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SHORT COMMUNICATION

AMELIORATING EFFECTS OF MESENCHYMAL STEM CELLS DRIVED FROM ADIPOSE AND BONE MARROW TISSUES ON CARDIOMYOPATHY OF DIABETIC RATS: A COMPARATIVE STUDY

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ABSTRACT

Diabetic cardiomyopathy (DCM) is considered one of the main diabetic complications, contributing to specific forms of heart failure independent from hypertension or ischemia. There are increased research efforts to further explore a new potential therapeutic strategy for preventing or reversing DCM progression. The present research aimed to explore which type of stem cell-based therapies could serve as an effective tool for the treatment of DCM in type 1 diabetic rats. Four groups of male Wistar rats have been used in this study including the control group, a diabetic-untreated group, and two diabetic rat groups treated with either mesenchymal stem cells (MSCs) derived from adipose tissue (AD-MSCs) or bone marrow (BM-MSCs). Interestingly, serum levels of heart dysfunction markers (LDH and CK-MB) in the diabetic rats were found to be declined to near-normal levels following injection with either of the two MSCs types. Also, BM-MSCs or AD-MSCs (1×10^6 cell/rat)-treated diabetic rats exhibited significant decreases in the cardiac xanthine oxidase activity, reactive oxygen species, and malondialdehyde level, accompanied with marked elevations in various antioxidants, compared with the diabetic untreated group. The results also clearly point out the excellence of AD-MSCs injection as a potential agent in alleviating the DCM over BM-MSCs injection.

INTRODUCTION

One of the cardiovascular disease major risk factors, which have been recognized a long time ago for carrying the same mortality risk of myocardial infarction (MI) itself, was diabetes mellitus (DM))[1]. Eventually, long-term uncontrolled DM can result in progressive structural and functional re-modeling of the myocardium caused by lipid accumulation in cardiomyocytes, myocardial fibrosis, and chronic inflammation without coronary atherosclerosis and hypertension; a disorder known as diabetic cardio-myopathy (DCM)[1]. Unfortunately, DCM is accounting for an estimated more than 80% of all diabetic deaths worldwide, making it one of the main mortality and morbidity causes in diabetic patients[2,3]. A long-standing hypothesis is that hyper-glycemia, hyperinsulinemia, and hyperlipid-

emia were considered the main characteristic metabolic disturbances evident in DM. All of these metabolic abnormalities induce the production of the reactive oxygen species (ROS) or/and reactive nitrogen species (RNS) leading to a specific altered cardiac structure and function, which plays an essential role in the DCM progress[4]. Collectively, energy deficit, lipid accumulation, ROS levels elevation, enhanced free radical generation, advanced glycation end-product (AGEs), and increased production of lipid peroxides were considered the main DCM hallmarks[2].

In recent decades, from a therapeutic perspective and facilitated by the ease of preparation and immunologic privilege, multipotent mesenchymal stem cells (MSCs) have been used systemically or locally as an extremely promising therapeutic agent to treat various diseases, including diabetes complications and heart diseases[1,5]. Therefore, MSCs transplantation has been widely used as an effective method of protecting the damaged myocardium and improving cardiac function in many non-ischemic or ischemic heart diseases, since they can migrate to injured cardiac sites and regenerate heart tissues by paracrine mediators that could alleviate the established DCM by supporting other cells' nutrition and environment[6]. MSCs were found to possess wide repertoires of growth factors including hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), and some cytokines/chemokines. Altogether play vital roles in accelerating cardiac vascularization and enhancing healing processes *via* various mechanisms involving neovascularization, cryoprotection, and apoptosis inhibition that collectively could minimize ischemic reperfusion injury. These paracrine effects of MSCs could eventually lead to antioxidative, anti-inflammatory, antifibrotic, and antiapoptotic activities, pro-angiogenic features, and endothelial-protective effects, which could protect the survival of existing cardiomyocytes besides activating and accelerating the proliferation of resident cardiac stem cells[7-9].

Bone marrow MSCs (BM-MSCs), followed by adipose tissue MSCs (AD-MSCs), and umbilical cord MSCs (UC-MSCs) were found to be the most evaluated MSCs prevalent sources in different pathological clinical trials[6]. However, there are still few studies focusing on the effect of MSCs on DCM. As far as we know, investigations on AD-MSCs role in treating DCM were almost non-existing, in contrast to many reports cleared that BM-MSCs have demonstrated potential in treating DCM. Therefore, the present study aimed to explore which MSCs type has the greater therapeutic potential of both BM-MSCs and AD-MSCs on cardiac dysfunction of DCM in rats afflicted with type 1 diabetes mellitus (T1DM).

MATERIAL AND METHODS

Chemicals

Both BM-MSCs and AD-MSCs constituents of culture media, in addition to streptozotocin (STZ), were purchased from Sigma Aldrich Co. (St. Louis, MO, United States).

Experimental animals and design

The experiment was conducted following the Faculty of Science Animal Ethics Committee guidelines, Arish University, North Sinai, Egypt. Male allogeneic Wistar rats (age: 6-8 weeks, weight: 100-120 g) were obtained from the laboratory animal facility of the National Research Center, Giza, Egypt. Rats were kept at room temperature (22±2°C) with humidity of 50±5%, 12/12-hours light/dark cycle, and were fed standard pellet chow (El-Nasr Chemical Co., Cairo, Egypt), where food and water were allowed *ad libitum*. After two weeks of acclimatization before dietary manipulation, four equal rat groups (n=6) were randomly selected from 24 rats as follows:

- Control group: Received an intraperitoneal injection (once) of sodium citrate buffer (pH 4.5)
- Diabetic untreated group: Received an intraperitoneal injection (once) of STZ (45 mg/kg

body weight dissolved in sodium citrate buffer, pH 4.5)
- AD-MSCs-treated diabetic group: Diabetic rats received an intraperitoneal injection (once) of AD-MSCs (1×10^6 cell/rat)
- BM-MSCs-treated diabetic group: Diabetic rats received an intraperitoneal injection (once) of BM-MSCs (1×10^6 cell/rat)

Following three days of induction of T1DM by STZ, only rats with tail vein fasting blood glucose (FBG) ≥ 250 mg/dL were considered diabetic[10] and participated in the study, while non-diabetic rats have been excluded. The experimental protocol was continued for 4 consecutive weeks. Both allografts of AD-MSCs and BM-MSCs were isolated from fresh subcutaneous adipose tissues and bone marrow of male Wistar rats, respectively. Both extraction and preparation of either BM-MSCs or AD-MSCs were carried out following the method of Hamza *et al*.[11] and Chen *et al*.[12], respectively.

Blood and heart samples collection

Overnight fasted rats were anesthetized by light diethyl ether, dissected, and blood samples were directly withdrawn immediately from the heart and centrifuged for 15 min at 1000 ×*g*. Blood sera were carefully separated, labeled, and preserved for subsequent biochemical analyses at –20°C. Meanwhile, heart specimens were removed and cleaned with saline solution, where an appropriate part was weighed, homogenized in cold distilled water forming 10% (weight/volume) homogenate, labeled, and preserved for later biochemical evaluations at –20°C, while the remnant part was preserved at –80°C until used for measuring viability by flow cytometric analysis.

Flow cytometric analyses

The percentages of viable cardiac cells (G0/G1) in addition to both positive (CD73, CD90, and CD105) and negative (CD11b, CD34, and CD45) surface markers analyses used for the phenotyping characterization of either AD-MSCs or BM-MSCs were evaluated by flow cytometry according to the method of Dean and Jett[13], using specific antibodies for rats purchased from Sigma Aldrich Company. The phenotype of cultured MSCs cells has been confirmed following the minimal criteria of the International Society for Cellular Therapy (ISCT) before performing the animal study. They highly expressed CD73, CD90, and CD105 markers and were negative for CD11b, CD34, and CD45 markers as described previously[14].

Biochemical assays

Serum lactate dehydrogenase (LDH) and creatine kinase (CK)-MB activities were assessed by using the SPINREACT diagnostics kits (Barcelona, Spain). Meanwhile, Biodiagnostic (Giza, Egypt) kits were used to estimate the levels of ROS, malondialdehyde (MDA), and reduced glutathione (GSH), and total antioxidant capacity (TAC), as well as xanthine oxidase (XO), glutathione-S-transferase (GST), superoxide dismutase (SOD), catalase (CAT), and heme-oxygenase 1 (HO-1) activities, in addition to AGEs in cardiac tissues. All measurements were performed according to the instructions of the supplier.

Statistical analysis

Obtained data were statistically evaluated with ANOVA followed by Tukey's multiple range tests using Statistical Package for the Social Sciences (SPSS) software (version 17.5) for Windows. Results were expressed as the Mean ± standard error (SE), where n=6, and the *P*-value ≤ 0.05 was considered significant.

RESULTS

Both LDH and CK-MB activities showed a marked increase ($P\leq0.05$) in the serum of diabetic rats, compared with the control group. However, comparable to untreated-diabetic rats, such parameters exhibited a significant decline in both MSCs-treated diabetic groups. Notably, such results reflected a great amelioration in cardiac function of diabetic rats treated with AD-MSCs than those treated with BM-MSCs (Table 1).

Table 1: Serum activities of LDH and CK-MB among the different groups.

	Control	Diabetic	Diabetic + AD-MSCs	Diabetic + BM-MSCs
LDH (U/L)	620.0±19.4	1212.3±30.9[a]	657.0±20.4[b]	943.7±22.6[abc]
CK-MB(U/L)	149.7±3.2	315.2±6.6[a]	165.0±2.9[b]	206.2±3.0[abc]

Values expressed as means ± their standard errors (n = 6). Significant differences ($P \leq 0.05$) compared with the control, diabetic, and AD-MSCs-treated diabetic groups were represented as [a, b] and [c], respectively. LDH: lactate dehydrogenase, CK-MB: creatine kinase isoenzyme, AD-MSCs: mesenchymal stem cells derived from adipose tissue, BM-MSCs: mesenchymal stem cells derived from bone marrow.

Table "2" illustrated significant elevations in some cardiac oxidative stress markers (XO activity as well as ROS, MDA, and AGEs levels) of diabetic rats as compared with the control rats. Interestingly, in comparison with the diabetic-untreated group, our data demonstrated a significant decline ($P \leq 0.05$) in the oxidative stress markers in both BM-MSCs- and AD-MSCs-treated diabetic groups. However, results of AD-MSCs injection to diabetic rats revealed a marked superiority than BM-MSCs injection in minimizing the cardiac oxidative stress development.

Table 2: Cardiac levels of oxidative stress markers among the different groups.

	Control	Diabetic	Diabetic + AD-MSCs	Diabetic + BM-MSCs
MDA (nmol/g)	67.1±3.6	162.1±5.1[a]	78.1±3.1[b]	113.5±3.2[abc]
ROS (nmol/g)	0.43±0.02	2.22±0.07[a]	0.56±0.02[b]	1.05±0.04[abc]
AGEs (AU/mg)	2.70±0.13	7.76±0.23[a]	2.81±0.15[b]	4.05±0.11[abc]
XO (U/mg)	37.3±0.1	88.0±2.3[a]	41.2±1.2[b]	55.4±1.2[abc]

Values expressed as means ± their standard errors (n = 6). Significant differences ($P \leq 0.05$) compared with the control, diabetic, and AD-MSCs-treated diabetic groups were represented as [a, b] and [c], respectively. MDA: malondialdehyde, ROS: reactive oxygen species, AGEs: advanced glycation end-product, XO: xanthine oxidase, AD-MSCs: mesenchymal stem cells derived from adipose tissue, BM-MSCs: mesenchymal stem cells derived from bone marrow.

Table "3" illustrated significant decreases in many antioxidant markers (HO-1, CAT, SOD, and GST activities, TAC, and GSH level) and viable cardiac cells (G0/G1) of diabetic rats, in comparison with the control rats. However, an obvious increase ($P \leq 0.05$) in cardiac antioxidants levels and viable cardiac cells (G0/G1) were recorded in both BM-MSCs- and AD-MSCs-treated diabetic groups, as compared with the diabetic-untreated group. Notably, AD-MSCs injection to the diabetic rats increased much more antioxidant capacity than BM-MSCs injection.

DISCUSSION

Approximately 10% of the world population is diabetic nowadays according to the last

WHO estimates. Interestingly, hyperglycemic diabetic patients were found to exhibit 8% enhancement in the heart failure risk progression with every HbA1c 1% rise[15]. It is well known that persistent hyperglycemia was found to cause various metabolic and molecular cardiomyocytes destructive changes *via* a series of secondary transducers. One of the main abnormalities is increased generation of AGEs that could initiate a nitric oxide (NO) deactivation, resulting in marked damage coronary vasodilation. AGEs can covalently crosslink both collagen and elastin resulting in impaired cardiac relaxation with increased myocardial stiffness[2]. Moreover, prolonged hyperglycemia could result in an overproduction of cardiac mitochondrial superoxide, which consequently increased oxidative stress *via* initiating excessive cardiac ROS formation from both mitochondrial and extramitochondrial sources; causing plentiful dangerous effects on the cardiovascular system either directly through damaging proteins and DNA resulting in cardiac cells' apoptosis, or indirectly *via* cellular damage by oxidation, redox signaling, and interference with NO, leading to vascular homeostasis disruption[16].

Table 3: Cardiac antioxidants and viable cell (G0/G1) percentages among the different groups.

	Control	Diabetic	Diabetic + AD-MSCs	Diabetic + BM-MSCs
GSH (mg/g)	51.5±3.2	24.1±1.0^{a}	49.5±2.2^{b}	39.1±2.2^{abc}
SOD (U/g)	5.76±0.22	1.70±0.14^{a}	5.50±0.33^{b}	3.90±0.78^{abc}
CAT (U/g)	0.65±0.06	0.20±0.03^{a}	0.62±0.06^{b}	0.43±0.03^{abc}
GST (U/mg)	5.20±0.54	1.90±0.14^{a}	4.90±0.32^{b}	3.50±0.44^{abc}
TAC (mg/g)	2.40±0.08	0.65±0.03^{a}	2.30±0.05^{b}	1.70±0.05^{abc}
HO-1(U/mg)	277.0±10.2	122.0±3.1^{a}	269.0±7.5^{b}	222.0±9.6^{abc}
G0/G1 (%)	95.3±2.7	53.4±2.1^{a}	94.2±2.7^{b}	81.5±2.2^{abc}

Values expressed as means ± their standard errors (n = 6). Significant differences ($P \leq 0.05$) compared with the control, diabetic, and AD-MSCs-treated diabetic groups were represented as $^{a, b}$ and ^{c}, respectively. GSH: reduced glutathione, SOD: superoxide dismutase, CAT: catalase, GST: glutathione-S-transferase, TAC: total antioxidant capacity, HO-1: heme-oxygenase 1, AD-MSCs: mesenchymal stem cells derived from adipose tissue, BM-MSCs: mesenchymal stem cells derived from bone marrow.

Interestingly, like AGEs, a raise in ROS diminishes the NO levels that could accelerate cardiomyocyte apoptosis and cellular DNA damage resulting in endothelial dysfunction and myocardial inflammation, *via* activating poly ADP ribose polymerase, a DNA reparative enzyme that could in turn redirects glucose metabolism from its usual glycolytic pathway to an alternative biochemical pathway[2]. Such cellular events could results in various mediators' development, causing marked hyperglycemia-induced cellular injuries; leading to a significant myocardial contractility reduction that could eventually initiate both myocardial fibrosis and dysfunction[2]. Additionally, gluconeogenesis, glycogenolysis, and impaired insulin-mediated glucose uptake in peripheral tissues in T1DM could result in

marked hyperglycemia accompanied by increased production of ROS in the diabetic heart *via* leakage of the mitochondrial electron transport chain, the interaction of AGEs with their receptors, endothelial nitric oxide synthase (eNOS) uncoupling, and increased activity of XO[17]. XO is an extra-mitochondrial enzyme found in the cytosol of cardiomyocytes, which could generate $O_2^{\bullet}$ and H_2O_2 during the hypoxanthine and xanthine metabolism into uric acid. In this line, a fourfold increase in XO mRNA has been recorded in dogs with induced dilated cardiomyopathy, compared with healthy dogs[16].

On the other hand, there have been numerous clinical trials that recently proposed MSCs as a promising therapeutic agent to treat several diabetic complications, including DCM[5,6]. Orlic *et al*.[18] demonstrated that locally delivered autologous BM-MSCs to mice with infarcted hearts could result in regeneration of damaged myocardium. Following our data, Liu *et al*.[9] cleared that DCM rats exhibited an improved cardiac function following intravenous injection with BM-MSCs, through being differentiated into cardiomyocytes to counteract the impairment of diabetic niche and improved angiogenesis and myogenesis *via* multidirectional differentiation. Recently, Ammar *et al*.[15] demonstrated that transplantation of BM-MSCs (one million cells/rat) prevented cardiac fibrosis and promoted angiogenesis in STZ-diabetic hearts of male Wistar rats.

The improvement in cardiac function after MSCs administration mainly rely on their direct differentiation into cardiomyocytes or by indirect paracrine secretion of paracrine trophic factors and chemokines mediators (such as B-cell lymphoma 2, hypoxia-regulated HO-1, HGF, and VEGF) to maximize survival and proliferation of cardiomyocytes and minimize both ROS production and the inflammatory response that could eventually attenuate cardiac remodeling[9]. So, MSCs can benefit the cardiomyocytes' local niche, leading to obvious myocardial viability and contractility improvement. Furthermore, MSCs secretion of various trophic mediators could partially initiate an insulin resistance enhancement, *via* their anti-inflammatory and immunosuppressive capacities[9].

Since impairment of the antioxidant defense system coupled with oxidative stress elevation was found to be the main feature of the diabetic myocardium that mediates the pathogenesis of DCM, decreasing oxidative stress in the heart through enhancement of the antioxidant system could exert a beneficial effect against DCM[16]. Hence, in line with many previous studies, decreasing XO activity in the heart of diabetic rats following injection of either AD-MSCs or BM-MSCs in our study was believed to enhance heart function in diabetic rats. In the study of Amado *et al*.[19], inhibition of XO markedly enhanced myocardial contractility and performance in dog's model for heart failure. Moreover, in C57/BL6 diabetic mice, XO inhibition was found to improve cardiac dysfunction through minimizing nitrosative/oxidative stress and fibrosis[20]. In addition, according to Gao *et al*.[21], attenuation of left ventricular dysfunction was recorded in heart of STZ-induced diabetic rats following inhibition of XO. Recently, plenty of studies revealed that AD-MSCs or BM-MSCs (1×10^6 cells/rat) injection to STZ-diabetic rats extremely modulated the increased levels of both ROS and MDA in various tissues including the heart, while rising many antioxidants' mRNA expression levels (SOD-1 and 3, CAT, glutathione peroxidase-1, 3, and 4, GSH, TAC, and HO-1), compared with diabetic untreated rats[12,14,22,23]. In fact, and in harmony with our findings, previously reported studies attributed MSCs capabilities in overcoming DCM to their notable antioxidant capacity in alleviating oxidative stress as a consequence of prolonged hyperglycemia.

In conclusion, evidence in the literature advocates that MSCs intervention is a potent tool in attenuating DCM. The beneficial effects of both MSCs types on the diabetic

myocardium were found to rely basically on amendment of the hyperglycemia-induced ROS-generating pathways, probably *via* secreting various paracrine trophic factors and cytokines, which could enhance cardiac cells' niche and function in T1DM. Our data confirmed AD-MSCs injection superiority over BM-MSCs as a predominant candidate for stem cell-based therapy in DCM.

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CONFLICT OF INTEREST
The authors have no potential financial conflict of interest.

AUTHORS' CONTRIBUTIONS
SGE, EIE, and HMR designed the work. Bioassays were performed by SGE, EIE, DYK, and HMR. All authors read and approved the manuscript.

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التاثيرات المُحَسنة للخلايا الجذعية الميزنكيمية المشتقة من الأنسجة الدهنية ونخاع العظام على اعتلال عضلة القلب في الجِرذان المصابة بمرض السكري: دراسة مقارنة

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يعتبر اعتلال عضلة القلب السكري أحد المضاعفات الرئيسية لداء السكري، حيث يساهم في أشكال معينة من قصور القلب بشكل مستقل عن ارتفاع ضغط الدم أو نقص التروية. وهناك جهود بحثية متزايدة لمواصلة استكشاف استراتيجية علاجية جديدة محتملة لمنع أو لتراجع تقدم اعتلال عضلة القلب السكري. لذلك كان الهدف من البحث الحالي هو تحديد أي من العلاجات القائمة على الخلايا الجذعية يمكن أن يكون بمثابة أداة فعالة لعلاج اعتلال عضلة القلب السكري في الجِرذان المصابة بداء السكري من الطراز الأول. تم استخدام أربع مجموعات من ذكور الجِرذان من سلالة "Wistar" في هذه الدراسة متضمنة المجموعة الضابطة، ومجموعة الجِرذان المصابة بداء السكري غير المعالجة، بالإضافة إلي مجموعتين من الجِرذان المصابة بداء السكري والمعالجة إما بالخلايا الجذعية الميزنكيمية المشتقة من الأنسجة الدهنية أو المشتقة من نخاع العظام. ومن المثير للاهتمام، أن مستويات المصل لعلامات ضعف القلب (LDH و CK-MB) في الجِرذان المصابة بداء السكري قد انخفضت إلى مستويات قرب الطبيعية بعد الحقن بالخلايا الجذعية الميزنكيمية. أيضًا، أظهرت الجِرذان المصابة بداء السكري التي عولجت بالخلايا الجذعية الميزنكيمية (مليون خلية/جِرذ) انخفاضًا إحصائيا ملحوظًا في نشاط إنزيم الزانثين أكسيديز، وطرز الأكسجين التفاعلية، ومستوى المالون داي ألديهيد في القلب، مصحوبًا بارتفاع ملحوظ في مضادات الأكسدة المختلفة، مقارنة مع مجموعة الجِرذان المصابة بداء السكري غير المعالجة. تشير النتائج أيضا بوضوح إلى تميز الحقن بالخلايا الجذعية الميزنكيمية المشتقة من الأنسجة الدهنية كعامل محتمل في التخفيف من اعتلال عضلة القلب السكري عن الحقن بالخلايا الجذعية الميزنكيمية المشتقة من نخاع العظام.