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Editorial

Urine Derived Stem Cells for Potential Application in Treatment of Diabetic Erectile Dysfunction

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Editorial

Diabetic men often have Erectile Dysfunction (ED) (arrange from 20% to 75%), and it often occurs 10-15 years earlier, and is more severe, than in non-diabetic men [1-3]. Diabetes-related ED involves impairments in endothelial cells that affect blood vessel, smooth muscle, and nerve function [4]. The endothelium's shift to a vasoconstrictor, pro-thrombotic and pro-inflammatory state is a major factor in development of diabetic ED. The pathogenesis of both endothelial Dysfunction and Diabetic ED is linked through decreased expression and activation of Endothelial Nitric Oxide Synthesis (eNOS), and the subsequent blunted physiological actions of NO occurring with diabetes. The mechanisms involved include impaired endothelial eNOS function in the cavern sum, smooth muscle cell dysfunction, and neurodegradation from increased generation of oxidative stress and overproduction of free radicals and Reactive Oxygen Species (ROS) [5,6,7] endothelial dysfunction is a major contributor to the high incidence of ED in patients with diabetes, particularly in the early stages [8-11]. It is critical to address erectile function before diabetic ED moves to an advanced stage. Oral medications are an important first-line treatment for ED, but only 50-60% of patients see improvements from these drugs [12] because diabetic ED decreases NO production. These results have motivated investigators to seek novel treatment approaches, one of which is stem cell therapy.

Mesenchymal Stem Cells (MSCs) can differentiate into various cell types, including endothelial, smooth muscle, Schwann cells, and neurons. In addition, MSCs can secrete porcine factors and cytokines that enhance cell survival and angiogenesis, and promote anti-apoptotic, pro-neurogenic, anti-inflammatory, and anti-fibrotic effects [13]. Intracavernous transplantation of Bone Marrow-Derived Stromal Cells (BMSCs) [14-16] or adipose stem cells (ASCs) [5,17] increased the number of eNOS-positive endothelial cells and smooth muscle content [5,15] and Numbers of Neuronal Nitric Oxide Synthesis (nNOS)-positive nerve fibers [14,17,18] in the corpus cavern sum in a rodent model. However, to obtain these stem cells, bone marrow or fat aspiration is usually required, with possible complications. MSCs used in most studies of diabetic ED were isolated from healthy donors [5,17,19-23] and not from patients' own tissues. For eventual clinical use, antilogous stem cells would be optimal because they would not cause immune rejection or other adverse events associated with allergenic or exogenous sources. Thus, antilogous stem cells obtained from a non-invasive, safe, reproducible, and low-cost approach would be highly desirable.

We discovered a subpopulation of cells isolated from urine that possess biological characteristics similar to adult stem cells, i.e. clonogenicity, cell growth patterns, expansion capacity [24-26] cell surface marker expression profiles, multipotent differentiation capacity [24-35] including endothelial and smooth muscle differentiation [24-26] pro-angiogenicparacrine effects [25,26,28,29] immunomodulatory properties [32] and easily-induced Induced Pluripotent Stem (iPS) cells [36,37]. We have termed these cells "Urine-Derived Stem Cells" (USCs).USCs are not MSCs and they most likely originate from the kidney [26].Our recent study showed that USCs give rise to functional endothelial cells [31,38] and myocytes [28,30,34,39] besides estrogenic, chondrogenic and adipogenic cell lineages in vitro and in vivo [24-26]. Like bone marrow stem cells, USCs also secrete antigenic growth factors and cytokines. In addition, USCs inhibit peripheral blood mononuclear cell (T and B cell) proliferation and secrete theimmunoregulatory cytokines interleukin (IL)-6 and IL-832. Our procedures with USCs have been successfully repeated by independent investigators in other institutes [27,37,40-49].

Obtained from healthy donors' voided urine, USCs can generate a large number of cells from a single clone [30, 35]. Importantly, 57-75% of the USCs collected from middle-aged individuals

expressed telomerase activity (USCs-TA+) and retained long telomere length50. USCs-TA+ possessed higher proliferative capacities and were maintained for up to 67 Population Doublings (PD), indicating that a single USC can generate up to 267 cells within 14 weeks. We can consistently obtain 100-140 USC clones/24 hr urine from each individual [24]. About 1 x106 cells are needed for use in diabetic ED therapy in a rodent model [5,51,52]. Thus, one 200 ml urine sample can provide ample cells for the purposes of cell implantation. Although USCs express certain embryonic stem cell markers and displayed telomerase activity, these cells displayed genetic stability after serial passages of culture and did not form any tumor clones in vitro [25,35]. No cancer cells appeared 3 months after USC implantation, either subcutaneously or under renal capsules [50].

The studies form others and us have demonstrated that ASCsor ASCs expressing VEGF significantly improved the erectile function in streptozotocin (STZ)-induced ED rat mode [l5,17]. Our recent studies demonstrated that use of implanted USCs obtained from healthy human donors or USCs expressing FGF2 displayed significantly higher Intracavernous Pressure/Mean Arterial Pressure (ICP/MAP) ratios 28 days after Intracavernous injection in vivo [53]. In addition, USCs or USCs expressing FGF2 were associated with significantly increased expression of endothelial markers (CD31, VEGF and eNOS), smooth muscle markers (desmin and smoothelin) compared to normal saline injection in the diabetic ED rat model [53]. Although few cell were detected within the implanted sites, histological and western blot analysis demonstrated an increased expression of endothelial and smooth muscle markers within the cavernous tissue following USC or USC-FGF2 injection. This study indicated that the paracrine effect of USCs or USCs-FGF2 induced improvement of erectile function in type 2 diabetic rats by recruiting resident cells and increasing the endothelial expression and contents of smooth muscle [53].

In addition, our most recent study showed that human USCs significantly improved renal function in a rat model of chronic renal insufficiency induced by gentamicin combined with renal ischemic insult, with a 50% decline in serum creatinine 2 weeks post-cell injection (5x106cells/kidney) maintained over 9 weeks, compared to controls. The implanted USCs were detected around the glomerulus and interstitial area. Numbers of macrophages and amount of collagen deposit significantly decreased in USC-treated nude rats. Furthermore, either local administration via per urethral injection of USCs or systemic administration via Intraperitoneal Injection (i.p.) significantly enhanced the sphincter function by increasing leak point pressure, and restored histologic features by protection against urethral sphincter injuries in a rat model one week after vaginal distention injury (unpublished data).These in vivo studies indicate that USCs promote tissue regeneration, reduce inflammation and improve urologic function via paracrine effects and cell differentiation.

Taken together, antilogous USCs provide an alternative cell source for cell therapy in treatment of andro-urological diseases including diabetes-related ED. The mechanism of USC therapy is involved with cell differentiation and paracrine effect to induce the endogenous regeneration potential.

References

1. Lu CC. Smoking habits and erectile dysfunction in type 2 diabetic patients. J Sex Med. 2010; 7: 1593.
2. Malavige LS, Levy JC. Erectile dysfunction in diabetes mellitus. J Sex Med. 2009; 6: 1232-47.
3. Sasaki H, Yamasaki H, Ogawa K, Nanjo K , Kawamori R, Iwamoto Y, Katayama Set al. Prevalence and risk factors for erectile dysfunction in Japanese diabetics. Diabetes Res Clin Pract. 2005; 70: 81-9.
4. Bivalacqua TJ, Usta MF, Champion HC, Kadowitz PJ, Hellstrom WJ. Endothelial dysfunction in erectile dysfunction: role of the endothelium in erectile physiology and disease. J Androl. 2003; 24: S17-37.
5. Liu G, Sun X, Bian J, Wu R, Guan X, Ougyanq B, Huang Y, Xiao H, Luo D, Atala A, Zhang Y, et al. Correction of diabetic erectile dysfunction with adipose derived stem cells modified with the vascular endothelial growth factor gene in a rodent diabetic model. PloS one. 2013; 8: e72790.
6. Long T, Liu G, Wang Y, Chen Y, Zhang Y, Qin D. TNF-alpha, erectile dysfunction, and NADPH oxidase-mediated ROS generation in corpus cavernosum in high-fat diet/streptozotocin-induced diabetic rats. J Sex Med. 2012; 9: 1801-14.
7. El-Sakka AI, Yassin AA. Amelioration of penile fibrosis: myth or reality. Journal of andrology. 2010; 31: 324-35.
8. Glina S, Fonseca GN, Bertero EB, Damião R, Rocha LC, Jardim CR, Cairoli CE, et al. Efficacy and tolerability of lodenafil carbonate for oral therapy of erectile dysfunction: a phase III clinical trial. J Sex Med. 2010; 7: 1928-36.
9. Fonseca V, Jawa A. Endothelial and erectile dysfunction, diabetes mellitus, and the metabolic syndrome: common pathways and treatments? Am J Cardiol. 2005; 96: 13M-8M.
10. Matfin G, Jawa A, Fonseca VA. Erectile dysfunction: interrelationship with the metabolic syndrome. Curr Diab Rep. 2005; 5: 64-9.
11. Fonseca V, Seftel A, Denne J, Fredlund P. Impact of diabetes mellitus on the severity of erectile dysfunction and response to treatment: analysis of data from tadalafil clinical trials. Diabetologia. 2004; 47: 1914-23.
12. Stuckey BG, Jadzinsky MN, Murphy LJ, Montorsi F, Kadioglu A, Fraige F, Manzano P et al. Sildenafil citrate for treatment of erectile dysfunction in men with type 1 diabetes: results of a randomized controlled trial. Diabetes Care. 2003; 26: 279-84.
13. Caplan AI, Correa D. The MSC: an injury drugstore. Cell Stem Cell. 2011; 9: 11-5.
14. You D, Jang MJ, Lee J, Jeong IG, Kim HS, Moon KH, Suh N, et al. Periprostatic implantation of human bone marrow-derived mesenchymal stem cells potentiates recovery of erectile function by intracavernosal injection in a rat model of cavernous nerve injury. Urology. 2013; 81: 104-10.
15. Qiu X, Lin H, Wang Y, Yu W, Chen Y, Wang R, Dai Y.et al. Intracavernous transplantation of bone marrow-derived mesenchymal stem cells restores erectile function of streptozocin-induced diabetic rats. J Sex Med. 2011; 8: 427-36.
16. Kendirci M, Trost L, Bakondi B, Whitney MJ, Hellstrom WJ, Spees JL. Transplantation of nonhematopoietic adult bone marrow stem/progenitor cells isolated by p75 nerve growth factor receptor into the penis rescues erectile function in a rat model of cavernous nerve injury. J Urol. 2010; 184: 1560-6.
17. Garcia MM, Fandel TM, Lin G, Shindel AW, Banie L, Lin CS, Lue TF. et al. Treatment of erectile dysfunction in the obese type 2 diabetic ZDF rat with adipose tissue-derived stem cells. J Sex Med. 2010; 7: 89-98.
18. Lin G, Qiu X, Fandel TM, Albersen M, Wang Z, Lue TF, Lin CS.et al. Improved penile histology by phalloidin stain: circular and longitudinal cavernous smooth muscles, dual-endothelium arteries, and erectile dysfunction-associated changes. Urology. 2011; 78: 970 e1-8.
19. Qiu X, Villalta J, Ferretti L, Fandel TM, Albersen M, Lin G et al. Effects of intravenous injection of adipose-derived stem cells in a rat model of radiation therapy-induced erectile dysfunction. J Sex Med. 2012; 9: 1834-41.
20. Sun C, Lin H, Yu W, Li X, Chen Y, Qiu X, Wang R, Dai Y. et al. Neurotrophic effect of bone marrow mesenchymal stem cells for erectile dysfunction in diabetic rats. Int J Androl. 2012; 35: 601-7.

21. Zhang H, Albersen M, Jin X, Lin G. Stem cells: novel players in the treatment of erectile dysfunction. Asian J Androl. 2012; 14: 145-55.

22. Huang YC, Ning H, Shindel AW, Fandel TM, Lin G, Harraz AM, Lue TF, Lin CS et al. The effect of intracavernous injection of adipose tissue-derived stem cells on hyperlipidemia-associated erectile dysfunction in a rat model. J Sex Med. 2010; 7: 1391-400.

23. Lin G, Banie L, Ning H, Bella AJ, Lin CS, Lue TF. Potential of adipose-derived stem cells for treatment of erectile dysfunction. J Sex Med. 2009; 3: 320-7.

24. Lang R, Liu G, Shi Y, Bharadwaj S, Leng X, Zhou X, Liu H, Atala A, Zhang Y. et al. Self-renewal and differentiation capacity of urine-derived stem cells after urine preservation for 24 hours. PloS one. 2013; 8: e53980.

25. Bharadwaj S, Liu G, Shi Y, Markert C, Andersson KE, Atala A, Zhang Y.et al. Characterization of urine-derived stem cells obtained from upper urinary tract for use in cell-based urological tissue engineering. Tissue Eng Part A. 2011; 17: 2123-32.

26. Bharadwaj S, Liu G, Shi Y, Wu R, Yang B, He T, Fan Y, Lu X, Zhou X, Liu H, Atala A, et al. Multipotential differentiation of human urine-derived stem cells: potential for therapeutic applications in urology. Stem cells. 2013; 31: 1840-56.

27. Zhou T, Benda C, Dunzinger S, Huang Y, Ho JC, Yang J, Wang Y et al. Generation of human induced pluripotent stem cells from urine samples. Nat Protoc. 2012; 7: 2080-9.

28. Liu G, Pareta RA, Wu R, Shi Y, Zhou X, Liu H, Deng C, Sun X, et al. Skeletal myogenic differentiation of urine-derived stem cells and angiogenesis using microbeads loaded with growth factors. Biomaterials. 2013; 34: 1311-26.

29. Liu G, Wang X, Sun X, Deng C, Atala A, Zhang Y. The effect of urine-derived stem cells expressing VEGF loaded in collagen hydrogels on myogenesis and innervation following after subcutaneous implantation in nude mice. Biomaterials. 2013; 34: 8617-29.

30. Bodin A, Bharadwaj S, Wu S, Gatenholm P, Atala A, Zhang Y. Tissue-engineered conduit using urine-derived stem cells seeded bacterial cellulose polymer in urinary reconstruction and diversion. Biomaterials. 2010; 31: 8889-901.

31. Liu G, Wu G, Bharadwaj S, Soker S, Atala A, Zhang Y. Implantation of autologous urine derived stem cells expressing vascular endothelial growth factor for potential use in the treatment of neurovascular erectile dysfunction. .J Urology. 2011; 185: American Urological Association (AUA) 2011 Annual meeting in Washington, D.C, May 14-19.

32. Wu RP, Soland M, Liu G, et al. Immunomodulatory Properties of Urine Derived Stem Cells. The 3rd Annual Regenerative Medicine Foundation Conference 2012 Abstract Book Charlotte, NC, USA. 2012; 18-19.

33. Wu S, Liu Y, Bharadwaj S, Atala A, Zhang Y. Human urine-derived stem cells seeded in a modified 3D porous small intestinal submucosa scaffold for urethral tissue engineering. Biomaterials. 2011; 32: 1317-26.

34. Wu S, Wang Z, Bharadwaj S, Hodges SJ, Atala A, Zhang Y. Implantation of autologous urine derived stem cells expressing vascular endothelial growth factor for potential use in genitourinary reconstruction. J Urol. 2011; 186: 640-7.

35. Zhang Y, McNeill E, Tian H, Soker S, Andersson KE, Yoo JJ, Atala A. et al. Urine derived cells are a potential source for urological tissue reconstruction. J Urol. 2008; 180: 2226-33.

36. Guan X, Shi Y, Markert CD, et al. Rapid generation of induced pluripotent stem cells (iPSCs) from the urine of a patient with Duchenne muscular dystrophy. Mol Ther. 2012; 20: S111.

37. Xue Y, Cai X, Wang L, et al. Generating a Non-Integrating Human Induced Pluripotent Stem Cell Bank from Urine-Derived Cells. PLoS one. 2013; 8: e70573.

38. Argus MV. New paleontological excavation techniques. Journal of Paleontology. 1993; 19: 234-7.

39. Tsai LR, Chen MH, Chien CT, Chen MK, Lin FS, Lin KM, Hwu YK, Yang CS, Lin SY. et al. A single-monomer derived linear-like PEI-co-PEG for siRNA delivery and silencing. Biomaterials. 2011; 32: 3647-53.

40. Chun SY, Kim HT, Lee JS, Kim MJ, Kim BS, Kim BW, Kwon TG. et al. Characterization of urine-derived cells from upper urinary tract in patients with bladder cancer. Urology. 2012; 79: 1186 e1-7.

41. Zhou J, Wang X, Zhang S, Gu Y, Yu L, Wu J, Gao T, Chen F.et al. Generation and Characterization of Human Cryptorchid-specific Induced Pluripotent Stem Cells from Urine. Stem Cells Dev. 2013.

42. Wang L, Huang W, Su H, Su H, Xue Y, Su Z, Liao B, Wang H, Bao X, et al. Generation of integration-free neural progenitor cells from cells in human urine. Nat Methods. 2013; 10: 84-9.

43. Chen Y, Luo R, Xu Y, Cai X, Li W, Tan K, Huang J, Dai Y.et al. Generation of systemic lupus erythematosus-specific induced pluripotent stem cells from urine. Rheumatol Int. 2013; 33: 2127-34.

44. Zhou T, Benda C, Duzinger S, Huang Y, Li X, Li Y, Guo X, Cao G, Chen S, Hao L, Chan YC, Ng KM, Ho JC, Wieser M, Wu J, Redl H, et al. Generation of induced pluripotent stem cells from urine. Journal of the American Society of Nephrology : J Am Soc Nephrol. 2011; 22: 1221-8.

45. Guan J, Zhang J, Li H, Zhu Z, Guo S, Niu X, Wang Y, Zhang C. et al. Human Urine Derived Stem Cells in Combination with beta-TCP Can Be Applied for Bone Regeneration. PLoS One. 2015; 10: e0125253.

46. Guan J, Zhang J, Guo S, Zhu Z, Li H, Wang Y, Zhang C, Chang J, et al. Human urine-derived stem cells can be induced into osteogenic lineage by silicate bioceramics via activation of the Wnt/beta-catenin signaling pathway. Biomaterials. 2015; 55: 1-11.

47. Gao P, Jiang D, Liu W, Li H, Li Z. Urine-derived Stem Cells, A New Source of Seed Cells for Tissue Engineering. Curr Stem Cell Res . 2015.

48. Afzal MZ, Strande JL. Generation of induced pluripotent stem cells from muscular dystrophy patients: efficient integration-free reprogramming of urine derived cells. J Vis Exp. 2015; 52032.

49. Guan J, Zhang J, Zhu Z, Niu X, Guo S, Wang Y, Zhang C et al. Bone morphogenetic protein 2 gene transduction enhances the osteogenic potential of human urine-derived stem cells. Stem cell research & therapy. 2015; 6: 5.

50. Shi YA, Liu GH, Bharadwaj S, Atala A, Zhang Y. Urine derived stem cells with high telomerase activity for cell based therapy in urology. J Urol. 2012; 187: e302.

51. Lin CS, Xin ZC, Wang Z, Deng C, Huang YC, Lin G, Lue TF. et al. Stem cell therapy for erectile dysfunction: a critical review. Stem Cells Dev. 2012; 21: 343-51.

52. Qiu X, Sun C, Yu W, Lin H, Sun Z, Chen Y, Wang R, Dai Y.et al. Combined strategy of mesenchymal stem cell injection with vascular endothelial growth factor gene therapy for the treatment of diabetes-associated erectile dysfunction. J Androl. 2012; 33: 37-44.

53. Ouyang B, Sun X, Han D, Chen S, Yao B, Gao Y, Bian J, Huang Y, Zhang Y, Wan Z et al. Human urine-derived stem cells alone or genetically-modified with FGF2 Improve type 2 diabetic erectile dysfunction in a rat model. PLoS one. 2014; 9: e92825.