Autologous Bone Marrow-derived Mesenchymal Stem Cells versus Tension-free Vaginal Tape for Treatment of Female Stress Urinary Incontinence

A Thesis

Submitted for partial fulfillment of MD Degree
in Obstetrics & Gynecology

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Rania Hassan Mostafa -2017

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List of Abbreviations

ACOG ..... American College of Obstetricians & Gynecologists

ACP..... American College for Physicians

ADRC ..... Adipose-derived regenerative cells

ADSCs..... Adipose-derived stem cells

ALPP..... Abdominal leak point pressure

bFGF..... Basic fibroblast growth factor

BM..... Bone marrow

BMI..... Body mass index

BMSCs..... Bone marrow-derived stem cells

CLPP……. Cough leak point pressure

CMG ..... Cystometrography

CRF..... Case record form

CT ..... Computed Tomography

DM ..... Diabetes Mellitus

DSD..... Detrusor sphincter dyssynergia

EDTA..... Ethylene-diamine-tetraacetic acid

EMG ..... Electromyography

ESC ..... Embryonic stem cells

EUS ..... External urethral sphincter

FDA.....Food & Drug Administration

HGF .....Hepatocyte growth factor

ICIQ-UI SF International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form

ICS .....International Continence Society

IFN-γ.....Interferon-γ

IGF-1.....Insulin-like growth factor-1

iPSC .....Induced pluripotent stem cells

I-QOL .....Incontinence Quality of Life Instrument Score

ISD .....Intrinsic sphincter deficiency

IUGA.....International Urogynecological Association

KHQ.....Kings Health Questionnaire

LPP .....Leak point pressure

MDSCs.....Muscle-derived stem cells

MNCs.....Mononuclear cells

MRI.....Magnetic resonance imaging

MS .....Multiple Sclerosis

MSCs.....Mesenchymal stem cells

MUCP .....Maximum urethral closure pressure

MUS .....Midurethral slings

NICE.....National Institute for Health & Clinical Excellence

OAB ..... Overactive bladder

Pabd ..... Abdominal pressure

Pdet ..... Detrusor pressure

PFMT..... Pelvic floor muscle training

PP ..... Per protocol

Pves ..... Intravesical pressure

PVR..... Postvoid residual urine volume

Qmax..... Maximum flow rate

SD ..... Standard deviation

SDF-1 ..... Stem cell-derived factor-1

SEM ..... Standard error of mean

SIS ..... Small intestinal submucosa

SLE ..... Systemic lupus erythematosus

SUI ..... Stress urinary incontinence

TVT..... Tension-free vaginal tape

TVT-O ..... Obturator approach for midurethral sling

USCs ..... Urine-derived stem cells

UPP …….. Urethral pressure profile

VLPP …… Valsalva leak point pressure

WMA ..... World Medical Association

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Introduction:

Urinary incontinence is a significant health problem with considerable social and economic impact affecting over 200 million people worldwide ***(Norton et al., 2006).*** The exact prevalence of urinary incontinence is difficult to estimate; partly due to variations in defining the degree & frequency, & the other problem is that it represents a social stigma; so many women don't seek medical evaluation & the condition is under diagnosed & underreported ***(Vasavada et al., 2013)***.

Urinary incontinence is defined by the International Continence Society as the involuntary loss of urine that represents a hygienic or social problem to the individual ***(Abrams et al., 2002).*** In the study by *Hannestad et al.,* the commonest type of female urinary incontinence was the stress urinary incontinence (SUI) representing 50% of patients, while 11% had urge incontinence, & 36% had mixed incontinence ***(Hannestad et al., 2000).*** Risk factors for SUI include increasing parity, advanced age, & obesity ***(Bump et al., 1998).*** Trauma to the pelvic floor musculature, connective tissue or nerves mostly after vaginal delivery becomes the most important risk factor for development of SUI ***(Meyer et al., 1998).*** SUI may be due to urethral hypermobility, or intrinsic sphincter deficiency (ISD), or both ***(McGuire et al., 1976).*** In fact; these mechanisms

represent two extremes of the spectrum of SUI; with the patients having varying degrees of both disorders ***(Kayigil et al., 1999)***.

Attempts to treat SUI with pharmaceuticals, including alpha-agonists have not been highly successful ***(Radley et al., 2001)***. Short-term success has been achieved with injectable bulking agents such as polytetrafluoroethylene, bovine collagen, silicone, carbon beads, and autologous ear chondrocytes ***(Nikolavsky et al., 2010)***. However, long-term complications of these treatments included chronic inflammatory reactions, foreign body giant cell responses, periurethral abscesses, erosion of the bladder and urethra, particle migration, obstruction of urinary tract causing retention, and even pulmonary embolism ***(Sweat et al., 1999)***. Surgical therapy seems to be one of the options for achieving long-term continence with the tension-free vaginal tape becoming the most popular procedure for SUI ***(Yang et al., 2013)***. However, surgery for SUI sometimes causes postoperative voiding difficulty and infection, and treatments are still very difficult in the patients with recurrent SUI after anti-incontinence surgery because primary intrinsic sphincter deficiency can't be remedied directly ***(Novara et al., 2007)***.

A novel therapeutic strategy for patient with SUI is needed to achieve a long term & stable curative result ***(Song et al., 2009)***.

Stem cell therapy represents a paradigm shift in treatment of many disorders, as these cells are characterized by their ability to self-renew & to differentiate along multiple lineage pathways ***(Mizuno, 2009)***. Stem cells are either embryonic stem cells or adult stem cells ***(Mizuno, 2009).*** The use of embryonic stem cells is somehow limited; due to ethical considerations, increased tumorigenicity potential, & regulations ***(Edwards, 2007)***. On the other hand; autologous adult stem cells are immunocompatible, & there're no ethical issues related to their use ***(Yang et al., 2013; Mizuno, 2009)***. Some safety concerns are still raised with the use of adult stem cells as regards tumorigenicity; either due to non-target organ seeding or in vitro culture of cells; however these initial concerns flawed, as experimental & clinical data have been coming out with such complication not reported so far ***(Sanchez PL et al., 2006).*** This was concluded from systematic reviews of previous stem cell studies; like the systematic review & meta-analysis by **Abdel-Latif A et al.** on adult bone marrow derived cells for cardiac repair; which included 18 studies, involving 999 patients & supports safety of bone marrow derived cells transplantation ***(Abdel-Latif A et al., 2007).*** Another systematic review by **Martin-Rendon E et al.** provides systematic assessment of the safety and efficacy of autologous bone marrow-derived stem cell transplantation in acute myocardial infarction based on clinical evidence. Thirteen trials with total 811 patients were

included, & none showed any malignant potential ***(Martin-Rendon E et al., 2008)***. As in the field of urology, a critical review by **Lin & Lue** on stem cell therapy for stress urinary incontinence included preclinical & clinical studies from the year 2002 till the year 2011, & no malignant potential or other harmful effects evolved ***(Lin & Lue, 2012).*** Adult mesenchymal stem cells (MSCs) could be obtained from bone marrow ***(Barry et al., 2004)***, adipose tissue ***(Zuk et al., 2002),*** skeletal muscle ***(Lu et al., 2009),*** hair follicle ***(Drewa, 2008),*** & urine ***(Zhang et al., 2008; Bharadwaj et al., 2011).*** As MSCs possess multilineage differentiation potential including skeletal & smooth muscles; these represent a promising option for sphincter regeneration; thus restoring structure & function of the urethral sphincter ***(Novara et al., 2007; Zhao et al., 2011).***

In this study; we'll evaluate periurethral injection of autologous bone marrow-derived mesenchymal stem cells in comparison to tension-free vaginal tape as a therapy for female stress urinary incontinence due to intrinsic sphincter deficiency.

1. Aim of the work:

1.1. Research hypothesis:

Adult mesenchymal stem cells derived from bone marrow have the capability for self-renewal & differentiation

according to the surrounding medium into many different cell types including smooth muscle cells & skeletal muscle cells. This could be used to restore & maintain the structure & function of urethral sphincter; & thus provides an effective therapy for stress urinary incontinence due to intrinsic sphincter deficiency.

1.2.Research question:

Whether periurethral injection of autologous bone marrow-derived mesenchymal stem cells cures or improves stress urinary incontinence due to intrinsic sphincter deficiency or not.

1.3.Primary outcome:

To measure efficacy of mesenchymal stem cell therapy compared to tension-free vaginal tape (TVT) in treatment of stress urinary incontinence; by: clinical examination (cough test, International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form [ICIQ-UI SF]**[appendix III]**) & urodynamic study before & after therapy each 3 months for one year (at 3m, 6m, 9m, 12m post-injection).

1.4.Secondary outcome:

To evaluate quality of life before & after therapy; By: The Incontinence Quality of Life (I-QOL) Instrument Score **[appendix IV]**.