protein, ↓ the accumulation of extracellular matrix and fibrosis	13
Albino rats	BM-MSCs	10^6	TGF β , TNF α , bcl2 and Bax	Improved urinary albumin, serum urea, and creatinine concentration, ↑ VEGF, and Bcl2 while ↓ TNF- α , TGF β , and Bax.	14
C57BL/6 and C57BL/6-Tg mice	BM-MSCs	0.5×10^6	The expression level of type I collagen, TGF-beta1, laminin-beta1, fibronectin, nephrin, bFGF, EGF, HGF, IL-4, IL-10, and GAPDH was detected	MSCs preserved renal function	15
NOD/scid mice	h-BM-MSCs	2.5×10^6	RT-PCR assay performed with 200 ng of target DNA, Alu-specific primers, and a fluorescent probe	↑ pancreatic insulin content and islet cell number ↓ renal macrophage infiltration Improvement in renal histology	16
C57BL/6 mice	BM-MSCs	0.5×10^6	-	↓ blood glucose levels ↓ albuminuria and glycosuria	17

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Table 1 continued

C57BL/6 mice	BM-MSCs	0.5×10^6	-		↓ albuminuria Improvement in renal histology No improvement in β -cell function and histology	18
Sprague-Dawley Rats	ADMSCs	1×10^7	p-ERK, p-JNK, p-p-38		↓ renal p-p-38, p-ERK and p-JNK ↓ renal MDA and carbonyl protein ↓ renal TNF- α , IL-1 β , IL-6 ↓ renal MnSOD and CuZn-SOD	19
Sprague-Dawley Rats	h-UCB-SCs	1×10^6	Fibronectin, α -SMA, E-cadherin		↓ blood glucose levels ↓ albuminuria ↓ renal fibronectin, α -SMA ↑ renal E-cadherin	20
Sprague-Dawley Rats	h-UCB-SCs	5×10^5	TGF- β 1, α -SMA, E-cadherin, BMP-7		↔ blood glucose levels ↔ albuminuria Improvement in renal histology ↓ renal TGF- β 1, α -SMA ↑ renal E-cadherin, BMP-7	21
Sprague-Dawley Rats:	BM-MSCs	1×10^6	TGF- β 1, synaptopodin, and IL-10		↓ blood glucose levels ↑ plasma insulin Attenuated β -cell damage ↓ albuminuria ↓ renal TGF- β 1 ↑ renal synaptopodin, IL-10 After UTMD: MSC homing was increased to kidneys (~2x) Permeability of renal interstitial capillaries and VCAM-1 expression ↑ after UTMD	22
Wistar rats	BM-MSCs	2×10^6	Fibronectin, Collagen 1, TGF- β 1		↓ renal fibronectin and collagen I ↓ renal MDA content ↓ renal TGF- β 1 ↓ renal ROS fluorescence ↑ renal SOD activity ↓ cellular glucose uptake mediated by GLUT1 in kidneys	23
Female Wistar rats	BM-MSCs	2×10^6	collagen I, collagen IV, α -SMA, TGF- β , P-smad3/sm2/3, E-cadherin, BMP7		↓ renal collagen I, collagen IV, α -SMA, TGF- β , P-smad3/sm2/3 ↑ renal E-cadherin, BMP7	24
Sprague-Dawley Rats	BM-MSCs	1×10^6	-		Improvement in renal histology	25
	(SDF-1-loaded microbubbles)					

Continued on next page

Table 1 continued

Male Sprague-Dawley (SD) rats	ADMSCs	1×10^5	Bax -3, Bcl-2, klotho	<div>↓ the rate of cellular apoptosis, ↓ Bax and Wnt/β-catenin levels, ↑ Bcl-2 and klotho levels. klotho knockdown reversed the effects of ADMSCs on the expression of apoptosis-related proteins and Wnt/β-catenin pathway members.</div>	<div>26</div>
male albino rats	BM-MSCs	1×10^6	-	<div>blood glucose level was improved, renal function was retained, body weight loss was ↓, insulin level and HBA1C percentage were ameliorated with improved oxidative stress in kidney tissue</div>	<div>27</div>

MESENCHYMAL STEM CELLS (MSCS)

MSCs are multipotent in nature and can be obtained from different sources. Many preclinical studies have demonstrated that mesenchymal stem cells (MSCs) enhance the regenerative wound microenvironment. In different animal models, full thickness excisional wounds²⁸, diabetic foot ulcers²⁹, pressure ulcers³⁰ and burn injuries³¹ can be treated by the administration of MSCs, which improves wound healing by the accelerated wound closure, reduced scarring, promoted collagen synthesis, angiogenesis, and improved tensile strength.

Advantages of MSCs for therapeutic uses include simple culturing technique, multilineage repopulation (differentiation), the potential of immunosuppressive effects, protection after inoculation of allogeneic cells and no ethical problems that transpire in case of human ESC application. Previous studies on disease models and clinical trials showed a positive therapeutic value of MSCs. MSCs can be isolated from different sources such as bone marrow, adipose tissues³², umbilical cord blood³³, peripheral blood³⁴ and amniotic fluid³⁵. However, bone marrow is the richest source of MSCs. Previous studies showed that MSCs can differentiate into insulin-producing β -cells³⁶, mesangial cells³⁷, tubular epithelial cells³⁸, endothelial cells, and podocytes³⁹. Due to its effectiveness and safety, allogeneic MSCs are also used in the treatment of acute kidney injury, clinical trials and cardiomyopathy patients, who are at elevated risk of post-operative chronic kidney diseases⁴⁰.

MESENCHYMAL STEM CELLS FOR DIABETIC NEPHROPATHY

Diabetic nephropathy is one of the complications of diabetes mellitus, which leads to end-stage renal damage in extreme case⁴¹. Around 25–40% of diabetic patients will develop DN. Until now, therapies for DN remain limited and none of them can completely reduce the risk of developing DN. Nowadays, the full renin-angiotensin system blockage, strict blood glycemic and lipid control are the main treatments of DN. On the other hand, DN gives rise to kidney failure, which requires kidney transplantation and inflicts huge medical and socio-economic encumbers⁴². There is an instant need to develop a regenerative strategy for which MSCs play a vital role⁴³. In animal models, streptozotocin (STZ) was induced to cause T1D in mice. Toxicity of streptozotocin was reduced by the administration of MSCs, which regenerated damaged nephrons due to DN and resulted in enhanced renal and pancreatic function⁴⁴. Injection

of human-derived MSCs in NOD/SCID mice reduced both mesangial thickening and macrophage infiltration⁴⁵.

Transplantation of MSCs enhanced proteinuria and podocyte injury in T1D rat model. The effect of MSCs on the regeneration of glomerular podocyte injury was investigated on Sprague-Dawley rats, the diabetic model was developed by the induction of STZ injection (65 mg/kg, intraperitoneally). Nephron and podocin expression levels, two major proteins involved in the formation of incision diaphragm were investigated. MSC injection extensively reduced diabetic-induced glomerular nephron and podocin expression. Most importantly, MSC injection increased BMP-7 but not VEGF levels (BMP-7 and VEGF are podocyte survival factors). The intra-arterial administration of MSCs averted the progression of albuminuria and the impairment of podocytes, although blood sugar levels were not improved. MSC protective role may be intervened by the rise of BMP-7 secretion⁹.

MSC administration enhanced kidney weight, renal to body weight index, urinary albumin to creatinine ratio and clearance in rats, moreover, the loss of podocytes was reduced. MSC therapy also eliminated foot processes and its widening, glomerular basal membrane thickening, and glomerular nephron and podocin loss. Similar results were observed when MSCs and ciclosporin A were injected intracardially in combination in rats⁴⁶.

In another study, MSCs were used to treat impaired podocytes by the induction of PAN (0.5 mg/g weight) in BALB/C mice via tail vein. The expressions of nephron, CD2AP, synaptopodin and TRPC6 were investigated. After administration of BMSCs, the expression of nephron, CD2AP, and synaptopodin was up-regulated, while TRPC6 was down-regulated. Administration of BMSCs reduced excretion of protein through urine and protected podocytes from deleterious effects of PAN¹⁰.

In a novel study, BM-MSCs along with human umbilical cord extract were used to enhance the proliferative capability of BM-MSCs against DN. The therapeutic potential of BM-MSCs was reduced in diabetic patients due to oxidative stress, while umbilical cord extract contained different growth factors, extracellular matrices, and exosomes, which enhanced the proliferation of BM-MSCs. The relative mRNA expression of *Igf-1* was downregulated, whereas *Ifn- γ* , *Il-1 β* , *Il-2*, and *Rantes* were up-regulated in treated rats as compared to controls. The expressions of α -Sma, which represented the stress fiber of MSCs, was also increased¹¹.

The mechanism of the renoprotective role of MSCs was not clear until a study showed a relationship between MSCs and macrophages in diabetic nephropathy. The hepatocyte growth factor (HGF) and pro-inflammatory cytokines expression at molecular and protein levels were studied, and animal groups administrated with MSCs showed elevated expression of HGF. Meanwhile, the expressions of IL-1 β , IL-6, and TNF α were extensively decreased. The results explained that in diabetic rats, MSC transplantation minimized DN through HGF secretion, which inhibited MCP-1 expression and reduced macrophages infiltration in renal tissue¹².

In rats, the effect of BMSCs on PAI-1 and renal fibrosis with DN was studied. Expressional levels of PAI-1, TGF- β 1 and Smad3 genes in a kidney of rat model were determined; in control group, the expression of PAI-1, TGF- β 1 and Smad3 were down-regulated as compared to the DN group. The pathway may be associated with the inhibition of TGF- β 1/Smad3 as the expression of PAI-1 protein was decreased and the accretion of ECM reduced, thus, balancing the fibrinolytic system¹³.

CONCLUSION

It is reported that MSC isolation methods in different laboratories or from different donors are highly diverse. Cell passage and *in vitro* culture conditions affect the phenotypes of bone marrow-derived MSCs. Moreover, aging and aging-related disorders drastically impair the survival and proliferative and differentiation potential of BM-MSCs, which limits its therapeutic efficiency. In diabetes, reactive oxygen species are generated, which affects the regenerative properties and survival of stem cells in patients with diabetes. The microenvironment under diabetic conditions is harsh for stem cells to survive or migrate to the targeted site and exert their reparative functions. Limited synthesis of proteoglycans and glycosaminoglycans in the surrounding environment causes minimal proliferation and viability of MSCs *in vivo*. The production of advanced glycosylated end products also inhibits proliferation of MSCs by activating apoptotic mechanism and reactive oxygen species production. In diabetic patients, oxidative stress may also influence the paracrine effects of MSCs under hypoxic conditions. In addition, the migratory capacity of MSCs is also impaired. High osteoprotegerin in diabetic patients neutralizes the pro-migratory activity of TNF-related apoptosis-inducing ligands, which promotes the migration of bone marrow stem cells.

The current review is based to summarize the work done for treatment of diabetic nephropathy and the gaps available for research. Accordingly, the use of antioxidants, growth factors or hormones along with MSCs in optimal combinations and concentrations will be appreciated.

FUTURE PROSPECTS

Stem cell-based therapy holds promising treatments for DN. Although kidney-specific stem cells have been identified in recent years, the involvement of these stem cells in the regeneration of the kidney is still in doubt. It is required to continue seeking a better and ideal cell source or to develop optimized manipulation methods for existing cells to treat DN. No matter whether the target is podocytes, PTECs or other cell types in DN, the ideal cell candidate for cell replacement should have the following properties: easy access with no safety or ethical issues, high survival rate during diabetic stress and differentiation potential into the desired cell types both *in vitro* and *in vivo*. Recently, iPSCs generated from somatic cells as well as functional kidney cells and tissues differentiation from pluripotent stem cells (ESCs and iPSCs) provide a wonderful platform to explore disease mechanisms and potential cell sources. However, the safety issue remains unsolved. Criteria for the validation of induced renal progenitor cells need to be established. The tumorigenic property of iPSCs based on viral transduction technology must be eliminated before clinical transplantation. The development of iPSCs without viral vectors might be helpful in the generation of iPSCs from an autologous source.

Bone marrow-derived MSCs remain an attractive autologous cell source mainly due to the ease of harvesting and their low immunogenicity. USCs or urine-derived iPSCs from DN patients might also serve as a suitable source of cells for investigating the pathogenetic mechanisms, screening new treatments and offering possibilities for future personalized regenerative therapies.

COMPETING INTERESTS

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

All the authors contribute equally to this paper.

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