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Ameliorative Effect of Mesenchymal Stromal Cells on Diabetic Nephropathy in Male Rats

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Abstract

Both types of diabetes mellitus (DM) are recognized by the destruction of pancreas or deficient function of Islets' cells causing several complications. Diabetes mainly affect the kidney leading to diabetic nephropathy (DN) in the late renal stage, which caused higher mortality in diabetic patients. Since diabetic disease appearance, nephropathy may be observed in patients with type 1 or 2 diabetes. Recently, cell culture can be used in the regenerative medicine as a new method for treating diabetes and DN. Therefore, the aim of the current study was to prove the beneficial effect of mesenchymal stromal cells (MSCs) transplantation on DN during the early stage. Male rats were randomized in 3 groups (each 20 rats): the 1st group was normal rats, while the 2nd was streptozotocin (STZ) diabetic rats and the 3rd was diabetic rats treated with a single intravenous dose of bone marrow mesenchymal stromal cells (BM-MSCs) after 3 days from STZ induction. Results indicated that STZ induced DN represented by weight loss, hyperglycemia, hypoinsulineamia, decreased glycated hemoglobin, leukocytosis and impairment of kidney function and oxidative stress in kidney tissue. After BM-MSCs treatment, blood glucose level was improved, renal function was retained, body weight loss was decreased, insulin level and HBA1C percent were ameliorated with improved oxidative stress in kidney tissue. BM-MSCs have the capacity to regenerate and differentiate into insulin- producing cells improving DM and DN.

Keywords: Diabetic Nephropathy, Streptozotocin, Oxidative Stress, Bone-Marrow mesenchymal stromal cell.

Introduction

Diabetes mellitus is followed by several complications mainly diabetic nephropathy (DN) [1], which leads to renal disease in late stage and consequently increases both morbidity and mortality in diabetic cases [2,3]. Oxidative stress is a major factor in diabetic vascular complications including DN [4,5] as it leads to disturbance in the detoxification of reactive oxygen species (ROS) by the body which controls any damage. ROS regulates some genes and proteins that cause morphological and structural cell damage. Glycemic control may decrease the oxidative stress as it causes reduction of producing the intracellular reactive oxygen species [6]. Common therapies involve intensive control of hyperglycemia and hypertension but have no effect on diabetic nephropathy [7], so there is an important need to explore new method targeting DN.

Stem cell therapy is used as a regenerative therapy in many diseases because of its self-renewal and differentiation properties [8,9] thus, it has the potential to be more effective than other drug therapies [10]. The most available type of these cells is mesenchymal stromal cell (MSCs), which easily obtained from human (blood, dermis, bone, bone marrow, adipose tissue and muscles) and has the ability to differentiate into other tissues as muscle, fat, cartilage and bone [11-13]. In the current study, we aimed to investigate the pancreatic and renoprotective effects of autologous transplantation of mesenchymal stromal cells derived from bone marrow (BM) in rats with streptozotocin (STZ) induced nephropathy.

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Material and Methods

Experimental design

The current study was carried out on 60 male albino rats with body weight of 200±20g obtained from Standard Animal Laboratory Colony, Helwan, Cairo, Egypt. They were provided with *ad libitum* standard chow and water throughout the study. Rat model was performed by the Intra-peritoneal (IP) injection of 60 mg/kg STZ (Sigma–Aldrich, USA) [14] for the induction of type 1 and type 2 diabetes. After 7 days for proliferation and following one night of fasting, diabetes was confirmed by measuring fasting blood sugar of reading >250 mg/dL for 3 continuous days. Male rats were divided into 3 groups (each 20 rats): the 1st group was non-diabetic rats received only vehicle, while the 2nd group was rat of type 1 diabetes that induced by I/P injection of a single dose of STZ and not treated and the 3rd group was diabetic rats, which received intravenous injection (I.V) of BM-MSCs in a single dose of 10^6cells/rat in 1 mL serum free medium (GIBCO) after 3 days from the induction of STZ.

Culture, characterization and labeling of MSCs

Bone marrow was collected and cultured for 14 days on Dulbicco′s Modified Eagle′s Medium (DMEM) supplemented with 10 % fetal bovine serum after flushing the femurs and tibiae of 6 male rats [15]. MSCs were identified by their adhesiveness and fusiform shape. Red fluorescent cell linker (PKH26) was used in the labeling process [16] with transduction method (Sigma, Saint Louis, Missouri, USA) according to the manufacturer's recommendations.

Sample collection and analysis

Blood samples were collected for separation of serum from the retro-orbital venous sinus after 4 weeks from STZ injection for testing the biochemical parameters and blood samples for measuring hematological parameters. Kidneys were removed and divided into two parts; the first part was preserved frozen at –80 °C for estimating the oxidative stress markers and the other part of kidney was stored in 4% formalin for histopathological examination. Also, the pancreas was stored in 4% formalin for histopathological examination and immunohistochemical analysis.

Fasting blood glucose levels were monitored along the experiment [17] while at the end of the experiment the glycosylated hemoglobin [18], insulin [19], creatinine [20] and urea [21] were estimated. On the day 27 after MSCs injection (1 month from diabetes induction) and adaptation at early phase of diabetic nephropathy induced by STZ, rats were scarified and pancreas and kidney were removed for preparing paraffin block then stained by hematoxylin-eosin for histopathologic analysis under light microscope. PKH26 labeled MSCs were examined under fluorescence microscope [22].

An immunohistochemical staining on 4 µm frozen pancreatic sections was performed according to the streptavidin biotin peroxidase complex (ABC) method using primary Anti-insulin antibody (guinea pig polyclonal to insulin, ab7842, Abcam, Cambridge, UK) and rabbit polyclonal secondary antibody (Rabbit polyclonal secondary antibody to guinea pig IgG - H&L Horse Radish Peroxidase (HRP), ab6771, Abcam, Cambridge, UK) on unstained positively charged slides from paraffin block [23]. Morphometric analysis was performed to measure the nuclear area and length of *β*-cells of islet of pancreases using National Institute of Health (NIH) technique 1.60 programs (NIH, Bethesda, Maryland, USA) [24]. The results were represented the effectiveness of the newly produced *β*-cells of pancreases. The malondialdehyde (MDA) content (thiobarbituric acid method [25]), the total superoxide dismutase (SOD) activity (xanthine oxidase method [26]) and reduced glutathione content of kidney homogenate (Ellman's method [27]) were measured with commercially available kits (Biodiagnostic Co. Cairo Egypt)

Statistical analysis

All data were represented by mean ± SE using Prism version 7 program. One-way ANOVA analysis was used to compare the different experimental groups.

Table 1: Effect of BM-MSCs on body weight, fasting blood sugar (FBS), glycated hemoglobin (HBA1C) and insulin in induced-diabetic rats (Mean±SE, N= 20)

Group variables	Control group	DN group[1]	BM-MSCs group[2]
Body weight (g)	303.3±8.5[a]	226.73± 6.93[b]	300.50± 12.57[a]
FBS (mg/dL)	96.50± 2.63[c]	269± 28.01[a]	175.62± 7.11[b]
HbA1C (%)	5.46± 0.30[c]	12.22± 0.23[a]	8.52± 0.33[b]
Insulin (μ/g)	0.75±0.04[a]	0.2±0.021[c]	0.54±0.04[b]

[1]DN group: rats of type 1 diabetes that induced by I/P injection of a single dose of STZ and not treated, [2]BM-MSCs group: diabetic rats, which received intravenously injection of BM-MSCs in a single dose of 10^6cells/rat in 1 mL serum free medium (GIBCO) after 3 days from the induction of STZ. Means carrying different superscript within the same row were significant different at $p < 0.05$.

Results and Discussion

Four weeks after STZ injection, rats in the DN group showed light body weight and high blood sugar ($P < 0.05$) when compared with the non-diabetic group, while rats of the BM-MSCs treated group revealed heavy body weight and low blood sugar ($P < 0.05$) when compared with the DN group (Table 1). Glycated hemoglobin showed a higher increase ($P < 0.05$) in the DN group when compared with the non-diabetic group, however it was significantly lower in the BM-MSCs group when compared with the DN group. Moreover, insulin was significantly decreased in the DN group when compared with the control one, while, it showed ameliorative effect in the treated group compared with DN group (Table 1). The serum urea and creatinine levels in the DN rats were higher than the non-diabetic rats and their levels were significantly reduced after the injection of BM-MSCs when compared with DN group (Table 2).

Table 2: Effect of BM-MSCs on renal functions and oxidative stress markers in the renal tissue of induced-diabetic rats (Mean±SE, N= 20)

Group variables	Control group	DN group[1]	BM-MSCs group[2]
Urea (mg/dL)	45.57± 2.48[c]	93.48±7.19[a]	62.67± 2.17[b]
Creatinine (mg/dL)	0.58±0.017[c]	2.78±0.22[a]	1.60±0.15[b]
[3]SOD (U/g)	195.5±12.67[a]	105.67±4.62[c]	171.72±11.6[b]
[4]MDA (nmol/mg)	1.78±0.28[c]	4.98±0.22[a]	3.2±0.22[b]
[5]GSH (U/g)	33.03±2.97[a]	22.51±0.55[b]	25.15±0.65[b]

[1]DN group: rats of type 1 diabetes that induced by I/P injection of a single dose of STZ and not treated, [2]BM-MSCs group: diabetic rats, which received I.V injection of BM-MSCs in a single dose of 10^6cells/rat in 1 mL serum free medium (GIBCO) after 3 days from the induction of STZ. [3]SOD: superoxide dismutase activity; [4]MDA: malondialdehyde content; [5]GSH: reduced glutathione content. Means carrying different superscript within the same row were significant different at $p < 0.05$.

Our results suggested that, BM-MSCs was able to control the alteration of the oxidative stress in the kidney homogenate of diabetic rats where the treated group exhibited a significant increase ($P < 0.05$) in the SOD activity and the GSH concentrations when compared with the DN group. In addition, the MDA concentration showed a significant decrease ($P < 0.05$) in the BM-MSCs treated group when compared with DN group (Table 2). These results were confirmed with the improvement in the histological examination of pancreas and kidney after BM-MSCs treatment (Figure 1). As a result of immunohistochemical (IHC) examination, there was small islets regeneration in the BM-MSCs treated group (Figure 2) confirmed by the improvement in insulin levels and blood glucose levels, which indicated the beneficial role of MSCs in amelioration of DN. The islets regeneration indicated also by morphometric analysis showed that the nuclear size and length of islet cell increased significantly after BM-MSCs transplantation when compared with the DN group (Table 3).

Table 3: Some nuclear morphometric features (Nuclear area and length) in different groups (Mean±SE, N= 20)

Morphometric feature	Control group	DN group[1]	BM-MSCs group[2]
Nuclear area (µm2)	11.57± 3.61[a]	6.42 ± 2.71[c]	10.29 ± 4.41[b]
Nuclear length (µm)	13.43 ± 2.10[a]	9.66 ± 0.2.29[c]	12.25 ± 2.85[b]

[1]DN group: rats of type 1 diabetes that induced by I/P injection of a single dose of STZ and not treated, [2]BM-MSCs group: diabetic rats, which received intravenously injection of BM-MSCs in a single dose of 10^6cells/rat in 1 mL serum free medium (GIBCO) after 3 days from the induction of STZ. Means carrying different superscript within the same row were significant different at $p < 0.05$.

Supporting to our results, blood sugar was reduced by a single injection of MSCs in STZ- induced diabetic rats [28,29]. Also, the intravenous injection of adipose-derived mesenchymal stem cells (ADMSC) in diabetic mice could significantly decrease the fasting blood sugar level and increase the secretion of insulin in the islet β-cells [30]. A previous study was performed by Tsai *et al.* [31] who found that mesenchymal stem cells (MSCs) derived from the human bone marrow were differentiated into new pancreatic cells alleviated the increase in blood glucose in diabetic group. On similar ground, a streptozotocin (STZ) diabetic rat model treated with MSC injection at the early (7 days) and late phase (21 days) could be able to control the hyperglycemia in diabetic rats with type 2 [32]. Zhang, *et al.* [33] reported that the increased blood glucose was associated with the decreased insulin secretion in the diabetic rats when compared with the non-diabetic rats and it was improved after treated with MSCs, which represented by tubular dilatation, mesangial expansion and glomerular sclerosis observed histopathologically under light microscope. Similar to our result, Lee *et al*. [34] and Ezquer *et al*. [35] showed that hyperglycemia and renal histology of diabetic rat was improved by MSC therapy when compared with the DN group. Lang and Dai [36] study showed that, there was an increase in the mesangial cells and mesangial matrix in diabetic rats when compared with the non-diabetic rats whereas in the MSC group, the histopathological changes were improved inhibiting the renal fibrosis compared with the DN group.

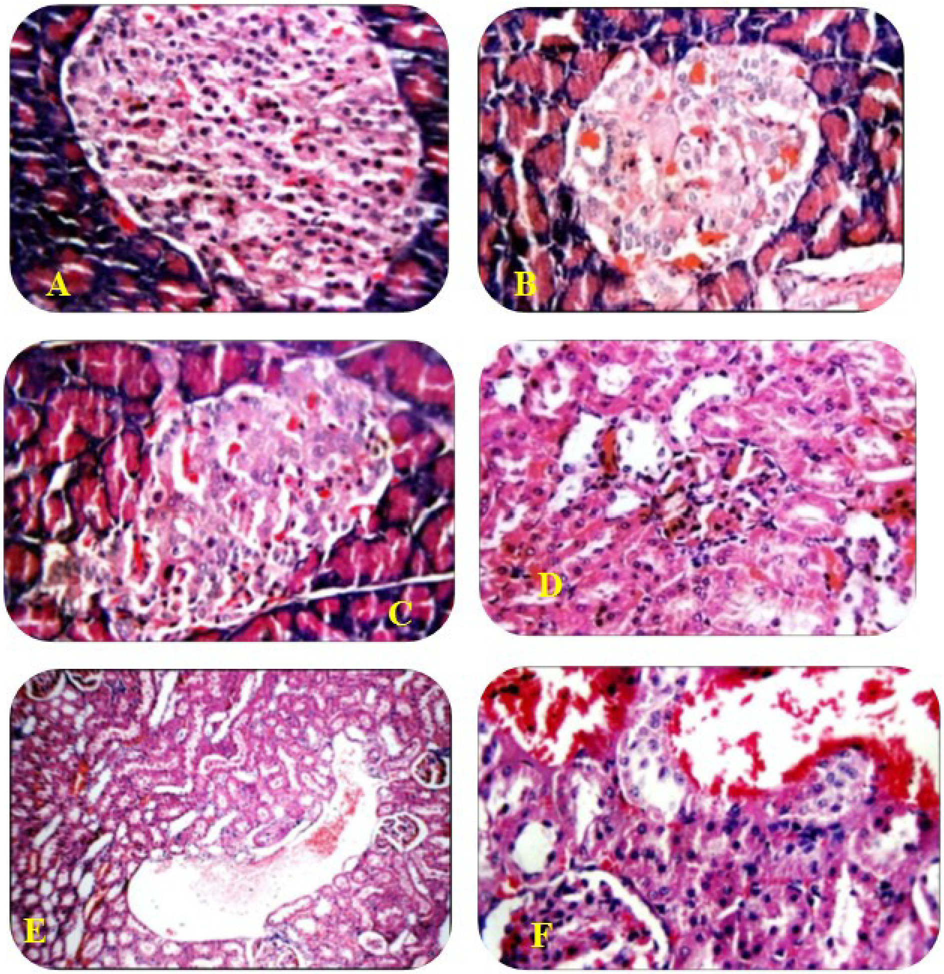

Figure 1: A- Normal pancreatic section from the control group (H&E X 360), B- The DN group showed necrotic Islets' cells of pancreas and marked edema (H&E X360), C- The BM-MSCs treated group showed more cellular Islets of pancreas (H&E X 360), D- Normal kidney section from the control group (H & E X 360), E- The DN group showed markedly dilated congested blood vessel in the kidney (H & E X 360), F- The BM-MSCs treated group showed average glomerulus and tubules in the kidney (H & E X 360).

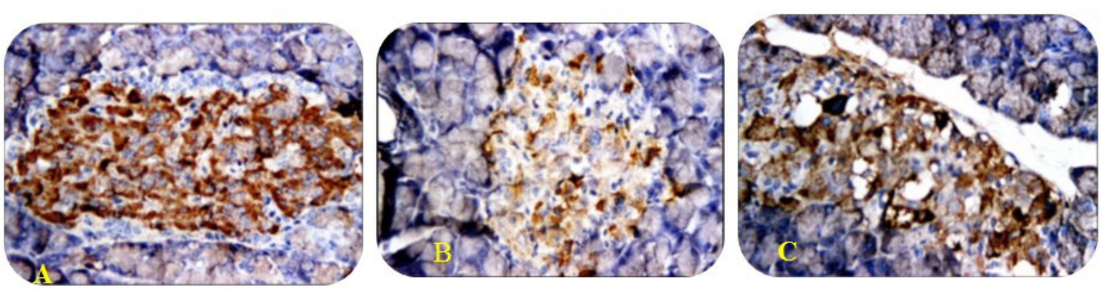

Figure 2: A- Normal pancreatic section from the control group showed marked cytoplasmic reactivity to insulin antibodies (insulin immunostain x 360). B- The DN group showed mild cytoplasmic reactivity to insulin antibodies (insulin immunostain x 360). C- The BM-MSCs treated group showed marked reactivity to insulin antibodies (insulin immunostain x 360).

Serum urea and creatinine were lowered after the BM-MSCs treatment due to the decrease protein degradation and the increase of their clearance by the kidney [37]. In contrary with our study, compared with the DN group, the single transplantation of MSCs didn't affect blood glucose levels in diabetic rats, whereas repeated injection for 7 days could significantly control it [38]. Moreover, a study of Ezquer *et al.* [39] demonstrated that, administration of MSCs in a mouse model did not result in hyperglycemia correction. In addition, Wang *et al.* [12] provided clear evidence that the injected MSCs prevented the development of albuminuria and loss of podocytes but there was no improvement in blood sugar levels. MSCs was used to ameliorate hyperglycemia, suppress oxidative stress in kidney homogenate and improve renal histopathological changes in diabetic rats with DN [40]. Liu *et al.* [41] reported that the IHC of the DN group showed mild cytoplasmic reactivity to insulin antibodies when compared with the control group and after treated with BM-MSCs, the pancreatic tissue showed marked reactivity to insulin antibodies (more than 75% of Islets' cells) when compared with the DN group, which supported our findings.

Conclusion

Bone marrow mesenchymal stromal cells had the ability to renew into islet cells and were differentiated into functional insulin secreting cells, which indicated its beneficial effects on diabetes-induced nephropathy and strongly recommended BM-MSCs in treating clinical cases of DM and DN as a future therapy.

Conflict of interest

The authors declare no conflict of interest.

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الملخص العربي

التأثير المحسن للخلايا الجذعية الوسيطه علي اعتلال الكلي السكري في ذكور الجرذان

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[٢]قسم الكيمياء الحيوية كلية الطب البيطري- جامعة الزقازيق
[٣]قسم الكيمياء الحيوية كلية العلوم- جامعة الزقازيق

مرض السكري بكلا نوعيه يتميز بتدمير البنكرياس أو الإعتلال الوظيفى لخلايا الأيلتز مما يتسبب فى مضاعفات عديدة ومنها إعتلال الكلى السكرى والذى يؤدى فى مراحله المتأخرة إلى إرتفاع معدل الوفيات منذ ظهوره فى مرض السكري بنوعيه١او٢. وتعد زراعة الخلايا الجذعية من الطرق الحيثة والامنة والفعالة فى علاج مرض السكرى ومضاعفاته ومنها الخلايا الجذعية الوسيطة التى تعد من أفضل أنواعها والتى تستخدم فى تحسين نسبة السكر بالدم لذلك الهدف من هذه الدراسة هو أظهار تأثير الخلايا الجذعية الوسيطة المعزولة من النخاع الشوكى على إعتلال الكلى السكرى فى مراحله المبكرة . حيث تم التقسيم العشوائى لذكور الجرذان إلى ثلاث مجموعات (كل مجموعة تحتوى على ٢٠ جرذ): المجموعة الأولى :هى المجموعة الضابطة و كانت تحتوى على جرذان طبيعية ،بينما المجموعة الثانية: كانت تحتوى على جرذان مصابة بالسكرى نتيجة للحقن بمادة الأستربتوزوتوسين والمجموعة الثالثة تحتوى على الجرذان المصابة بالسكرى والمعالجة بعد ثلاث أيام من الاصابة بالخلايا الجذعية الوسيطة المعزولة من النخاع الشوكى . وقد أظهرت النتائج أن الجرذان المصابة باعتلال الكلى السكرى قد إظهرت فقدان فى الوزن ،إرتفاع معدل السكر فى الدم، إنخفاض معدل الانسولين فى الدم،إرتفاع الهيموجلوبين السكرى فى الدم ،زيادة عدد الكرات البيضاء بالدم وإختلال فى وظائف الكلى والاجهاد التأكسدى لأنسجة الكلى وباستخدام الخلايا الجذعية تم ملاحظة تحسن فى مستوى السكر ووظائف الكلى ، وتم إنخفاض فقدان الوزن وتحسن فى معدل الانسولين والهيموجلوبين السكرى مع تحسن الاكسدة فى نسيج الكلى لذلك الخلايا الجذعية الوسطية المعزولة من النخاع الشوكى لديها القدرة على تجديد الخلايا المنتجة للانسولين مما يؤدى الى تحسن مرض السكرى وإعتلال الكلى المصاحب له.