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REVIEW ARTICLE

Mesenchymal Stem Cell-Based Therapies against Podocyte Damage in Diabetic Nephropathy

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Abstract Injury to podocytes is an early event in diabetic nephropathy leading to proteinuria with possible progression to end-stage renal failure. The podocytes are unique and highly specialized cells that cover the outer layer of kidney ultrafiltration barrier and play an important role in glomerular function. In the past few decades, adult stem cells, such as mesenchymal stem cells (MSCs) with a regenerative and differentiative capacity have been extensively used in cell-based therapies. In addition to their capability for regeneration and differentiation, MSCs contributes to their *milieu* by paracrine action of a series of growth factors *via* antiapoptotic, mitogenic and other cytokine actions that actively participate in treatment of podocyte damage through prevention of podocyte effacement, detachment and apoptosis. It is hoped that novel stem cell-based therapies will be developed in the future to prevent podocyte injury, thereby reducing the burden of kidney disease.

Keywords Mesenchymal stem cells · Podocyte damage · Diabetic nephropathy · Kidney ultrafiltration · Glomerular function

Abbreviations

AD-MSCs	Adipose-derived mesenchymal stem cells
Ang II	Angiotensin II
ASCs	Adult stem cells
bFGF	Basic fibroblast growth factor
BM-MSCs	Bone marrow mesenchymal stem cells
BMP-7	Bone morphogenetic protein-7
DN	Diabetic nephropathy
EGF	Epidermal growth factor
ERK	Extracellular signal-regulated kinase
ESCs	Embryonic stem cells
FGF2	Fibroblast growth factor 2
FM-MSCs	Fetal membranes mesenchymal stem cells
GBM	Glomerular basement membrane
GDNF	Glial cell-line derived neurotrophic factor
HGF	Hepatocyte growth factor
IGF-I	Insulin-like Growth Factor-I
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
iPSCs	Induced pluripotent stem cells
JNK:c	Jun amino-terminal kinase
MAPK	Mitogen-activated protein kinase
MSCs	Mesenchymal stem cells
PKC-α	Protein kinase C-alpha
ROS	Reactive oxygen species
SCs	Stem cells
TGF-β R′	Transforming growth factor beta receptor
TGF-β	Transforming growth factor beta
TNFα	Tumor necrosis factor alpha
UC-MSCs	Umbilical cord mesenchymal stem cells

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VEGF Vascular endothelial growth factor

1 Introduction

Diabetic complications comprise the dysfunction of several major organs, including kidney, heart, blood vessels, nerves and eyes leading to serious health problems such as nephropathy, cardiac dysfunction, atherosclerosis, neuropathy and retinopathy [1, 2]. Diabetic nephropathy (DN) is a complication of diabetes mellitus types 1 and 2 and is caused by the angiopathy of glomerular capillaries [3]. DN is a major cause of progressive kidney disease, about 20–40% of patients with diabetes develops evidence of nephropathy [4]. The earliest clinical hallmark of DN is microalbuminuria followed by thickening of glomerular basement membrane (GBM), glomerular hypertrophy and mesangial expansion leading to proteinuria, renal fibrosis, eventually progressing to irreversible end stage renal disease over years or decades. Currently we are short of effective medications for treatment of DN. However, control of hyperglycemia and hypertension at early stages of kidney damage is effective at retarding disease progression. Dialysis or kidney transplant might be helpful for treatment of renal failure. Unfortunately, clinical application of kidney transplantation is limited due to rejection by the immune system and shortage of kidney donors. An effective and safe method of treatment for DN is required. In recent years, stem cell therapy has become an attractive and novel therapeutic strategy for DN.

Numerous recent studies have indicated that podocyte injury is an early event in diabetes and highlighted the importance of podocytopathy in the pathogenesis of DN [5, 6]. In this review, we focused on the potential role of mesenchymal stem cells (MSCs) in the treatment of DN with particular emphasis on therapeutic effect of MSCs in diabetic podocyte injury.

2 Podocyte injury in DN

Many different cell types have been reported to undergo cellular changes in diabetes. Major cellular abnormalities were reported in podocytes. Podocytes are glomerular visceral epithelial cells. They are unique and highly specialized cells that cover the outer layer of kidney ultrafiltration barrier. They play an important role in glomerular function. The podocytes consist of three major structural parts: cell body, cell processes and foot processes (Fig. 1). The foot process is the most noticeable feature of podocytes. The interdigitated foot processes leave filtration slits in between, known as slit diaphragm, which establish a size-selective barrier to prevent proteinuria [7–9]. In addition to slit diaphragm proteins, several metabolic and endocrine factors modulated podocyte function, including growth hormones [10, 11], sex hormones [12], components of renin-angiotensin system [13–16], vitamin D [17], insulin [18] and adiponectin [19].

Numerous studies have been carried out to explore the role of podocytes in pathogenesis of DN. These studies demonstrated a positive correlation between diabetic proteinuria and podocyte injury [5, 20–22]. Foot process effacement, dedifferentiation and apoptosis have been identified as the main types of podocyte damage in DN [23–27].

An initial response of podocytes to any type of injury is a change in podocyte shape also known as podocyte foot effacement. Recent work showed that in diseases such as DN, alterations in the interaction of the podocyte actin cytoskeleton with slit pore proteins resulted in abnormally flattened and ‘spread-out’ podocyte shape with subsequent foot-process effacement and proteinuria [28, 29]. Podocytes lose contact with GBM as consequent to alterations in actin dynamics and podocyte–GBM interactions. Mutations in several genes encoding slit pore proteins, such as nephrin and podocin have been documented to result in nephrotic syndrome and proteinuria [25, 30]. Nephrin plays a major role in the integrity of podocyte actin cytoskeleton, podocyte survival signalling and insulin-stimulated glucose uptake [31]. In response to high glucose concentration, protein kinase C-alpha expression (PKC-α) increases which promotes nephrin endocytosis. This leads to a decline in nephrin surface expression and eventually contributes to proteinuria [32]. The second phenotype of podocyte injury in DN is dedifferentiation of podocytes causing them to lose their specialized feature as a glomerular filtration barrier [33].

Finally, apoptosis of podocytes have been shown to be associated with reduction of podocyte density in DN. Podocyte depletion in diabetic patients is the strongest predictor of progressive nephropathy and many clinical studies have documented reduced podocyte density in renal biopsy of individuals with type 1 or type 2 diabetes [34–39].

Chronic hyperglycemia and advanced glycation end products (AGEs) stimulate transforming growth factor beta (TGF-β) secretion in mesangial cells and expression of TGF-β receptor (TGF-β R’) in podocytes. Latent TGF-β complex may be stored in mesangial matrix and then localized to podocyte surface when activated by angiotensin II (Ang II) [40]. Over expression of TGF-β1 and mechanical stretch will suppress α3β1 integrin eventually resulting in decreased podocyte adhesion and apoptosis [41]. Another contributing factor to podocyte apoptosis in diabetes is activation of p38MAPK and caspase-3, mediated by reactive oxygen species (ROS). Role of ROS in this process and protective effect of various ROS inhibitors in

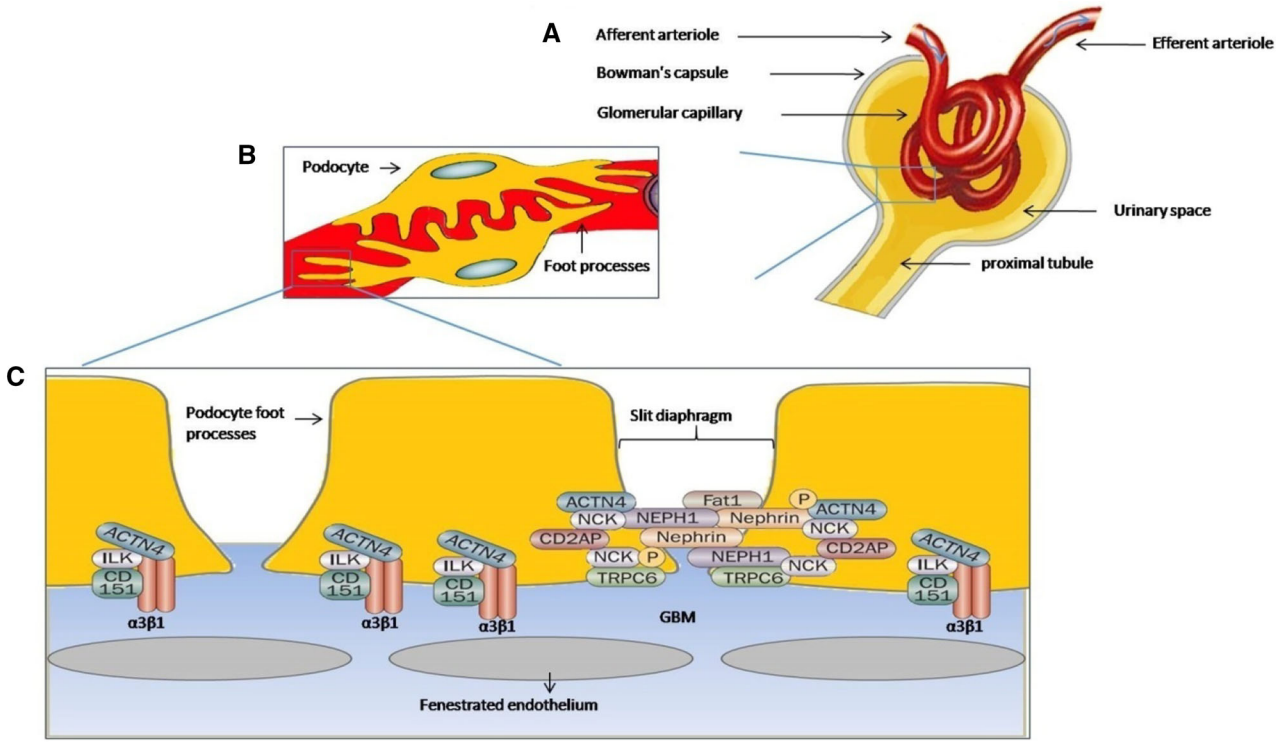

Fig. 1 Structure of the glomerular filtration barrier. **A**) Fluids from blood in the glomerulus are collected in the Bowman's capsule that empties into proximal tubules. **B**) The glomerular filtration barrier consist of three layers: the innermost fenestrated endothelium, the glomerular basement membrane (GBM), and the podocyte layer. **C**) The foot process of neighboring podocytes interconnected by several slit diaphragm molecules. Proteins that anchor foot processes to the GBM (α3β1 integrin, α-actinin-4 [ACTN4], integrin linked kinase [ILK], and the tetraspanin CD151) and those associated with the slit diaphragm (nephrin, NEPH1, podocin [P], Fat1, ACTN4, the adaptor protein NCK, CD2-associated protein [CD2AP], and transient receptor potential cation channel 6 [TRPC6]) are important in maintaining of filtration barrier

dampening activation of caspase *in vivo* and *in vitro* have been shown by others [42].

Hyperglycemia also resulted in activation of angiotensin receptor type 1 in podocytes leading directly to apoptosis independent of blood pressure effects [43, 44]. Angiotensin-II upregulated cyclin-dependent kinase inhibitor (p27Kip1) culminating in cell cycle arrest and driving cells towards hypertrophy [45]. Vascular endothelial growth factor (VEGF) also contributed to podocytopathy in DN. During diabetes, podocytes induce VEGF up-regulation leading to overproduction of matrix in mesangial cells and diabetic glomerulosclerosis [40, 46]. Mechanisms of podocyte injury in DN are as shown (Fig. 2).

3 Mesenchymal stem cells

Stem cells (SCs) are undifferentiated cells with remarkable capabilities for self-renewal, they are able to differentiate into specialized cells [47]. According to their source and malleability, stem cells are classified as fetal, adult stem cells (ASCs) and embryonic stem cells (ESCs) [48, 49]. Recently, a new kind of high-potential stem cells called induced pluripotent stem cells (iPSCs) was developed which were neither 'embryonic' nor 'adult' stem cells. iPSCs were generated from terminally differentiated cells, such as fibroblasts via a process of re-programming [50, 51].

Although both ASCs and ESCs share the capability for self-renewal and differentiation to specialized cell types, they differ in other attributes. ESCs are pluripotent and can differentiate into any cell type. They have an infinite proliferative potential and are able to grow in culture to provide sufficient cell numbers for stem cell transplantation and tissue engineering. Their clinical application is however limited due to their tumorigenic potential and the ethical problems associated with their use [52]. In contrast, ASCs are multipotent meaning that their ability for differentiation is limited. ASCs are easy to access and are considered safe as they are harvested from adult tissue [53]. A number of tissue specific stem cells have been isolated from organs including skin, brain, gastrointestinal tract and kidney [54–58]. Renal stem cells exist in adult human kidney and are capable of differentiating into different kidney cell types. Many studies have reported the successful isolation of kidney-derived stem cells [59]. Stem

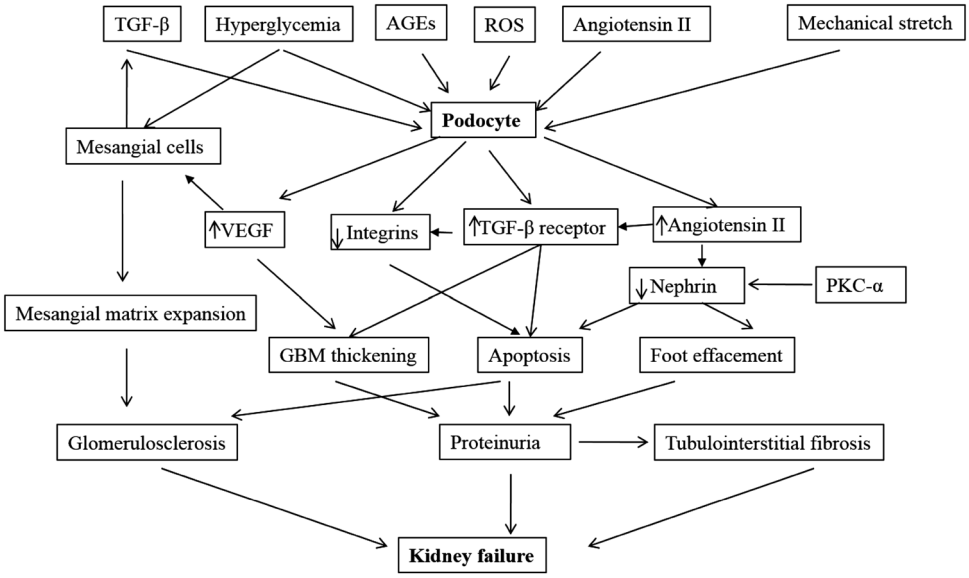

Fig. 2 Podocyte damage in diabetic nephropathy. In diabetic condition, metabolic factors (TGF-β, glycated proteins, hyperglycemia, ROS, Angiotensin II (Ang II) and hemodynamic factors (via mechanical stretch) lead to increased VEGF and Ang II production by podocytes. Podocyte-derived VEGF leads to overproduction of matrix in mesangial cells and diabetic glomerulosclerosis. Chronic hyperglycemia and advanced glycation end products lead to TGF-β secretion in mesangial cells and expression of TGF-β R' in podocytes. The latent TGF-β complex may be stored in mesangial matrix and then localized to the podocyte surface via activation by Ang II. The TGF-β type II receptor interaction stimulates the over production of extracellular matrix by podocyte and mesangium (leading to GBM thickening and mesangial matrix expansion). Over expression of TGF-β and mechanical stretch suppress α3β1 integrin and leads to decreased podocyte adhesion and apoptosis. In response to high glucose concentration, protein kinase C-alpha (PKC-α) expression increase which promotes nephrin endocytosis. This leads to a decline in nephrin surface expression and eventually contributes to proteinuria. Worsening proteinuria coupled glomerulosclerosis and tubulointerstitial fibrosis, leads to progressive renal insufficiency

cells isolated from papilla of adult mice and rats expressed epithelial and mesenchymal markers when grown in culture and under appropriate conditions, these displayed evidence of plasticity by differentiation into myofibroblasts and into cells which expressed neuronal markers [60]. Stem cells isolated from adult human kidney were differentiated into epithelial and endothelial cells and showed formation of tubular structures and functional vessels both *in vivo* and *in vitro* [61]. A population of stem cells was harvested from microdissected proximal tubules and was identified by expression of stem cell markers such as Sca-1 and Musahi-1, these cells were differentiated into mature tubular cells in appropriate culture medium [62]. Mesenchymal stem cells isolated from kidneys of adult mice displayed the capability of differentiating into erythropoietin producing fibroblasts [63].

Adult stem cells that have the highest therapeutic potential are MSCs [51]. MSCs represent a class of adult progenitor cells that possesses the ability to differentiate into chondrocytes, osteoblasts and adipocytes. The role of MSCs in regulating the proliferation and function of immune cells, such as B and T lymphocytes, NK cells, dendritic cells and neutrophils have been demonstrated [64]. In addition, antifibrotic, anti-apoptotic, bactericidal and pro-angiogenic factors have been shown to be secreted by MSCs [65].

The enormous expansion potential, ease of harvest, low immunogenicity and lesser ethical concerns rendered MSCs attractive candidates in cell-based therapy for treatment of a variety of inflammation related diseases and subsequent tissue regeneration and repair of damaged tissue [66]. MSCs may promote endogenous repair of the kidney via chemotaxins with homing to injured tissue *in vivo*, and paracrine action of different cytokines [67–70]. In humans, MSCs were extracted from several sources including bone marrow (bone marrow mesenchymal stem cells; BM-MSCs), umbilical cord (umbilical cord mesenchymal stem cells; UC-MSCs), adipose tissue (adipose-derived mesenchymal stem cells; AD-MSCs), and fetus (fetal membrane mesenchymal stem cells; FM-MSCs) [71, 72]. Of these, BM-MSCs are the most used in cell-based therapy and tissue engineering despite the low numbers of MSCs derived from bone marrow which limit their application. Both BM-MSCs and AD-MSCs are equally capable of differentiating into cells and tissues of mesodermal origin. Compared with BM-MSCs, AD-MSCs are readily available and can be easily harvested in large quantities with little patient

discomfort and therefore have been extensively used in preclinical and clinical studies [73, 74].

4 MSCs as treatment for diabetic nephropathy

In the last few decades, there has been much interest in the potential therapeutic effects of MSCs particularly BM-MSCs and AD-MSCs on DN and podocyte injury. Numerous studies have been carried out to explore the potential role of MSCs in the treatment of DN (Table 1). MSCs can significantly reduce hyperglycemia and proteinuria and improve renal pathological changes, including glomerular sclerosis, tubule dilatation, mesangial proliferation and protein casts [75–78]. MSCs were isolated from subcutaneous adipose tissue of SD rats and transplanted autogenously four week after induction of diabetes. The successful homing of MSCs was confirmed by double stain of CM-Dil and 4′, 6-diamidino-2-phenylindole (DAPI). The MSCs transplantation resulted in restoration of mesangial matrix expansion, inhibition of oxidative stress and reduction of proinflammatory

Table 1 MSCs as treatment for DN

Source of MSCs	Experimental model	Route of injection	*In vivo* localization of MSCs	Mechanism of action	Findings
AD-MSCs	SD rats + STZ n = 8/group	Intravenous	Kidney	Effect on MAPK signaling pathway, suppression of oxidative stress and inflammatory response.	AD-MSCs treatment reduced oxidative damage and expression of pro-inflammatory cytokines, p-p38, p-ERK and p-JNK [75]
BM-MSCs	Wistar rats + STZ n = 16/group	Intravenous	Kidney	Suppression of inflammatory response and inhibition of MCP-1 expression by secreting HGF.	AD-MSCs treatment reduced hyperglycemia and albuminuria, decreased the expression of fibronectin, Collagen I, MCP-1 and pro-inflammatory cytokines while the expression of HGF was up-regulated [77]
	NOD/scid mice + STZ n = 9/group	Intracardiac	Pancreas and kidney	Increased insulin secretion and improved renal lesions.	Successful homing of human BM-MSCs in the kidney of diabetic mice resulted in improvement of mesangial thickening and macrophage infiltration [76]
	SD rats + STZ n = 16/group	Intracardiac	Heart, Pancreas and kidney	Decreased blood glucose	BM-MSCs treatment ameliorated DN characterized by decreased blood glucose, albumin/creatinine ratio and renal hypertrophy [78]
	C57BL/6 mice + STZ n = 8/group	Intravenous	Pancreas and kidney	β-pancreatic islets regeneration	BM-MSCs treatment resulted in regeneration of pancreatic islets and prevented kidney damage [3]
	C57BL/6 mice + STZ n = 20/group	Intravenous	Kidney and bone marrow	Produced renotrophic factors or anti-inflammatory cytokines	MSC treated mice maintained basal levels of albuminuria and only showed slight tubular dilatation [79]
	Wistar rats + STZ n = 12/group	Intravenous	Kidney	Inhibited oxidative stress and reduced cellular glucose uptake mediated by GLUT1	BM-MSCs treatment reduced hyperglycemia, albuminuria and renal mass index. Glomerulosclerosis, expression of collagen I and fibronectin was significantly reduced. Oxidative stress was also markedly reduced. The expression of TGF-β and membrane localization of GLUT1 was also down-regulated by MSCs [80]
	Albino rats + STZ n = 20/group	Intravenous	Kidney	Paracrine action via different growth factors such as VEGF, TGFβ & TNFα and antiapoptotic action via bcl2 & Bax genes	BM-MSCs treatment decreased albuminuria, normalized serum urea and creatinine levels, increased VEGF, and bcl2 while decreasing TNF-α, fibrogenic growth factor TGF β, and Bax [95]
UC-MSCs	NRK-52E SD rats + STZ n = 7/group	Intravenous	Kidney	Secretion of humoral factors	UC-MSCs treatment prevented DN. However, renal hypertrophy was observed. There was no effect on blood glucose level [90].

cytokines. The decrease in proinflammatory cytokines was shown to be due to the effect of MSCs on MAPK signaling pathway [75]. It has been well documented that the expression of pro-inflammatory cytokines is regulated by activation of the MAPK pathway. MSC implementation attenuated the increased phosphorylation of p38, extracellular signal-regulated kinase (ERK) and c-Jun amino-terminal kinase (JNK) in diabetic animals [75]. Human BM-MSCs were injected into the cardiac ventricle of NOD/scid mice after induction of diabetes [76]. This animal model is immune-deficient that lacks functional B and T cells which can facilitate transplantation without host immune rejection. The human DNA infused as human BM-MSCs was detected in pancreas and kidney but not in liver, lung or spleen of the experimental animals suggesting the successful and selective homing of MSCs. Intracardiac infusion of MSCs decreased trapping of the cells in the capillary beds of the lung, however the highest level were observed in pancreas and kidneys which might be due to specific signals from injured tissues. Infusion of MSCs resulted in lower blood glucose and increased blood insulin. In addition, MSCs infusion improved glomerular morphology of diabetic animals. However, it is not clear whether it was a direct effect on the kidney or the effect was secondary to lower blood glucose levels. In the study human skin fibroblasts were used as control where the infusion of these cells did not show any effect in blood glucose level [76]. In a similar study, BM-MSCs were injected into the cardiac ventricle of SD rats four weeks after induction of diabetes [78]. BrdU labeling confirmed the localization of MSCs in heart, pancreas and kidneys. MSCs transplantation resulted in decreased blood glucose, urine albumin/creatinine and kidney/body weight ratios especially at the early phase of the treatment. Administration of cyclosporine strengthened these effects by suppressing the host immune response. However, proliferating cell nuclear antigen (PCNA) immunostaining showed MSCs did not proliferate in the kidney which suggest the renoprotective effects of MSCs through paracrine mechanisms [78]. Endovenous injection of MSCs prevented renal failure in diabetic mice as characterized by maintenance of basal levels of albuminuria and improvement of tubular dilation. However, blood glucose and insulin levels were unchanged [79]. Similarly, MSC treatment of diabetic mice did not result in a reduction in blood glucose and there was no regeneration of pancreatic β-cells although high glucose-induced alterations in kidney structure was reversed [3].

MSCs secreted hepatocyte growth factor (HGF) which may play an important role in the treatment of DN by reducing macrophage infiltration and down-regulation of interleukin-1β (IL-1β), interleukin 6 (IL-6), tumor necrosis factor-α (TNFα) expression in renal tissue [77, 80].

Administration of MSCs prevented glomerular hyperfiltration as indicated by decreased creatinine clearance. Even though the creatinine clearance level normalized after MSCs treatment, the long term effect of lowered GFR need to be investigated [75].

The HGF secreted by MSCs has also been reported to down regulate the expression of high glucose induced TGF-β, thus down-regulating the expression of GLUT1 [80]. It has been reported that TGF-β stimulates glucose uptake by enhancing GLUT1 expression in mesangial cells [81]. A similar study reported paracrine action of MSCs as therapeutic mechanism in DN. Engraftment of UC-MSCs in kidneys and glomeruli of STZ-diabetic rats effectively prevented proteinuria, fractional mesangial area, and excessive accumulation of extracellular matrix without affecting hyperglycemia and renal hypertrophy. Renoprotective effect of MSCs was reported to be through secretion of growth factors such as VEGF and insulin-like growth factor (IGF)-1 [82]. Administration of BM-MSCs in diabetic rats improved kidney function and regenerated kidney tissue by increasing expression of VEGF and anti-apoptotic protein BCL2 while decreasing the expression of TNF-α, TGF-β, and pro-apoptotic protein, Bax [83].

It has been reported that infused MSCs were detected predominately in the glomeruli early after administration [70]. BM-MSCs may home to injured glomerular endothelium and differentiate into endothelial cells [84], or replace injured mesangial cells [85]. Bone marrow transplant–derived podocytes has been reported to be found in wild-type mice [86], genetic mouse models with diffuse mesangial sclerosis [87] and Alport's syndrome [88]. In contrast, podocyte replacement by BM-MSCs was not observed in aminoglycoside-induced nephropathy and renal ablation models [89]. The discrepancy may have been caused by animal model differences or by predominant podocyte regeneration from a parietal epithelial cell niche. However, the ability of MSCs to replace damaged podocyetes need to be more explored in DN models. In addition to regenerative and differentiative capability, MSCs have been shown beneficial effects against DN by secretion of a number of factors, including HGF, basic fibroblast growth factor (bFGF) and IGF-I, which may have contributed to the amelioration of kidney damage via their antiapoptotic, mitogenic, and other cytokine actions [90].

5 MSCs as treatment of podocyte injury in diabetic nephropathy

Recently, scientists have focused on MSCs as attractive prospect for stem cell-based therapies as treatment of podocyte injury in DN. A few studies have been conducted to investigate the use MSCs in the treatment of podocyte

injury (Table 2). In a recent study, the protective effects of MSCs derived from human adipose tissue (hAD-MSCs) against high glucose-induced podocytic apoptosis and injury was investigated [83]. Mouse podocyte clone 5 (MPC5) were exposed to high glucose to establish a model of high glucose podocytic apoptosis for 24, 48 and 72 h. Podocytic apoptosis was reduced by hAD-MSCs via a decline in caspase-3 protein expression at all time points. The study also showed MSCs maintained integrity of glomerular filtration barrier by increasing podocytic synaptopodin and nephrin expression. It was suggested that high levels of epithelial growth factor (EGF) in MSCs conditioned medium (MSCs-CM) was the key factor in prevention of apoptosis and injury of podocytes where anti-EGF in MSCs-CM completely blocked the effect [83].

It is possible that harvesting and injecting MSCs-CM containing EGF may be sufficient to prevent podocyte apoptosis without the need for injection of MSCs Ali, Brazil [82]. UC-MSCs protected podocytes from apoptosis induced by high glucose via secretion of HGF [91]. Co-culture of podocytes with UC-MSCs increased the expression of Bcl-2 and normalized the arrangement of podocytic podoplanin. The beneficial effects of UC-MSCs was reversed in the absence of HGF [91].

In a similar study, repeated intravenous injection of AD-MSCs attenuated proteinuria in STZ-diabetic rats even at the overt nephropathy stage [92]. Apparently, AD-MSCs treatment prevented high glucose-induced podocyte injury and maintained the integrity of the podocyte actin cytoskeleton by increasing the expression of Wilm's tumour (WT1) and synaptopodin proteins. A series of growth factors, including fibroblast growth factor 2 (FGF2), epidermal growth factor and glial cell-line derived neurotrophic factor (GDNF) were shown to be secreted by AD-MSCs in culture media. GDNF is a podocyte survival factor which is secreted by AD-MSCs, it may also play a major role in the amelioration of podocyte injury. The study did not support the theory that stem cell differentiation was responsible for the prevention of DN, rather, the authors highlighted the involvement of endocrine mechanisms in the protection of the diabetic podocyte injury [92].

Intravenous injection of MSCs may not be appropriate due to low uptake of MSCs at the site of injury [91]. Instead, direct intra-arterial injection of MSCs should provide adequate homing of MSCs as confirmed by presence of florescent labelled cells in kidneys of experimental animals. The study showed that treatment with BM-MSCs improved physical and biochemical markers viz proteinuria and creatinine clearance rate [91]. In addition, MSCs ameliorated ultra-structural abnormalities, such as loss of podocytes, GBM thickening and podocyte foot process effacement. VEGF and bone morphogenetic protein-7 (BMP-7) are known as podocyte survival factors. High amounts of VEGF and BMP-7 released by MSCs has shown to exert beneficial effects in chronic kidney disease and acute kidney injury models [68, 94]. Beneficial effects of MSCs at maintenance of podocyte integrity and improvement of proteinuria were associated with

Table 2 MSCs as Treatment of Podocyte Injury in DN

Source	Experimental model	Route of injection	*In vivo* localization of MSCs	Mechanism of action	Findings
AD-MSCs	Mouse podocyte clone 5 cells (MPC5)	_	_	Secretion of soluble epithelial growth factor	AD-MSCs reduced podocytic apoptosis reduced the expression of podocytic cleaved caspase-3, maintained integrity of glomerular filtration barriers by increasing podocytic synaptopodin and nephrin expression [83]
	SD rats + STZ and MPC5, n = 11	Intravenous	Lung, spleen and a small number in kidney and pancreas	Secretion of GDNF	AD-MSCs attenuated proteinuria, prevented high glucose-induced podocyte injury and maintained the integrity of the podocyte actin cytoskeleton by increasing the expression of WT1 and synaptopodin proteins [92]
BM-MSCs	SD rats + STZ, n = 14	Intra-arterial	Kidney	Increased BMP-7, nephrin and podocin secretion	BM-MSCs ameliorated loss of podocytes, GBM thickening and podocyte foot process effacement. By restoration of expression of nephrin and podocin [94]
UC-MSCs	Mouse podocyte clone 5 cell (MPC5)	_	_	Secretion of soluble epithelial growth factor	UC-MSCs decreased the podocytic apoptosis rate and the expression of PARP, increased the expression of Bcl-2, normalized the expression and arrangement of podocytic podoplanin [91]

MSCs Mesenchymal stem cells; *AD-MSCs* Adipose-derived mesenchymal stem cells; *BM-MSCs* Bone marrow mesenchymal stem cells; *AD-MSCs* Adipose-derived mesenchymal stem cells; *UC-MSCs* Umbilical cord mesenchymal stem cells; Sprague–Dawley (SD) rats; *STZ* Streptozotocin; *GBM* Glomerular basement membrane; *GDNF* Glial derived neurotrophic factor; *WT1* Wilms tumor protein 1; *Bcl-2* B cell lymphoma-2; *PARP* Poly ADP ribose polymerase

restoration of expression patterns for nephrin and podocin. Level of bone morphogenetic protein-7 (BMP-7), the survival and differential factor of podocytes, increased after MSC treatment [91].

In addition, MSCs secreted a number of factors, including HGF, basic fibroblast growth factor (bFGF) and IGF-I, which may have contributed to the amelioration of kidney damage via their antiapoptotic, mitogenic, and other cytokine actions [93]. Therapeutic effect of MSCs against DN may primarily be mediated through paracrine actions [94].

Although these data are encouraging, further studies need to be done using non-MSC cell controls to confirm these beneficial effects were unique to stem cells. In addition, MSCs have shown to secrete high levels of a number of growth factors which may contribute in amelioration of DN. However it is not clear whether the effect is specific to these growth factor. Blockage of these factors may help to address the issue. The studies reviewed in this paper either used immunosuppressants or autogenic stem-cell transplantation to minimize host immune response. However, administration of an irrelevant cell as a negative control may help to address the issue. In addition, in some of the studies reviewed in this paper nonparametric statistics would be more appropriate due to small sample size. Collectively, the possible mechanisms of action of MSCs against DN are paracrine action and fusion or transdifferentiation.

6 Conclusion

Mesenchymal stem cells have become an attractive prospect for stem cell-based therapies aimed at treatment of podocyte injury in DN. MSCs are multipotent stromal cells which are capable of differentiating into multiple cellular lineages. MSCs demonstrated therapeutic effect in treatment of podocyte injury not only by their regenerative and differentiative capability, but also by secretion of a series of growth factors via antiapoptotic, mitogenic and other cytokine actions. Although recent studies demonstrated successful treatment of diabetic podocyte injury with MSCs, the challenge for future studies is to identify and confirm key molecular mechanisms involved. In addition, clinical trials are required to confirm MSCs as new and specific therapies for diabetic podocyte injury. Successful treatment of diabetic podocyte injury with MSCs holds great promise for the development of novel, MSC-based therapy that can alter the deleterious effects of podocyte injury in DN.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest.

Ethical statement There are no animal experiments carried out for this article.

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