

ORIGINAL ARTICLE

Stem cell therapy for erectile dysfunction: Preliminary results from a single-center pilot study in Greece

Vassilis Protogerou^{1,2}, Efstathios Michalopoulos³, Panagiotis Mallis³, Ioanna Gontika³, Christos Liakouras², Catherine Stavropoulos-Giokas³, Michael Chrisofos², Charalampos Deliveliotis⁴

¹Dpt of Anatomy and Surgical Anatomy, Medical School of Athens, National and Kapodistrian University

²2nd University Urological DPT, Attikon Hospital, Medical School of Athens, National and Kapodistrian University

³Hellenic Cord Blood Bank, BRFAA (Biomedical Research Foundation Academy of Athens)

⁴2nd university Urological Dpt, Sismanogleion Hospital, Medical School of Athens, National and Kapodistrian University

Abstract

Introduction: Stem cell therapy is a novel therapy that aims in regenerating tissues and organs and therefore, improves their condition or treats current diseases. The use of stem cell therapy in organic erectile dysfunction is a new alternative to the till now used treatments for erectile dysfunction.

Material-Methods: This is a pilot study to evaluate the safety and the efficacy of adipose derived stem cell therapy in erectile dysfunction (ED). Fifteen patients (aged 45-75) will be enrolled and divided in three groups: group A will be treated with adipose derived stem cells (ADSCs) plus Platelet Lysate Plasma (PLP), group B with ADSCs and group C with PLP. In each patient blood samples will be taken for hormonal and metabolic evaluation and CT scans of the abdomen, thorax and brain will be performed to rule out other pathologies. ED evaluation will be performed at the entry visit and then at 1st, 3rd, 6th and 12th month

visit through IIEF questionnaire and penile triplex. ADSCs will be collected from subcutaneous abdomen fat through punch biopsy or liposuction and after processing will be injected to the penis.

Key words

stem cells, erectile dysfunction; mesenchymal stem cells; adipose derived stem cells (ADSCs); Platelet Lysate Plasma (PLP)

Results: Five patients have been enrolled in group A and they have completed three months offollow up. In all patients there is a significant improvement in erectile function. Morning erections have reappeared or improved in all patients. Unassisted hard erections or erections with the use of oral PDE-5i are present in patients that needed Intracavernous injections (ICI) before treatment or were unable to have erections at all. No side effects or complications are noted so far.

Conclusion: Stem cell therapy with ADSCs for ED seems a promising therapy with encouraging results. Further studies and long follow up period is needed to fully evaluate this experimental treatment.

Citation

Protogerou V, Michalopoulos E, Mallis P, Gontika I, Liakouras C, Stavropoulos-Giokas C, Chrisofos M, Deliveliotis C. Stem cell therapy for erectile dysfunction: Preliminary results from a single-center pilot study in Greece. *Hellenic Urology* 2017, 29 (3): 00-00

Corresponding author:

Vassilis Protogerou, E-mail: vassilis_protogerou@hotmail.com

Introduction

Erectile dysfunction (ED) affects 150 million men worldwide and is considered that by 2,025,322 million will be suffering from erectile dysfunction [1]. Endothelial dysfunction is considered to be an early step in vascular ED. The currently available treatments although they improve endothelial function and enhance erections they cannot be considered as curative. Stem cell therapy is a novel treatment aiming at restoring endothelial dysfunction and thus, provides a possible cure for ED. After many years of animal research there is a growing number of studies in humans with encouraging results. This the first pilot study in Greece which uses adipose derived stem cell (ADSC) for treating patients with erectile dysfunction and we present the preliminary results.

Hypothesis - Aim

This is a pilot study in order to define and to quantify the improvement in ED and provide data to form sample size estimation in order to design a clinical trial as well as to test the feasibility and potential adverse effects.

Material and Methods

Design

Fifteen patients with ED will be enrolled (age 45 to 75 years). Patients will be divided in three groups. Group A (5 patients) will be treated with ADSCs and platelet lysate plasma (PLP); group B (5 patients) will be treated with ADSCs; group C (5 patients) will be treated with PLP. Exclusion criteria are psychogenic, neurologic or hormonal erectile dysfunction, injuries to penis others than Peyronie's disease and all cases of cancer.

All patients should undergo hormonal evaluation (Testosterone, Estradiol, LH, FSH, PRL, FT3, FT4, TSH, α -FP, CEA, CA 19-9), metabolic evaluation (Glucose, Cholesterol, Triglycerides) and PSA. CT scan of the abdomen, thorax and brain will be performed in all patients in order to exclude other pathologies. ED will be evaluated with penile triplex and through IIEF-5 questionnaire. All patients will sign informed consent and the protocol has been approved by the Scientific Committee of Attikon Hospital.

Adipose Derived Stem cells and PLP preparation

ADSCs and PLP preparation will be done at the Good

Manufacturing Practice rooms of the Hellenic Cord Blood Bank's laboratory of BRFAA. ADSCs culture was prepared according to the following protocol. Briefly, the subcutaneous adipose tissue or lipoaspirate was incubated in an orbital shaker at 37°C and 345 rpm for 4 hours along with collagenase. After incubation, the collagenase was inactivated with PBS and centrifuged at 500 g for 6 min. The supernatant was discarded and the cell pellet was reconstituted with complete medium (15% FBS, 1% P-S and 1% L-glut). The cell pellet was transferred to tissue culture flask and incubated at 37°C and 5% CO₂ until confluency. Flow cytometric analysis was performed to ADSCs using a panel of antibodies. Specifically ADSC were positive for HLA-ABC CD29, CD-90, CD105, CD73 and negative for CD19, CD31, CD45, CD73, CD44, CD3, CD14, HLA-DR. Platelet Lysate Plasma (PLP) was prepared from peripheral whole blood after centrifugation at 1800 rpm for 15 min at 20°C. The supernatant was centrifuged at 3,500 rpm for 15 min at 20°C and 3/4 of the plasma volume was discarded, allowing only the platelet rich plasma. The PLP was stored at -20°C until further using.

Patient's treatment and follow up according to the protocol

First visit: Includes physical evaluation, history, penile triplex, completion of the IIEF-5 questionnaire, collection of blood samples and evaluation of CT scans. In eligible patients ADSCs harvesting is organized and performed either through punch biopsy or through liposuction. Blood for PLP is obtained through typical blood collection from a peripheral vein (arm). ADSC infusion is performed once all necessary laboratory tests have been performed (flow cytometry analysis, aerobic/anaerobic culture) from BRFAA laboratory and the sample has the required number of ADSCs.

ADSCs Infusion

ADSCs were reconstituted with 2 ml of PLP and transferred into 1.8 ml of sterile cryotube until infusion was performed. ADSCs plus/or PLP will be infused to the penis with the base of penis clumped for a period of 10 minutes.

Patients should be re-evaluated at 1st, 3rd, 6th and 12th month post infusion. Each follow up appointment includes physical and Andrological evaluation, IIEF- 5 questionnaire completion and penile triplex. At the last appointment CT scans will be repeated.

Patient	Age	Comorbidities
1	62	Hypertension, Hypercholesterolemia
2	52	Diabetes, Hypercholesterolemia
3	52	Hypertension, Diabetes
4	66	Peyronie's disease
5	52	Diabetes, Hypertension, Hypercholesterolemia

Patient	Number of stem cells (x10 ⁶)
1	9.5
2	43.2
3	37.2
4	53.2
5	51.4

Patient	Before therapy	1st month	3rd month	6th month
1	6	17	12	23
2	10	12	12	
3	6	5	6	
4	14	20	22	
5	16	16	20	

Patient	Before therapy	1st month	3rd month	6th month
1	35/11	30.5/7.8	39/12	42/10.5
2	40.3/8.6	25.4/ 6.0	40.8/11.0	
3	16.1/4.7	35/8.9	61.2/20.6	
4	57/15	78.2/16.6	97.9/22	
5	45.5/17.8	49.4/14.7	62.6/25.8	

Results

Five patients have been included in the protocol so far all of them in group A. Three months follow up is completed and patient 1 has completed 6 months follow up. In all patients CT scans and hormonal evaluation were normal. Patient's age and comorbidities are presented in **Table 1**.

Number of ADSCs used per patient are listed on **table 2**.

IIEF score is presented in **Table 3**. In all patients there is an increase in IIEF score. A notable exception is patient 3 and the reason will be explained in the Discussion section.

Penile triplex results are shown on **Table 4**. In all patients there is an improving trend on Peak Systolic Ve-

locities (PSV) while there is a more variable pattern on the End Diastolic Velocities (EDV). Patient 1 and 2 had a decrease on the first month but PSV increased the following months. Morning erections results are shown on **Table 5**. In all patients either reappeared or become stronger compared to pre-stem cells period. In detail, patient 1, and 3 noticed that morning erection return on the 1st month follow up, patient 2 had morning erections on the 3rd month while patients 3 and 4 that had low quality erections before stem cell therapy noticed that morning erection became harder and appeared more often.

Before ADSC therapy, patients were unable to have erections on their own or with oral PDE-5i. Patient 1 could have erections hard enough for intercourse only

Patient	Morning erections Before therapy	1st month	3rd month
1	-	+	+
2	-	-	+
3	-	+	+
4	-/+	+	+
5	-/+	+	+

Patient	Erectile function Before therapy	Erectile function 1st month	Erectile function 3rd month
1	Only with ICI, unable to climax	Hard erections with oral PDE5-I, normal ejaculation	Hard erections with oral PDE5-I, normal ejaculation
2	No erections	Some increase in hardness	Hard erections with oral PDE5-I
3	Moderate erections with ICI	Improvement only in morning erections	Hard erections with oral PDE5-I
4	Moderate erections with ICI	Hard erections with oral PDE5-I	Unassisted hard erections
5	Hard erections only with ICI	Unassisted hard erections short duration	Unassisted hard erections

with Intracavernosal Injections (ICI) but it was difficult for him to climax. Patient 2 had no erections, patient 3 had moderate erection with ICI but it was difficult for him to use them and therefore, he was negative in the idea of having sex. Patient 4 used to have good erections on ICI but progressively the quality of erections had decreased, while patient 5 had hard erections with ICI. Changes in erectile function as reported by the patients are presented in **Table 6**.

There were no significant complications from ADSC therapy. Patient felt a minor stinging pain during injection that resolved spontaneously a couple of minutes later.

Two of the diabetes patients noticed a significant decrease in their blood sugar levels. Patient 2 had a significant decrease and had to drastically decrease his insulin doses and patient 3 he also noticed significant decrease in his blood levels. Nevertheless, since the protocol did not include blood sugar measurement these data are provided by the patient's own measurements.

Discussion

In this paper we report the preliminary data from a single-center pilot study evaluating the effect of ADSC

therapy on ED. Due to the small follow up period and since the study is not yet completed we did not perform any statistical evaluation. Nevertheless both clinical and subjective results were quite remarkable and it was considered that it is worth reporting them.

Since current treatment of ED cannot be considered as curative the need for new treatment that can actually treat and reverse the damages in the penis that cause erectile dysfunction is necessary. ADSC therapy and its regenerative potential is a new treatment on this field.

Stem Cell Basics

Stem cells by definition are cell that can renew themselves indefinitely but also give birth to other type of cells. There are several ways to characterize and classify Stem Cells. According to their differentiation potential they are characterized as Totipotent that can give birth to all cell lines, Pluripotent that can differentiate to all germ layers but not to extra-embryonic cell lines, Multipotent that differentiate to all cell types within their germ layer and Unipotent that can differentiate to a specific cell line. Example of each type is the zygote for totipotent SC, embryonic cells taken from the inner cell mass of blastocysts for pluripotent SC, hematopoi-



etic and mesenchymal SC for multipotent SC and epithelial cells for Unipotent SC [2].

According to their origin, they can be either Embryonic stem cells (ESC) originating from embryonic tissue (inner cell mass of blastocyst) or Adult Stem Cell (ASC) arising from adult tissue. ESC are pluripotent while in general ASC are considered multipotent. Recently though, it has been shown that ASC can also be pluripotent [3]. Mesenchymal SC is a type of ASC with pluripotent potential [4]. They can be found in bone marrow, adipose tissue, skeletal muscle, dental pulp and cord blood [5-9]. Depending on their tissue origin or the tissue type they can differentiate into, ASCs can be further classified into hematopoietic, neural, epithelial, and mesenchymal. Mesenchymal SC are the most frequently used. They can differentiate into mesenchymal tissues, such as bone, cartilage, and fat. They were first identified in the bone marrow but have now been shown to exist in virtually all postnatal tissues, including skeletal muscle and adipose tissue [10,11]. Initially bone marrow stem cells (BMSC) were used but the discovery of adipose derived stem cells (ADSC) has replaced the BMSC due to the simplicity of collection and the similar characteristics [12].

Preclinical and clinical studies on Stem Cells for ED

A great number of preclinical (animal) studies have been performed using different models of erectile dysfunction (Aging, Diabetes, Hyperlipidemia, Cavernous nerve damage, Tunica Albuginea damage, post-radiation damage) as well as different type of stem cells, the majority being ADSC and BMSC [13]. These animal studies presented encouraging results regarding the efficacy and safety of stem cells treating ED.

The first clinical study was published at 2010 from Korea and included 7 diabetes patients that were proven unresponsive to previous medical therapies (oral phosphodiesterase 5 inhibitor, or PGE1 injection) for more than 6 months, and all were awaiting penile prostheses. They were treated with Human umbilical cord blood stem cells. The results were very encouraging: 3 patients experienced morning erections, 1 month after treatment, and all but 1 regained morning erections by the second month; this was maintained for at least 3 months. Six patients experienced an increase in penile hardness and 2 could achieve penetration with the use of PDE-5i [14].

A case report on 35 years old with erectile dysfunction unresponsive to oral PDE5 inhibitors was published on 2013. The patient was a smoker and had a history of hypercholesterolemia and was unresponsive for at least 6 month on Caverject injections. Bone marrow stem cells were administrated. Three weeks later the patient experienced erections hard enough for penetrations and three months later he was able to have intercourse [15].

Another study was published on 2015: 6 diabetic patients with erectile dysfunction unresponsive to oral PDE-5i or PGE1 injections were treated with Adipose Stem Cells. Four patients experienced morning erection 1 month post treatment and all but one had morning erections at the second month. None had morning erections prior to stem cells administration. All patients experienced an increase in the hardness of their erection but were still insufficient for penetration. With the addition of oral PDE-5i, 5 patients were able to have erection hard enough for penetrative sex till orgasm and 4 patients keep this ability up to 12 months [16].

The next year 3 new studies were published. For the first time cancer patients were treated with stem cells. The first study included 17 prostate cancer patients with post RP severe erectile dysfunction and Adipose Derived Regenerative Cells were used. In overall 8 out of 17 patients had an improvement on erectile function and were able to complete intercourse. Notably continent men had better results than incontinent men [17]. The other study [18] included 12 prostate cancer patients with localized cancer that have been treated with radical prostatectomy and had severe erectile dysfunction. Bone Marrow mononuclear cells have been used on 4 different doses. Six month post administration there was an increase on penile hardness during erection and overall 9 out of 12 patients reported successful intercourses with vaginal penetration on medication. Higher doses of stem cells were found more effective. The final study was not on cancer patients, on the contrary prostate cancer was an exclusion criterion. Eight patients with erectile dysfunction that had to use trimix to achieve erection were treated with placental matrix-derived mesenchymal stem cells. During the 6 months follow up, three patients were able to achieve and sustain erections without medication, 4 needed low-dose oral medication, and 1 patient continued to use the trimix solution to achieve erections [19].

In overall, in the above studies there is an obvious improvement in erectile dysfunction. There is a return on morning erections and some patients experienced erections hard enough to have sex without any additional treatment while others needed additional treatment which prior to stem cell therapy was ineffective.

In our pilot study there was an improvement in IIEF score in all patients. Patient 3 although he noticed an improvement in his morning erections and an increase in the hardness of his penis still reports low IIEF score. The reason is that many questions on the IIEF are regarding the quality of erections during intercourse. This patient for personal reasons did not have any intercourse and so he replied negatively in all these questions providing a low score. On the other hand this patient due to the significant improvement in his erectile function he is considering starting having sex soon, something that he was avoiding for quite a long time.

Penile triplex results show also an improvement. Patient 1 and 2 had a decrease in PSV the first month but over the next months there was continuous increase in arterial flow while patients 3, 4 and 5 had a steady increase in PSV. EDV pattern is not steady and there is a fluctuation. Patient 1, 2 and 5 experienced an initial decrease the first month and afterwards there was an increase (with a decrease for Pt 1 on the 6th month) while patient 3 and 4 had a continuous increase. Although, penile triplex is a very valuable tool in evaluating erectile dysfunction could be affected by an unrelated reason to ED such as, stress during the examination. Also, venous leak can be related to structural penile reasons other than endothelial dysfunction. Nevertheless, the available data till now showed an improvement in penile perfusion.

Morning erections reappeared in patients 1 and 3 first month post treatment while on patient 2 on the 3rd month. Patients 4 and 5 although they had morning erections prior to stem cell therapy there were not hard enough. They noticed a notable improvement regarding the frequency and the hardness of their erection from the first month post treatment.

Erectile function was generally improved. Patient 1 used Intracavernous injections with trimix but he could not climax, something that caused him frustration and anxiety. Following stem cell therapy, he noticed an increase in spontaneous erections and he could have sexual intercourse with oral treatment. He also no-

ticed that his sexual performance was generally improved as he could now ejaculate and that helped him in the psychological domain too. Patient 2 was unable to have erection before treatment even with PDE5-is. The first month he noticed that his penis presented episodes with some spontaneous hardness but he could not consider them as erections. On the 3rd month he had developed satisfactory erections with the use of PDE5-is. Patient 3 before treatment had only minor erection with ICI but due to the fact that he stopped using them he abandoned sex. He reported that had sexual intercourse with the use of PDE-5i three months post treatment, something that was impossible before ADSC therapy. Patient 4 did not respond satisfactory to ICI before treatment. On the first month he noticed a significant improvement in his erections and he could have intercourse with the use of oral PDE5-i. During the first month and due to other reasons he developed depression and he started treatment with sertraline (Zoloft). At the 3rd month appointment he reported that his erections improved and he could now have sex without any treatment at all. This is quite remarkable since both depression and anti-depressive treatment can have a negative result on erectile function. Patient 5 had also significant improvement. Prior to treatment he had to use ICI in order to have sex while on the 1st month appointment he reported spontaneous erections that were hard enough but they did not last. On the 3rd month appointment the erections were better and although he felt that there were adequate for sexual intercourse he preferred to use ICI because he felt insecure. He also reported that he was very hard working (he has a tavern) and the daily job activities were very exhausting and he felt that if he was more relaxed he could have even better erections.


In the first patient fat harvesting was performed through punch biopsy. We decided that the expansion of the cells obtained in this way was not adequate and so in the remaining patients we performed liposuction in order to obtain the amount of tissue needed. Therefore Pt 1 has been treated with significant less numbers of stem cells (**Table 2**).

Two diabetic patients noticed a significant decreased in their blood sugar levels and they had to change their treatment. Patient 2 experienced hypoglycemic episodes and drastically decreased his insulin doses. This patient reported that he had not changed any-

thing in his diet or in his daily activities that might have caused this effect. So, it is logical to attribute this effect on blood sugar levels, on ADSC treatment. Patient 3 also reported significant decrease in his blood sugar levels. In this case though, the patient reported that he had started some exercise (walking) and he was more careful with his diet in order to manage to decrease his sugar levels. Although he had started this effort several months before stem cell treatment, the results appeared just after stem cell injection. Thus, although we cannot attribute the results to stem cells alone, it seems that they have played a role in this. Our study did not measure blood levels at each visit and this is a finding reported by the patients. Although it can be questioned, it is in accordance with the findings in another study [14].

There were no significant complications from this treatment, only minor pain on the site of injection. Patient reported that the treatment was easy to toler-

ate but yet someone needs to have in mind that it is a two-step procedure with the one (liposuction) needing anesthesia. So, although it is a minor procedure with low rates of complication still may not be accepted from all patients.

Our study has the limitations of a pilot study. It is not a randomized study and has not a control group. Also, we do not know the long term results. In all previous studies the follow up was not more than a year and it is doubtful if the results will be permanent. Also, despite the fact that stem cell therapy has been used for several indications in many patients, the long term results regarding erectile dysfunction are yet unknown. Nevertheless the short results are quite impressive and look very promising in the battle against erectile dysfunction. 

Conflicts of interest

The author declared no conflict of interest.

Περίληψη

Σκοπός: Η θεραπεία με βλαστοκύτταρα είναι μια πολλά υποσχόμενη θεραπεία που αποσκοπεί στην αναγέννηση των ιστών και αποκατάσταση με τον τρόπο αυτό ιστικών βλαβών και των διαφόρων παθήσεων. Η εφαρμογή των βλαστικών κυττάρων για τη θεραπεία της Στυτικής Δυσλειτουργίας είναι μια νέα πολλά υποσχόμενη θεραπεία.

Μέθοδος: Πρόκειται για μια πιλοτική μελέτη με σκοπό τη διερεύνηση της ασφάλειας και της αποτελεσματικότητας της μεθόδου. Θα μελετηθούν 15 ασθενείς σε τρεις ομάδες. Η ομάδα Α θα αποτελείται από 5 ασθενείς στους οποίους θα χορηγηθούν βλαστοκύτταρα προερχόμενα από λιπώδη ιστό και PLP, η ομάδα Β από 5 ασθενείς στους οποίους θα χορηγηθούν μόνο βλαστοκύτταρα προερχόμενα από λιπώδη ιστό και η ομάδα Γ από 5 ασθενείς στους οποίους θα χορηγηθεί μόνο PLP. Εξετάσεις αίματος για ορμονολογικό και μεταβολικό έλεγχο θα πραγματοποιηθούν σε κάθε ασθενή καθώς και αξονική τομογραφία άνω/κάτω κοιλίας, θώρακος κι εγκεφάλου για τον αποκλεισμό άλλων παθήσεων. Η στυτική λειτουργία θα παρακολουθείται με τη χρήση του IIEF ερωτηματολογίου

Λέξεις ευρητηριασμού

Βλαστοκύτταρα, στυτική δυσλειτουργία, μεσεγγυματικά βλαστικά κύτταρα, βλαστικά κύτταρα λιπώδη ιστού, πλάσμα πλουσιο σε αυξητικούς παραγοντες

και με τρίπλεξ πείκων αρτηριών και οι ασθενείς θα παρακολουθούνται σε διαστήματα 1,3,6 και 12 μηνών από τη χορήγηση. Τα βλαστοκύτταρα προερχόμενα από λιπώδη ιστό θα ληφθούν από το υποδόριο λίπος είτε με λήψη τεμαχιδίου ή με λιποαναρρόφηση και θα χορηγηθούν με ενδοπεϊκική ένεση. **Αποτελέσματα:** Πέντε ασθενείς της ομάδας Α έχουν ολοκληρώσει μέχρι τώρα την τρίμηνη παρακολούθηση. Σε όλους τους ασθενείς πρωινές

στυσεις έχουν επανέρθει ή έχουν βελτιωθεί. Οι ασθενείς μπορούν πλέον να έχουν στυσεις μόνοι τους ή με τη βοήθεια από του στόματος PDE-5i ενώ πριν είτε χρειαζόντουσαν ενδοπεϊκές ενέσεις ή δεν μπορούσαν να έχουν στυσεις. Παρενέργειες ή επιπλοκές μέχρι τώρα δεν έχουν παρατηρηθεί.

Συμπέρασμα: Η εφαρμογή των βλαστοκυττάρων με βλαστοκύτταρα προερχόμενα από λιπώδη ιστό για τη θεραπεία της Στυτικής Δυσλειτουργίας είναι μια πολύ υποσχόμενη θεραπεία με ενθαρρυντικά αποτελέσματα. Ωστόσο περαιτέρω έρευνα χρειάζεται και μακρύτερη παρακολούθηση για να αξιολογηθεί επαρκώς αυτή πειραματική ακόμα θεραπεία.

References

1. Ayta IA, McKinlay JB, Krane RJ. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. *BJU Int* 1999; 84: 50-6.
2. Stem cells: Novel players in the treatment of erectile dysfunction. *Asian Journal of Andrology* 2012; 14: 145-155.
3. Lin CS, Xin ZC, Deng CH, Ning H, Lin G, et al. Recent advances in andrology-related. Stem cell research. *Asian J Androl* 2008; 10: 171-5.
4. Hipp J, Atala A. Sources of stem cells for regenerative medicine. *Stem Cell Rev* 2008; 4: 3-11.
5. Erices A, Conget P, Minguell JJ. Mesenchymal progenitor cells in human umbilical cord blood. *Br J Haematol* 2000; 109: 235-42.
6. Phinney DG, Prockop DJ. Concise review: Mesenchymal stem/multipotent stromal cells: The state of transdifferentiation and modes of tissue repair-current views. *Stem Cells* 2007; 25: 2896-902.
7. Gronthos S, Mankani M, Brahimi J, Robey PG, Shi S. Postnatal human dental pulp stem cells (DPSCs) *in vitro* and *in vivo*. *Proc Natl Acad Sci USA* 2000; 97: 13625-30.
8. Williams JT, Southerland SS, Souza J, Calcutt AF, Cartledge RG. Cells isolated from adult human skeletal muscle capable of differentiating into multiple mesodermal phenotypes. *Am Surg* 1999; 65: 22-6.
9. Rodriguez AM, Elabd C, Amri EZ, Ailhaud G, Dani C. The human adipose tissue is a source of multipotent stem cells. *Biochimie* 2005; 87: 125-8.
10. Mesenchymal stem cells reside in virtually all post-natal organs and tissues. *Journal of Cell Science* 2006; 119 (11): 2204-2213.
11. M. Crisan, S. Yap, L. Casteilla, et al. A perivascular origin for mesenchymal stem cells in multiple human organs. *Cell Stem Cell* 2008; 3 (3): 301-313.
12. Lin G, Garcia M, Ning H, Banie L, Guo YL, et al. Defining stem and progenitor cells within adipose tissue. *Stem Cells Dev* 2008; 17: 1053-63.
13. Ching-Shwun Li. Advances in Stem Cell Therapy for Erectile Dysfunction, *Advances in Andrology*. Volume 2014, ID 140618, 20 pages.
14. Bahk JY, Jung JH, Han H, Min SK, Lee YS. Treatment of diabetic impotence with umbilical cord blood stem cell intracavernosal transplant: Preliminary report of 7 cases. *Experimental and Clinical Transplantation* 2010; 8(2): 150-160 .
15. Ichim TE, Warbington T, Cristea O, Chin JL, Patel AN. Intracavernous administration of bone marrow mononuclear cells: A new method of treating erectile dysfunction? *Journal of Translational Medicine* 2013; 11:139.
16. Garber MG and Carlos ND. Intracavernous Administration of Adipose Stem Cells: A New Technique of Treating Erectile Dysfunction in Diabetic Patient, Preliminary Report of 6 Cases. *MOJ Cell Sci Rep* 2015;2(1): 00018.
17. Haahr MK, Jensen CH, Toyserkani NM, Andersen DC, Damkier P, Sørensen JA, et al. Safety and Potential Effect of a Single Intracavernous Injection of Autologous Adipose-Derived Regenerative Cells in Patients with Erectile Dysfunction Following Radical Prostatectomy: An Open-Label Phase I Clinical Trial. *EBioMedicine* 2016; 5: 204-210.
18. Yiou R, Hamidou L, Birebent B, Bitari D, et al. Safety of Intracavernous Bone Marrow-Mononuclear Cells for Post-radical Prostatectomy Erectile Dysfunction: An Open Dose-Escalation Pilot Study. *Eur Urol* 2016;69(6): 988-91.
19. Levy JA, Marchand M, Iorio L, Cassini W, Zahalsky MP. Determining the Feasibility of Managing Erectile Dysfunction in Humans With Placental-Derived Stem Cells. *J Am Osteopath Assoc* 2016;116(1): e1-e5.