A novel regenerative treatment for female stress urinary incontinence: short-term outcome of three patients undergoing periurethral injection of autologous adipose-derived regenerative cells

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Hypothesis / aims of study
We created a novel treatment strategy to regenerate the urethral sphincter function, using autologous adipose-derived regenerative cells (ADRCs) without the need of cell culture (Fig 1). We previously demonstrated the safety and favorable long-term efficacy of periurethral injection of autologous ADRCs for the treatment of male stress urinary incontinence (SUI) following prostatectomy [1]. Briefly, SUI improved progressively in eight patients (72.7%) during the 1-year follow up, as determined by a 55.8% decrease in the leakage volume in the 24-h pad test, decreased frequency and amount of incontinence, and improved quality of life. One patient obtained complete continence at 6 months after treatment. In the present study, we report the short-term outcome (9 to 12 months) of the first three female patients with SUI undergoing periurethral injection of autologous ADRCs.

Study design, materials and methods
Three female patients with SUI were included in this preliminary clinical trial. No patients had urgency incontinence. After liposuction of 250 mL of adipose tissue from the abdomen, we isolated ADRCs by using the Celution™ system. Subsequently, these ADRCs and a mixture of ADRCs and adipose tissue were transurethrally injected into the rhabdosphincter and submucosal space of the urethra, respectively. Unlike other cell therapies, this treatment is entirely autologous, does not require cell culture, and is performed as a single surgical procedure. In the protocol, the primary outcome is assessed by a 24-hour pad test, at baseline, 2 weeks, 1 month, and every 3 months thereafter until 36 months after treatment. Secondary outcomes included a validated patient questionnaire (the International Consultation on Incontinence Questionnaire-Short Form, ICQ-SF), urethral pressure profile, contrast-enhanced transvaginal ultrasonography, and magnetic resonance imaging (MRI). Here, we report the outcomes of treatment efficacy and safety at the 9-12 months follow-up in the 3 cases.

The present study was approved by the Ethics Committee of the Nagoya University Graduate School of Medicine, and also by the committee of Japanese Ministry of Health, Labor and Welfare according to the Guidelines on Clinical Research using Human Stem Cells. Written informed consent was obtained from all the patients.

Patients
In the present study, 3 patients with uncomplicated genuine SUI were enrolled. Patients’ ages were 40, 39, and 64 years, respectively. No patients had a history of previous surgery for SUI and co-existing disorders.

Harvesting adipose tissue and isolation of ADRCs
After liposuction of 250 mL of adipose tissue from the anterior abdominal wall, ADRCs were isolated from the harvested adipose tissue by using the Celution™ system. Briefly, adipose tissue was introduced into the Celution™ cell-processing device which automatically and asceptically extracts and concentrates the mononuclear fraction of adipose tissue and removes unwarranted or deterritorialized cells, cell and matrix fragments. It required around 1 hour to process 250 mL of liposuction tissue. The final concentrated cell output collected using the Celution™ System was counted using a NucleoCounter (Phenomenex, CA, USA) and is performed as a single surgical procedure.

Advantage
Our treatment strategy has an important advantage over the use of other stem cells.

1. Since adipose tissue contains abundant multipotent regenerative cells as well as key mature cells and progenitor cells, therapeutic levels of ADRCs can be obtained rapidly using the Celution™ system.

2. Unlike other cell therapy strategies, the treatment is all autologous, requires no cell culture and is performed in the context of a single surgical procedure.

Possible mechanisms for the ADRC-mediated improvement of the sphincteric function [2]

1. A bulking effect produced by the injected adipose tissue fraction mixed with ADRCs

(Persistent bulking effect indicates the survival and growth of the injected adipose tissue, which could also be attributed to the presence of ADRCs).

2. Differentiation of injected cells into mature adipose tissue and possibly into contractile cells

3. Increased blood flow due to angiogenesis effect of the cytokines secreted by the injected ADRCs. (The increased blood flow might have a positive effect on the regeneration of the injected adipose tissue and impaired intrinsic sphincteric function).

Conclusions
The results of this preliminary study showed that periurethral injection of autologous ADSCs is a safe and feasible treatment modality for female patients with SUI caused by urethral sphincter deficiency.