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ORIGINAL PAPER

Autologous mesenchymal stem cell therapy for diabetic men with erectile dysfunction. Is it promising? A pilot study

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Summary ***Purpose: to assess safety and efficacy of autologous mesenchymal bone marrow stem cell injection in penile cavernosal tissue for erectile dysfunction therapy in diabetic men.***
Methods: The subjects of this study were diabetic men suffering erectile dysfunction, non-responding to maximum dose of oral PDE5I. Mesenchymal bone marrow stem cells were aspirated and injected after preparation in both corpora cavernosa at 3, 9 o'clock position. Erectile function was assessed by the International Index of Erectile Function and penile Doppler study, before and after 6 months after injection.
Results: 4 patients out of 10 achieve hard erection adequate for satisfactory coitus, and 2 patients achieved penile hardness with addition of pharmacological therapy with sildenafil 100mg. Peak systolic velocity increased significantly in 4 patients (2 arteriogenic and 2 mixed erectile dysfunction), from 12~22 cm/s to 32~69 cm/s. Variations in end-diastolic velocity increased substantially in 2 patients with venogenic insufficiency alone at follow-up from 4~5 cm /s to -4~-3 cm/s.
Conclusions: Despite promising stem cell treatment efficacy for patients with erectile dysfunction, more clinical studies and researches are still warranted.

KEY WORDS: Erectile dysfunction; Diabetes; Stem cell.

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In 1995, the global *erectile dysfunction* (ED) prevalence was evaluated to be 152 million and is expected to reach 322 million by 2025 (2). ED may be organic, psychogenic or a combination. ED organic type is divided into vasculogenic, neurogenic, cavernous, drug-induced, systemic disease-related and hormonal categories (2). Diabetic men tend to experience ED more frequently and 10-15 years earlier than non-diabetic men (3). Diabetes-related ED is a serious issue that has a significant influence on patients' life quality and family harmony (4).
In addition, ED in diabetic people is more resistant and severe to treatment than in nondiabetic patients (5). Pathogenic impact of diabetic ED comprises endothelium malfunction, smooth muscle composition reduction, neuronal degeneration, and fibrosis, all of which lead to the erectile dysfunction development (6). Although *phosphodiesterase type 5 inhibitors* (PDE5i) are beneficial in treating erectile dysfunction in the majority of patients, their effectiveness is much reduced in diabetic people (7). This is likely due to the decreased generation of *nitric oxide* (NO) as a consequence of endothelial dysfunction (8). ED linked with diabetes is similarly very resistant to PDE5i therapy, with a 44% success rate opposed to an 85% success rate for hypogonadal ED patients (9).
Patients with diabetes and erectile dysfunction had the greatest incidence of therapy termination with PDE5Is (28/36, or 78 percent) (10). Therefore, finding an effective therapy for ED linked with diabetes is one of the most significant goals of modern ED research. Recent treatment techniques, like as gene therapy and stem cell therapy, are being investigated to treat diabetic ED more successfully. Stem cell is a possible therapy for diabetic ED. Multiple stem cell types have been utilized to cure ED, including BMSC, ADSC, and USC (11-13). Stem cells may develop into several cell types, such as *smooth muscle cells* (SMC), neurons and vascular endothelial cells. In addition, they may emit paracrine substances that may boost angiogenesis and cell survival (14).
A study was conducted in our *Urology Department* from March 2016 to September 2018.

METHODS

The study was conducted after ethical committee approval. For all men included in the study, explanation of the study procedures was done and informed consent was onbtained before enrollment.

Inclusion criteria

Diabetic adult men with HbA1c between 6.5% and 10% with diagnosis of diabetes mellitus dated more than 5 years. Having a consistent sexually active partner. Inadequate sexual activity in spite of taking the maximal dosage of oral PDE5I during the last eight weeks.

Exclusion criteria

History of bone marrow disorders, neurogenic ED, gentamycin hypersensitivity. History of severe cardiovascular disease (angina, arrhythmias, cardiac failure, and stroke), renal failure, and respiratory failure as life-threatening conditions. Positive HIV, HBV, HCV, and syphilis tests. Cancer history during the last five years. HbA1c levels more than 10 percent. Uncontrolled hypertension or hypotension (systolic blood pressure > 170 or 90 mm Hg, diastolic blood pressure > 100 or 50 mm Hg).

Anticoagulant therapy. Severe infectious disease. Testosterone concentration less than 200ng/dL Having a penile implant or be open to getting one, Patients with alterations in penis morphology. Subjects participating in additional clinical studies in the previous 30 days. Subjects unable to comply with procedure. All participants were subjected to detailed medical and sexual history including IIEF questionnaire, physical examination including (general and genital examination) and laboratory work up including testosterone level, HBA1C, prolactin, LH and FSH. Evaluation of general condition by *cell blood count* (CBC), liver function, renal function, and thyroid function tests, lipid and coagulation profile was done for all patients. Penile Doppler Ultrasound was done for all patients. Normal peak systolic velocity was defined as a value ≥ 35 ml/second and normal end diastolic velocity was defined as a value ≤ 3 ml/second.

Table 1.
6-question IIEF Questionnaire.

1-How often were you able to get an erection during sexual activity?
2-When you had erections with sexual stimulation, how often were your erections hard enough for penetration?
3-When you attempted intercourse, how often were you able to penetrate (enter) your partner?
4-During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
5-During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
6-How do you rate your confidence that you could get and keep an

IIEF Patient Questionnaire

The 6-question IIEF Questionnaire (Table 1) is a validated, multidimensional, self-administered study that has shown beneficial in clinical studies for assessing erectile dysfunction and treatment effects. This questionnaire in addition to the penile Doppler were performed before and 6 months after injection.

Patients with poor IEEF scores (17 out of 30) in D (Erectile Function) were eligible for mesenchymal stem cell treatment.

Procedures

Under sterile conditions with local anesthetics, ten ml *mesenchymal stem cell* (MSCs) were aspirated from the bone marrow of the iliac crest of the candidate. After lab processing, the sample was brought to the operative theater. In the operation room, the patient was positioned in the supine position.

Genitalia were sterilized and penile block was performed. Then genitalia were sterilized again, MSCs were injected in both corpora cavernosa at 3 and 9 o'clock position.

Outcome measures

Six months following injection, IIEF and *Peak systolic velocity* (PSV) and *End diastolic velocity* (EDV) were tested for changes from baseline (preoperative).

Statistical analysis: Using *statistical program for social sciences* (SPSS) version 23.0 for Windows, the acquired data were edited, structured, tabulated, and statistically analyzed. Data are displayed as mean, SD, frequency, and percentage. Student's t test was used to compare continuous variables (two-tailed). We compared categorical variables using the chi-square (2) and Fisher's exact tests (if needed). The level of significance was accepted if the P value < 0.05.

RESULTS

This study included 10 diabetic patients complaining of ED, mean age 52 years and HBA1c range from 6.5 -9.5. Hyperlipidaemia was detected in 6 (60%) patients. Table 2 demonstrates the demographic characteristics of the studied patients.

Erectile function was assessed by IIEF- score and penile Doppler study. Two patients have pure arterial insufficiency, 4 (40%) patients have pure veno-occlusive disor-

Table 2.
Demographic characteristics of the studied patients.

Parameters	**All cases n = 10**
Age (years) Mean + SD	52.3 ± 6.4
Range (Min-Max)	25 (40-65)
Residence	**N (%)**
Rural	3 (30.0%)
Urban	7 (70.0%)
Education	**N (%)**
Illiterate	5 (50.0%)
Secondary	3 (30.0%)
High	2 (20.0%)
Socio-economic level	**N (%)**
Low	4 (40.0%)
Middle	3 (30.0%)
High	3 (30.0%)
Medical diseases	**N (%)**
Diabetes	10 (100.0%)
Hyperlipidemia	6 (60.0%)

der and 4 (40%) patients mixed arteriogenic and vasculogenic insufficiency as declared by penile Doppler study, Table 3 shows the ED type among the studied patients.
The effect of single intracavernosal injection of BMSc on erectile function were assessed using IIEF-6 questions as shown in Table 4 and penile Doppler study at 6 months, as in Table 5 and 6, comparing the PSV and EDV before and after injection at 6 months.

Table 3.
Classification of erectile dysfunction in the studied patients.

	All cases n = 10
Type	**N (%)**
Single	6 (60.0%)
Mixed	4 (40.0%)

Table 4.
Comparison of International Index of Erectile Dysfunction before and after injection (Total n = 10).

	Before treatment Mean ± SD	After treatment Mean ± SD	P-value
All cases n = 10	12.7 ± 2.16	19.2 ± 5.75	0.026 S

Table 5.
Comparison of peak systolic velocity (PSV) before and after injection at 6 months (Total n = 10).

	Before injection Mean ± SD	After injection Mean ± SD	P-value
All cases n = 10	25 ± 12.5	40.9 ± 18.9	0.016 S
Mixed cases n = 4	13.75 ± 6.13	25.5 ± 13.2	0.16 NS
Arteriogenic cases n = 6	16.33 ± 6.21	38.8 ± 22.8	0.036 S

Table 6.
Comparison of End Diastolic velocity EDV before and after injection at 6 months (Total n = 10).

	Before injection Mean ± SD	After injection Mean ± SD	P-value
All cases n = 10	3.9 ± 5.4	0.9 ± 4.09	0.026 S
Mixed cases n = 4	5.07 ± 2.08	3.33 ± 1.15	0.37 NS
Arteriogenic cases n = 6	6.12 ± 2.7	2.37 ± 3.8	0.022 S

Discussion

DM is a systematic disease that affects every part of the body. In the penis, it is associated with reduced contents of all three key components for erectile function, namely, *cavernous nerve* (CN), *cavernous endothelial cells* (CEC) and *smooth muscle cells* (CSMC) (15-19). The reduction of CEC content is likely due to DM-induced apoptosis in CEC as demonstrated by immune-histochemical analysis of *corpora cavernosa* (CC) samples between diabetic and nondiabetic patients (20).Thus, how to prevent and/or reverse these pathological processes is critically important for the effective treatment of DM-associated ED. In this regard, *stem cells* (SC) therapy has been considered promising, due to SC's well-known regenerative capacity (18). MSCs, initially isolated from bone marrow, have later been isolated from many adult tissues such as adipose tissue, skeletal muscle, brain and skin. As their name suggests, MSCs are defined by their ability of self- renewal and differentiation into various phenotypes (multipotency).
The therapeutic effect of MSCs has consistently been demonstrated and these benefits are mostly attributed to their ability to produce an array of bioactive molecules.
This is known as paracrine action of MSCs and it involves stimulation of angiogenesis and revascularization, modulation of immune and inflammatory responses, inhibition of apoptosis and trophic effects such as stimulation of mitosis, proliferation and differentiation of intrinsic stem progenitor cells (21).
Different routes have been suggested for the delivery of stem cells, and research continues to assess the most effective route of instillation. Some studies have involved the direct injection of cells into the organ of concern (22-24). Other studies have investigated intraperitoneal or intravenous injections of stem cells (25). Studies have shown that less than 1% of stem cells infused via the intravenous route reach the target tissue, and those that do reach the target tissue dissipate after a few days (26).
In preclinical studies, the intravenous injection of ADSCs has been shown to lead to improvements in erectile function (27). The intracorporal injection of stem cells for ED treatment has been commonly evaluated in preclinical studies, as it is both straightforward and logical (28). Periprostatic injection, with or without a concurrent intracorporal injection, has also been attempted (29, 30).
Many preclinical trials have been performed to investigate the safety, efficacy, and mechanisms of stem-cell therapy for ED in animal models. *Soebadi et al.* in 2016 summarized these studies (31). As stated by those authors, these preclinical trials have provided ample data on the utilization of both bone marrow stem cells and ADSCs for ED. Almost all of the studies reported improved erectile function in various animal models of CN injury, vascular insufficiency, diabetes mellitus, hyperlipidemia, and aging.
Human data on stem-cell therapy for ED are finally emerging approximately 10 years after the first reports on animal models. We have 4 very important published human clinical trials which employed stem cells in patients with ED, as summarized below.
Bahk et al. (24) injected 1.5×107 umbilical MSC into the corpora of 7 ED patients with DM and noted improvement when coupled with oral PDE5i. The *International Index of Erectile Function* (IIEF)-5, global assessment questionnaire, erection diary, blood glucose diary, and medication dosage were monitored for 9 months. Three participants regained morning erections in 1 month, 2 participants achieved erection successful for penetration in conjunction with PDE5i for 6 months. *Yiou et al.* (22) administered BMSC in men with ED after radical prostatectomy. Four equal groups of patients were given escalating doses of BMSC (2 ×107, 2 × 108, 1 × 109, and 2 × 109, respectively). IIEF-15, erection hardness scale, penile duplex and penile NO release tests were all used to assess erectile function. Significant improvement was noted in 9 of 12 patients treated in combination with an oral PDE5i.
Haahr et al. (23) injected ASC into 17 men with a history of prostatectomy to determine safety and efficacy. Five patients had minor adverse events related to liposuction,

Table 7.
Results of clinical trials on stem-cell therapy for erectile dysfunction.

Results	Assessment	Treatment	Cause of ED	Number of men	First author (year)
Improved rigidity in 2/7, able to penetrate with PDE5i	IIEF-5, SEP, GAQ	Umbilical blood SC	Diabetes	7	*Bahk (2010)* (33)
3/8 improved erection; IIEF change not significant	PSV, IIEF	Placental-derived SC	Organic	8	*Levy (2016)* (36)
8/11 continent men and 0/6 incontinent men recovered erection	IIEF-5	Adipose-derived SC	5~18 months after radical prostatectomy	17	*Haahr (2016)* (35)
1/12 hard erection; 9/12 needed ICI, PDE5i, or VCD. Impreved EHS and IIEF	IIEF-15, EHS, color Doppler ultrasound	Bone marrow mononuclear cells	22 months after radical prostatectomy	12	*Yiou (2016)* (34)

2 men has redness or swelling at the injection site, and 1 patient developed a scrotal and penile hematoma. They used IIEF-5 to evaluate erectile function and found 8 of 17 men able to achieve an erection for successful intercourse with no mention of use of oral medications. *Levy et al.* (32) injected adult placental-matrix-derived stem cells (unknown cell number) in a study of 8 men with ED, and assessed peak systolic velocity, end-diastolic velocity, stretched penile length, penile width. Five patients at 3 months achieved erections for successful intercourse with use of PDE5i. The only measure significantly improved was peak systolic velocity.

We summarized this previously mentioned 4 published clinical trials on stem-cell therapy for ED in Table 7.

The present study includes 10 diabetic patients type 2 aged 40-65 complaining of erectile dysfunction. After clinical examination and evaluation, the cause of erectile dysfunction in these patients has been cleared: four patients had mixed arteriogenic and vasculogenic insufficiency, four patients had pure venogenic insufficiency and two patients had pure arteriogenic cause. These patients cannot satisfy sexual activity with proper sexual stimulation in spite of taking maximum dose of oral PDE5I within last 8 weeks.

In this study we injected patients with MSC-derived stem cells and followed them for 6 months with Doppler parameters and the IIEF questionnaire.

All patients agreed that bone marrow stem-cell therapy had some effect on ED, although it was insufficient in some patients. The effects of treatment on erectile function and penile vascular parameters were assessed using the IIEF-15 and by color duplex Doppler ultrasound.

The peak systolic velocity was found to have improved to a statistically significant extent in 4 patients (2 arteriogenic and 2 mixed ED), from 12~ 22 cm/s to 32~69 cm/s. Changes in end-diastolic velocity were found to have improved to statistically significant extent in 2 patients with venogenic insufficiency at follow-up from 4~5 cm/s to -4~-3 cm/s.

At follow-up, in two patients (mixed ED), changes in PSV were not statistically significant for both PSV and EDV. Two patients with venogenic ED had no improvement in EDV measurement after injection of MSCs.

Changes in end-diastolic velocity were found to be not statistically significant in four patients (two withe venogenic insufficiency and two with mixed ED).

Four patients achieved hard erection adequate for satisfactory coitus, and two achieved penile hardness with addition of pharmacological therapy with sildenafil 100 mg.

As regard to our study all patients with arteriogenic ED have significant improvement in duplex penile U/S and penile hardness, and improvement in PSV was observed in two patients with mixed ED; in four patients with venogenic ED, two patients had significant improvement in duplex U/S and penile hardness and two patients no significant improvement; two patients with mixed ED had no significant increase in both peak systolic velocity and end diastolic velocity and no improvement in penile hardness.

Conclusions

Autologous stem-cell therapy is considered a viable treatment option for diabetic ED patients. Despite this overwhelming enthusiasm, several questions remain to be answered before the widespread use of these complex techniques. First, the mode of action still needs to be determined and the safety of the treatment to be established. Next, most effective mode of delivery has yet to be ascertained, although intracorporal injection seems to be the route of choice based on the clinical trials that have been published. Additionally, the ideal timing, type, source and dosage of stem cell for treatment still need to be established. Finally, further researches and wide based clinical trials on stem cell therapy for erectile dysfunction are warranted.

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