

# Evaluation of fat grafting technique using autologous micro-fragmented adipose tissue (Lipogems®) in female patients suffering from stress urinary incontinence

Janice Santos Cortes\* and Danielle Velez

Department of Surgery, Urology, The Warren Alpert School of Medicine of Brown University, RI, USA

## Abstract

Stress urinary incontinence (SUI) is a common occurrence in women. Although causes may be multi-factorial, the ultimate consequence of urethral sphincter weakness is urinary leakage with increase in intra-abdominal pressure. The gold standard treatment for SUI is urethral sling, for which the patient may not be a candidate, versus injection of synthetic bulking agents, which requires repeat injections over the patient's lifetime. Autologous mesenchymal stem cells are an area of great interest within regenerative medicine to offer longer lasting effects over synthetic bulking agents. Microfragmentation of the harvested fat, to isolate the mesenchymal stem cells, is a novel technique that has shown great promise in other fields. Here, we present our preliminary data for 11 women with primary stress urinary incontinence after mid-urethral injection of autologous mesenchymal stem cells. Eight women were at least one-year post-Lipogems® injection and had an average improvement in VAS score from 9 to 4.7, and a decrease in pad count from 5.3 to 4.2. Two women had complete resolution of their SUI (VAS 0, pad count 0) at 18 and 24 months post-Lipogems® injection. Only one patient had a harvest site hematoma, and three patients had post-op urinary retention which resolved. These preliminary results are supportive of the regenerative potential of autologous mesenchymal stem cells for the treatment of stress urinary incontinence.

## Introduction

### Urinary incontinence

Urinary incontinence affects more than 200 million people worldwide. In a recent survey for National Health and Nutrition of 4,229 women older than 20 years, 49.6% reported urinary incontinence symptoms. Of them, 49.8% were stress urinary incontinence (SUI), 15.9% were urge incontinence (UI), and 34.3% were mixed incontinence (MUI) [1]. Stress urinary incontinence is defined as involuntary leakage of urine with increased abdominal pressure, including cough, sneeze, laugh, or Valsalva. Urge incontinence is the involuntary leakage of urine secondary to bladder hyperactivity, and MUI is a combination of the two. In women, incontinence may be secondary to urogenital injury from childbirth, loss of estrogen stimulation resulting in vaginal atrophy and loss of vaginal muscle turgor, decreased urogenital diaphragm tone, and urethral sphincter weakening [2].

There are many surgical options for SUI. The mid-urethral sling is the gold standard; however, it carries the risk of bleeding, infection, mesh erosion, urinary retention, failure, and chronic pain. Furthermore, although mesh is still approved for mid-urethral sling, many women are hesitant to proceed with implantation, given the recent controversies in mesh for prolapse and anti-incontinence surgeries. Furthermore, synthetic mesh was removed from the market by the FDA for prolapse. An alternative to mid-urethral sling is urethral bulking agents. Mid-urethral bulking increases bladder resistance, thereby decreasing leakage. However, there is no permanent or long-lasting effect: the average success rate at one year is only 63%, with patients requiring re-application [3].

### Regenerative bulking agents

Given the limited options for SUI management, SUI is a subject of great research. Mesenchymal stem cells in particular are a novel class of injectables, representing multi-potent stromal stem cells, with the potential to differentiate into a number of cell types and stimulate cell signaling to create a regenerative environment, inducing angiogenic, anti-apoptotic and anti-fibrotic responses [4-6]. As such, MSCs have been referred to as "Medicinal Signaling Cells [7]." Additionally, these cells can be readily obtained from adipose tissue by isolating the pericytes through liposuction, yielding anywhere from 50 mL to 6 L of tissue. Liposuction is a non-invasive procedure, easily performed under local anesthesia, and results in minimal discomfort for the patient.

However, to isolate the mesenchymal stem cells from adipose is challenging. Enzymatic separation results in prolonged expansion, senescence and a decreased multipotency. Cell preservation is also difficult due to poor cell survival from the freezing/thawing cycle, poor delivery efficiency (< 5% of transplanted cells are retained after transplantation), and uncertain fate *in vivo* [8].

The Lipogems' system relies on gentle mechanical forces within a closed system to microfracture harvested fat with minimal cellular trauma, isolating pericytes without relying on damaging enzymes and

\*Correspondence to: Janice Santos Cortes, Department of Surgery, Urology, The Warren Alpert School of Medicine of Brown University, 2 Dudley Street Suite 185, Providence, RI 02906, USA, E-mail: jasmd25@gmail.com

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using the adipose tissue as a scaffold. Below, we describe our prospective trial using the Lipogems® system to isolate mesenchymal stem cells for the treatment of patient with predominant stress urinary incontinence.

## Methods

Patients with primary SUI or MUI with a predominant SUI component were recruited from a private academic urology practice. Women with a present diagnosis of cancer, untreated vaginal prolapse, incontinence of unknown etiology, overflow incontinence, neurogenic bladder, concomitant pelvic floor disorders, vulvar dermatosis, herpes simplex or active or recurrent urinary tract infections, chronic steroid use, or under the age of 18 were excluded. Prior to undergoing Lipogems®, anti-incontinence medications were withheld for an appropriate washout period, and then video urodynamics were performed to obtain baseline filling and voiding parameters.

Subjective (patient visual analog score) and objective (patient reported pad counts, and physician documented cough stress test) measurements were performed at baseline (pre-treatment), three, six, and twelve months post-operatively. Urodynamics were repeated at six months to measure the leak point pressure (LLP) if leakage was present.

The patient was restricted from taking nonsteroidal anti-inflammatory medications for three days prior to and for two weeks after Lipogems® treatment to minimize risk of bleeding. Steroids were also withheld for three days prior to and for 12 months after so as not to affect the regenerative process.

## Harvesting of adipose tissue and micro-fragmentation of the lipoaspirate with Lipogems® technique

The lipoaspiration procedure involves two steps: infiltration and aspiration. The harvesting site is chosen by the patient's body habitus: lower abdomen, lower back, hips, or outer thighs. The goal is to collect 60 ml, and then the aspirated adipose tissue is inserted into the Lipogems® device. The adipose is then micro-fragmented, filtered, and purified from oils and residual blood cells. Ultimately, ~20% of the original 60 mL is obtained as final lipoaspirate and used for mid-urethral injections through a needle of 21 G.

## Re-inoculation

An injection needle, inserted via a cystoscope, is used to inject 10-20 mL of Lipogems® at the sphincteric level, typically at the 3, 6, 9 and 12 o'clock positions, as well as at the bladder neck and in the peri-urethral space. Injected volume is dictated by the individual patient and condition; more severe weakness requires greater volume of injection.

After withdrawal of the cystoscope, the bladder is drained with an 8-French foley catheter and the patient is given the opportunity to void.

## Results

Patients were recruited from June 1, 2017 until June 15, 2019. In total, 11 patients underwent Lipogems® harvesting and then mid-urethral injection. Patient history, harvest sites, amount injected, and outcomes are summarized in Table 1. The majority of our patients had stress urinary incontinence, with only 3 of the 11 having mixed urinary incontinence with a primary stress component. Average volume of Lipogems® injected was 14.7 mL, which was relatively stable over the study period.

At the time of this publication, eight patients were at least one year from Lipogems® injection; three patients had only one month of follow-

up. For these eight patients, four had 12 months of follow-up (Patients 1, 3, 4, and 5) and two were reached via telephone for long-term VAS and pad counts (Patients 2 and 8). Patients 6 and 7 were lost to follow-up. Table 1 lists the outcomes per patient. Of the patients with 12 months of follow-up, VAS improved from an average of 9 to 4.7 and pad count decreased from 5.3 to 4.2. A telephone follow-up was completed for Patient #3, who chose to undergo Coaptite mid-urethral injection for worsening urinary incontinence at the conclusion of the trial. Of note, Patient #3 had previously undergone mid-urethral sling, which eroded, and required removal. As a result, she also had intrinsic sphincter deficiency with a LPP of 77 mmHg. Patient #5 was also reached via telephone follow-up, and her pad count had decreased from a baseline of 5 to 3 at 21 months post-Lipogems®. Patient #2 was reported a VAS of 0 and pad count of 0 two years after undergoing Lipogems® injection. During follow-up for Patient #8, she had had significant difficulty distinguishing her SUI from her UUI. After reprogramming her sacral nerve stimulator and exchanging its battery, her VAS and pad count both improved to zero, 18 months after undergoing Lipogems®.

Four patients returned for six-month urodynamics. Three patients had an improvement in their LPP: 185 (Patient 1), 4 (Patient 3), and 15 (Patient 7). The fourth patient had a decrease in her LPP of 81 mmHg. We aim to report long-term results after Patients 9, 10, and 11 reach one-year follow-up.

There was a learning curve in harvesting the Lipogems®. All complications occurred in the first five patients, and there were no 30 or 90-day complications in the last six patients. Only one patient (the first one) had hematoma at her harvest site, and three patients had post-operative urinary retention, which resolved within one week. Two major changes were moving from oral sedation in an operating room setting to general anesthesia (sedation) in an operating room. For ease of injection, we transitioned to an injection cystoscope with a 21G implant syringe.

## Discussion

We present preliminary results for the use of Lipogems® for stress urinary incontinence in 11 women. Autologous mesenchymal stem cells have been investigated in a number of regenerative and reconstructive fields with promising early results [9,10].

However, this was the first clinical trial using Lipogems® derived autologous mesenchymal stem cells for the treatment of stress urinary incontinence. The patients with the most successful outcomes had mild to moderate stress urinary incontinence. We chose to include patients with a complicated urogynecologic history as they had no other surgical options or were hesitant to attempt mid-urethral sling for their severe urinary incontinence.

Three patients had (Patients #2, 5 and 8) partial improvement or complete resolution of their stress urinary incontinence for over six months. Lipogems® injection does provide a temporary bulking effect, which acts similarly to Coaptite or Macroplastique injection for stress urinary incontinence but would be expected to wear off after six months. We believe the persistent improvement in these patients is evidence of the regenerative properties of Lipogems®, especially in patients with mild to moderate urinary incontinence, who wish to avoid the possibility of mid-urethral sling complications. Although mesh is still approved for the treatment of SUI with a mid-urethral sling, the banning of mesh for prolapse surgeries may influence patients away from implantation of a foreign body or chemical, opting instead for autologous materials. Autologous fascial slings are an alternative

**Table 1.** Outcomes per patient

Patient	History	Harvest sites	mL Injected	Month 0	Month 1	Month 3	Month 6	Month 12	Last follow-up	Complications
1	63 years of age SUI; uterine prolapse, managed with pessary	Flank, bilateral	15	VAS: 9 # Pads: 6 Exam: +SUI	Lost to follow-up	Lost to follow-up	VAS: 8 # Pads: 5 Exam: +SUI LPP increase by 185	VAS: 9 # Pads: 6 Exam: +SUI	N/A	Harvest site hematoma, urinary retention
2	42 MUI	Lower abdomen	12	VAS: 8 # Pads: 7 Exam: +SUI	VAS: 1 # Pads: 1 Exam: No SUI	Lost to follow-up	VAS: n/a # Pads: 1	Lost to follow-up	Telephone follow-up, 2 years: VAS: 0 # Pads: 0	Urinary retention
3	50 SUI, ISD; history of mid-urethral sling, erosion, explantation	Lower buttocks, bilateral	15	VAS: 8 # Pads: 8 Exam: +SUI	VAS: 6 # Pads: 7 Exam: +SUI	VAS: 4 # Pads: 7 Exam: +SUI	VAS: 7 # Pads: 10 Exam: +SUI LPP increase by 4	VAS: n/a # Pads: 10 Exam: +SUI	Telephone follow-up, 1 year, underwent coaptite injection: # Pads: 7	none
4	63 SUI, ISD	Lower abdomen	15	VAS: 9 # Pads: 2 Exam: +SUI	VAS: 4 # Pads: 1 Exam: +SUI Improved urgency	VAS: 7 # Pads: 2 Exam: +SUI	VAS: 6 # Pads: 1 Exam: +SUI Baseline urgency	VAS: 5 # Pads: 1 Exam: +SUI	Elected to repeat Lipogems® injection as it had significant improved her incontinence at 12 months	None
5	47 SUI	Hips, bilateral	15	VAS: 10 # Pads: 5 Exam: +SUI	VAS: 0 # Pads: 0 Exam: No SUI	Lost to follow-up	Lost to follow-up	VAS: 0 # Pads: 0	21 months after Lipogems®: VAS: 9 # Pads: 3	Urinary retention
6	59 SUI	Lower abdomen	15	VAS: 7 # Pads: 5 Exam: +SUI	Lost to follow-up	Lost to follow-up	Lost to follow-up	Lost to follow-up	N/A	None
7	60 SUI	Lower abdomen	13	VAS: 8 # Pads: 5 Exam: +SUI	VAS: 4 # Pads: 3 Exam: No SUI	VAS: 2 # Pads: 2 Exam: No SUI	VAS: 0 # Pads: 0 Exam: no SUI LPP increase by 15	Lost to follow-up	N/A	None
8	55 SUI, with detrusor overactivity on UDS. Interstim for OAB (2005)	Lower abdomen	15	VAS: 9 # Pads: 4 Exam: +SUI	VAS: 4 # Pads: 4 Exam: +SUI	VAS: 8 # Pads: 4	VAS: 8 # Pads: 4 + SUI, exam + UUI LPP decrease by 81	Lost to follow-up	18 months after Lipogems® and Interstim reprogramming + battery exchange: VAS: 0 # Pads: 0	None
9	45 SUI	Lower abdomen	15	VAS: 10 # Pads: 1 Exam: +SUI	VAS: 5 # Pads: n/a	Pending	Pending	Pending	N/A	None
10	57 MUI		18	VAS: 10 # Pads: 10 Exam: +SUI	VAS: 8 # Pads: 6 Exam: +SUI	Pending	Pending	Pending	N/A	None
11	36 MUI	Bilateral outer thighs	14	VAS: 2 # Pads: 9 Exam: +SUI	VAS: 7 # Pads: 2 Exam: +SUI	Pending	Pending	Pending	Felt her urinary urgency had greatly improved	None

method, they are invasive, requiring an abdominal or thigh incision. Furthermore, Lipogems® harvesting and mid-urethral injection does not preclude future procedures should the patient have suboptimal results, as evidenced by Patient #3, who chose to undergo subsequent injection. As synthetic urethral bulking agents will definitely require repeat injection, the possibility of a single procedure using autologous mesenchymal stem cells is a superior option.

Lipogems®-derived mesenchymal stem cells have been used with success in other disease states, as shown in several case studies. Much like our preliminary results, each study is notable for having short follow-up and small volume of patients. One study of six patients with hip osteoarthritis, who were failing conservative treatment, underwent

intra-articular injection of Lipogems®-derived mesenchymal stem cells [11]. All patients had improvement in their pain, mobility, and deformity scores, and average visual analog scores (VAS) decreased from pre-operative 4.6 to six months post-operative of 1.5. In three fecal incontinence patients, injection of Lipogems®-derived mesenchymal stem cells had an increase in resting pressure of at least 10 mmHg, and improved thickness of the internal anal sphincter at the six-month follow-up [12].

A larger study of 19 patients with history of complex anal fistula, in which the internal opening of the fistula was surgically closed, received Lipogems®-derived mesenchymal cells into the mucosal and muscular layers and into the fistula tract. Ten patients were treated with

**Table 2.** Average outcomes

	Average	Range	n
Age	52.5	36-63	11
Incontinence Type			
Stress			8
Mixed			3
Intrinsic Sphincter Deficiency			2
Leak Point Pressure	127.0	73-200	10
Volume injected (mL)	14.7	12-18	11
Visual Analog Score			
Baseline	8.2	2-10	11
Month 1	4.4	0-8	9
Month 3	5.3	2-8	4
Month 6	5.8	0-8	5
Month 12	4.7	0-9	3
Pad Counts			
Baseline	5.6	1-10	11
Month 1	3.0	0-7	8
Month 3	3.8	2-7	4
Month 6	3.5	0-10	6
Month 12	4.3	0-10	4
Cough Test	Yes	No	n
Baseline	11	0	11
Month 1	5	3	8
Month 3	2	1	3
Month 6	4	1	6
Month 12	3	0	2

Lipogems<sup>®</sup>-derived mesenchymal stem cells as a first-line therapy, and 9 had failed other management strategies. Healing was defined as closure of the internal and external openings, without discharge. At an average of nine months follow-up, the overall healing rate was 83.3% and 57.1% in the patients using Lipogems<sup>®</sup> as a first and second-line treatment, respectively [13].

In one case study, a 50-year old female with female sexual dysfunction, namely vaginal dryness, anorgasmia, and dyspareunia, was treated with Lipogems<sup>®</sup>-derived mesenchymal stem cells, injected into the anterior and posterior vaginal canal, lateral walls, and circumferentially around the introitus. At ten months follow-up, the patient noted improvement in her lubrication, resolution of her dyspareunia, and she was able to achieve satisfactory orgasm [4].

The examples represent small case series, with short follow-up times. The mechanism behind mesenchymal stem cells is thought to be multi-factorial, first offering a bulking effect from volume injection, followed by a longer-term regenerative phase, marked by stromal tissue repair, revascularization, and an anti-fibrotic response [4]. Understanding there is a learning curve and that the harvesting and purification methods are based on calculations from non-urolologic literature, we are encouraged by the initial results. The purpose of this study was not to measure the volume of mesenchymal stem cells in the urethral sphincter after treatment, but rather to determine if patients had persistent clinical improvement in their stress urinary incontinence beyond the average effect seen by injection of synthetic urethral bulking agents. Indeed, even if patients did not achieve long-lasting

regenerative results from their injection, they may perceive benefit from bulking material derived from an autologous source. Patient #4 elected to repeat Lipogems<sup>®</sup> after her one year-follow-up appointment. In the first procedure, she received 15 mL, but tolerated 24 mL during the second injection, which was the highest volume of tissue thus far. At one month-follow-up, she had a VAS and pad count of 0.

With these preliminary results, the authors believe autologous-derived mesenchymal stem cells, isolated through micro-fragmentation of a patient's fat, is an alternative option for women with mild to moderate stress urinary incontinence, who may not be a candidate for a urethral sling, or for women who desire a longer-term, natural bulking option over synthetic agents.

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