III. 研究成果の刊行に関する一覧表

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雑誌

発表者氏名	論文タイトル名	発表雑誌	巻号	ページ	出版年
Gotoh M, Yamamoto T, Kato M, Majima T, Toriyama K, Kamei Y, Matsukawa Y, Hirakawa A, Funahashi Y	Regenerative treatment of male stress urinary incontinence by periurethral injection of autologous adipose-derived regenerative cells: 1-year outcomes in 11 patients.	Int J Urol	21	294-300	2014
Kim H, Mizuno M, Furuhashi K, Katsuno T, Ozaki T, Yasuda K, Tsuboi N,Sato W, Suzuki W, Matsuo S, Itoh W, Maruyama S	Rat adipose tissue-derived stem cells attenuate peritoneal injuries in rat zymosan-induced peritonitis accompanied by complement activation.	Cytotherapy	0	1e12	22014
山本徳則、後藤百万	腹圧性尿失禁に対する経尿道的脂肪組織由来幹細胞注入治療：臨床再生医療と TR 研究	臨床泌尿器科	68	389-396	2014
山本徳則	血流イメージング	Jpn J Med Ultrasonics	41	811-818	2014
Hirose Y, Murakami M, Hayashi Y, Osako Y, Yamamoto T, Gotoh M, Nakashima M	Augmentation of Regenerative Potential of Mesenchymal Stem Cells by Granulocyte-colony Stimulating Factor (G-CSF) Induced Mobilization	J Stem Cell Res Transplant	1	10-19	2014

IV. 研究成果の刊行物・別刷り

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Original Article: Clinical Investigation

Regenerative treatment of male stress urinary incontinence by periurethral injection of autologous adipose-derived regenerative cells: 1-year outcomes in 11 patients

Momokazu Gotoh,[1] Tokunori Yamamoto,[1] Masashi Kato,[1] Tsuyoshi Majima,[1] Kazuhiro Toriyama,[2] Yuzuru Kamei,[2] Yoshihisa Matsukawa,[1] Akihiro Hirakawa[3] and Yasuhito Funahashi[1]

Departments of [1]Urology and [2]Plastic and Reconstructive Surgery, and [3]Biostatistics Section, Center for Advanced Medicine and Clinical Research, Nagoya University Graduate School of Medicine, Nagoya, Japan

Abbreviations & Acronyms
ADRC = adipose-derived regenerative cells
ASC = adipose-derived stem cells
FPL = functional profile length
GFP = green fluorescent protein
HoLEP = holmium laser enucleation of the prostate
ICIQ-SF = International Consultation on Incontinence Questionnaire-Short Form
MRI = magnetic resonance imaging
MSC = mesenchymal stem cells
MUCP = maximum urethral closing pressure
QOL = quality of life
RP = radical prostatectomy
SD = standard deviation
SUI = stress urinary incontinence

Correspondence: Momokazu Gotoh M.D., Ph.D., Department of Urology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-855, Japan. Email: gotoh@med.nagoya-u.ac.jp

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Objectives: To assess the efficacy and safety of a novel cell therapy for male stress urinary incontinence consisting of periurethral injection of autologous adipose-derived regenerative cells, and to determine the 1-year outcomes.

Methods: A total of 11 male patients with persistent stress urinary incontinence after prostate surgery were included in the study. The Celution system was used to isolate adipose-derived regenerative cells from abdominal adipose tissue obtained by liposuction. Subsequently, these regenerative cells, and a mixture of regenerative cells and adipose tissue were transurethrally injected into the rhabdosphincter and submucosal space of the urethra, respectively. The 1-year outcomes were assessed using a 24-h pad test, a validated patient questionnaire, urethral pressure profile, transrectal ultrasonography and magnetic resonance imaging.

Results: Stress urinary incontinence improved progressively in eight patients during the 1-year follow up, as determined by a 59.8% decrease in the leakage volume in the 24-h pad test, decreased frequency and amount of incontinence, and improved quality of life. One patient achieved total continence. The mean maximum urethral closing pressure and functional profile length increased from 35.5 to 44.7 cmH_2O, and from 20.4 to 26.0 mm, respectively. Magnetic resonance imaging showed the sustained presence of the injected adipose tissue, and enhanced ultrasonography showed a progressive increase in blood flow to the injected area in all patients. No significant adverse events were observed peri- or postoperatively.

Conclusion: Periurethral injection of autologous adipose-derived regenerative cells might represent a safe and feasible treatment modality for male stress urinary incontinence.

Key words: adipose-derived regenerative cells, adipose-derived stem cells, cell therapy, prostatectomy, stress urinary incontinence.

Introduction

Cell therapy can be used for the regeneration of damaged tissues in several diseases, and it has been experimentally investigated in many fields. MSC are multipotent adult stem cells that can proliferate into a variety of cell types in culture.[1–4] Experimental studies have reported the use of MSC obtained from the bone marrow, adipose tissue or skeletal muscle for the treatment of SUI, with the objective of regenerating the sphincter.[5–11]

Multipotent stem cells are 100-fold more abundant in adipose tissue than in the bone marrow. The human body is rich in adipose tissue, and adipose tissue can be easily and safely harvested in large quantities with minimal morbidity. Therefore, adipose tissue has attracted attention as a source for cell therapy. ASC showed the ability to differentiate into bone, cartilage, adipose, nerve, blood vessel and muscle cells.[1,3,4,12] We therefore developed a treatment method for SUI caused by sphincter deficiency, based on the regeneration of the sphincter using ASC. The rationale and efficacy of periurethral injection of cultured ASC for the treatment of SUI were showed in animal experiments.[13] However, the clinical application of cell therapy requires the use of autologous cells, and the procurement of enough cells without the need for cell culture. We used ADRC to develop a novel treatment strategy for the regeneration of the urethral sphincter, which meets these criteria. We previously reported the favorable short-term outcomes of three cases of the first in-human study using this treatment strategy.[14] Here, we report the 1-year outcomes in 11 male patients enrolled in the preliminary clinical study.

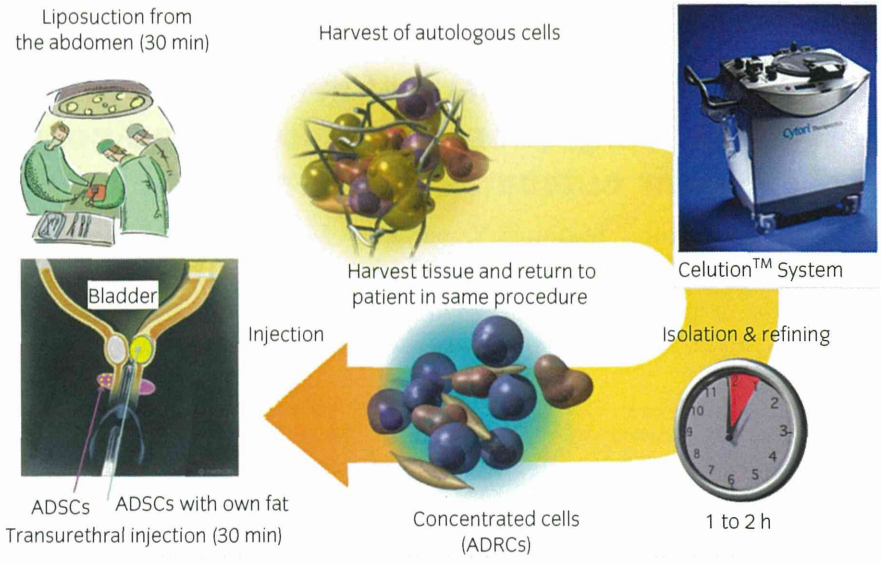

Fig. 1 A brief outline of the treatment strategy. The autologous tissue source was harvested from the abdomen by liposuction. ADRC were isolated from the tissue without culture using the Celution system. Finally, ADRC were transurethrally injected into the urethral sphincter. This treatment can be completed as a single surgical procedure within 3 h.

Table 1 Patients' characteristics, and outcomes on isolation and injection of ADRC

Patients	Age (years)	Duration of SUI (months)	Type of prostate surgery	Time for ADRC isolation (min)	Time for ARDC injection (min)	No. isolated cells	Viable cells (%)
1	68	20	HoLEP	98	25	7.5×10^6	93.8
2	76	54	RP	110	31	2.2×10^7	91.2
3	85	104	RP	118	54	2.2×10^7	90.1
4	72	74	RP	103	17	7.3×10^6	91.4
5	78	78	RP	110	27	2.4×10^7	89.7
6	78	52	RP	80	33	3.3×10^7	90.2
7	71	29	RP	79	40	7.5×10^6	93.8
8	74	66	HoLEP	74	30	2.5×10^6	94.2
9	75	40	RP	117	48	1.8×10^7	90.0
10	79	61	RP	73	39	2.3×10^7	88.6
11	77	74	RP	119	30	3.3×10^7	90.9
Mean (SD)	76 (5)	59 (24)		98 (18)	34 (11)	1.8×10^7 (1.1)	91.3 (1.9)

Methods

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

A brief outline of the treatment strategy in the present study is shown in Figure 1. The autologous tissue source was harvested from the abdomen by liposuction. ADRC were isolated from the tissue without culture using the Celution (Cytori Therapeutics, San Diego, CA, USA) system. Finally, ADRC were transurethrally injected into the urethral sphincter. This treatment can be completed as a single surgical procedure within 3 h.

Patients

A total of 11 patients were treated and followed up for more than 1 year (Table 1). The causes of SUI were sphincter deficiency after radical prostatectomy in nine patients and holmium laser enucleation of the prostate in two patients. The inclusion criteria for the patients with prostate cancer were persistence of SUI for more than 2 years after surgery, localized prostate cancer of good risk with a preoperative prostate-specific antigen level of <10 ng/mL and Gleason score of 6 points or less, negative surgical margin on pathological examination of the resected prostate specimen, and no evidence of recurrence or metastasis with undetectable levels of prostate-specific antigen.

Harvesting adipose tissue (liposuction)

Under spinal anesthesia, 250 mL of adipose tissue was harvested from the anterior abdominal wall by making two 3-mm incisions. Ringer's lactate was first infused in the subcutaneous layer, and the adipose tissue was harvested. The suctioned adipose tissue was placed in saline, and allowed to stand for settling of the blood and cellular debris; adipose tissue floated at the top of the mixture.

Isolation of ADRC

ADRC were isolated from the harvested adipose tissue using the Celution system,[15] which is a commercially available kit designed to isolate ADRC from human adipose tissue in a short time. This instrument allows the isolation of therapeutic doses of autologous ADRC after liposuction without the need for culture. The nucleated cell composition of ADRC includes approximately 0.6–1.6% ASC, as well as both mature and progenitor endothelial and smooth muscle cells, CD45+ hematopoietic cells and resident tissue macrophage/monocytes, pericytes, and preadipocytes, as well as other less well characterized stromal fibroblastic cell populations.[15] The final concentrated cell output was measured using a NucleoCounter (Chemometec, Allerod, Denmark), which exclusively detected nucleated cells. By using the Celution system, we could finally obtain a 5-mL solution containing concentrated ADRC.

Periurethral injection of ADRC

After liposuction and isolation of ADRC, transurethral endoscopic injection of ADRC was carried out. For periurethral injection, two distinct formulations were produced: 1 mL of the isolated ADRC fraction alone was preserved for direct injection, and another 4 mL of the fraction were mixed with intact autologous adipose cells, yielding a total of 20 mL of this combined solution.

A 22-Fr rigid endoscope was used for injecting the processed ADRC solution. Under endoscopic vision, a puncture needle was passed through the endoscope into the urethra at the region of the external urethral sphincter. The 18-G needle was 35 cm in length and graduated in centimeters, and was specially ordered. The ADRC solution was injected after puncturing the urethra at the region of the external urethral sphincter under endoscopic vision. Initially, a 1-mL solution was injected to a depth of 5 mm into the rhabdosphincter at 5 and 7 o'clock positions. Subsequently, 20 mL of the formulation containing ADRC and adipose tissue was equally injected into the submucosal spaces at 4, 6, and 8 o'clock positions to facilitate complete coaptation of the urethral mucosa. After the solution was injected, a 6-Fr urethral balloon catheter was placed and removed the next day.

Primary outcome measure

The amount of incontinence was evaluated by a 24-h pad test, and the total daily leakage volume was calculated. The 24-h pad test was carried out consecutively for 4 days in each evaluation period (baseline, 2 weeks, and 1, 3, 6, 9 and 12 months). Changes in the mean daily leakage volume during the 4 days from baseline to 12 months after treatment were evaluated as a primary outcome measure.

Secondary outcome measures

Urethral sphincter function was objectively assessed by urethral pressure profile using a urodynamic system (MMS, Enschede, the Netherlands). MUCP and FPL were measured at baseline, 2 weeks, and 1, 3 and 6 months after treatment.

Subjective symptoms and QOL were evaluated using a validated disease-specific questionnaire, the ICIQ-SF.[16,17] In the ICIQ-SF, the therapeutic effects in terms of frequency of urinary incontinence (0–5 point scores), amount of leakage (0–6 point scores) and impact on everyday life (0–10 point scores) were examined, and the total score ranging from 0 to 21 points was calculated. A high score indicates unfavorable conditions. These parameters were assessed at baseline, and repeated at 2 weeks, and 1, 3, 6, 9 and 12 months after treatment.

The blood flow to the area where the ADSC were injected was assessed using contrast-enhanced transrectal ultrasonography after intravenous injection of perflubutane at each evaluation period. Power Doppler imaging was obtained 5 min after perflubutane injection.

The morphological condition of the injected area was monitored using MRI at baseline, and 3, 6 and 12 months after treatment.

Voiding function was evaluated by uroflowmetry, and measurement of post-void residual urine volume at baseline, 2 weeks, and 1, 3, 6 and 12 months.

Statistical analyses

For each patient, the change and/or percent change between baseline and 6 (or 12) months with respect to the primary and secondary outcome measures were calculated. The means (standard deviations) of them were calculated and the Wilcoxon signed-rank test was carried out. A two-sided $P < 0.05$ was considered to be statistically significant. The analyses were carried out using SAS (version 9.3; SAS Institute, Cary, NC, USA).

Results

Liposuction was carried out in the abdomen without significant morbidity, and 250 mL of adipose tissue was harvested in all cases. The isolated adipose tissue solution contained 7.3×10^6 to 3.3×10^7 ADRC (6.7×10^6 to 3.0×10^7 viable cells; Table 1). The mean time of cell extraction was 98 min, and the mean time of periurethral injection was 34 min (Table 1).

The means of change and percent change between baseline and 12 months for daily leakage volume in 11 patients were −86.8 g ($P = 0.054$) and −40.9% ($P = 0.010$), respectively. These improvements were mainly attributable to a progressive decrease of daily leakage volume in eight patients (Table 2). In contrast, no change in daily leakage volume was observed in the remaining three patients. In the eight patients showing decreased leakage volume, urinary incontinence improved immediately after injection, deteriorated approximately 1 month after injection, and progressively improved thereafter up to 6–12 months (Fig. 2).

The means of change and percent change between baseline and 12 months for MUCP in 11 patients were 9.2 cmH2O ($P = 0.017$) and 38.8% ($P = 0.019$), respectively. The mean MUCP increased both in the patients with improved and those with unimproved leakage volume on the 24-pad test (Fig. 3a). The means of change and percent change between baseline and 12 months for FPL in 11 patients were 5.6 mm ($P = 0.006$) and 40.1% ($P = 0.006$), respectively. The mean FPL increased in patients with improved leakage volume, but not in those with unimproved leakage volume (Fig. 3b). No significant increase of post-void residual urine volume was observed in any of the

Table 2 Outcomes on incontinence, urethral sphincter function and post-void residual urine

Patients	Daily leakage volume (g)				MUCP (cmH2O)				FPL (mm)				PVR (mL)			
	Baseline	12 Months	Change	Percent change (%)	Baseline	6 Months	Change	Percent change (%)	Baseline	6 Months	Change	Percent change (%)	Baseline	12 Months	Change	Percent change (%)
Improved																
1	49.5	20.0	−29.5	−59.6	50	44	−6.0	−12.0	39	40	1.0	2.6	50	30	−20.0	−40.0
2	32.0	0.0	−32.0	−100.0	29	42	13.0	44.8	14	32	18.0	128.6	40	30	−10.0	−25.0
3	37.7	14.4	−23.3	−61.8	21	36	15.0	71.4	20	27	7.0	35.0	20	10	−10.0	−50.0
4	100.3	63.3	−37.0	−36.9	49	60	11.0	22.4	26	30	4.0	15.4	40	20	−20.0	−50.0
5	171.7	86.3	−85.4	−49.7	48	51	3.0	6.3	16	20	4.0	25.0	36	40	4.0	11.1
6	122.3	55.3	−67.0	−54.8	40	53	13.0	32.5	20	30	10.0	50.0	25	23	−2.0	−8.0
10	900.0	385.0	−515.0	−57.2	35	31	−4.0	−11.4	13	20	7.0	53.8	12	0	−12.0	−100.0
11	430.0	180.0	−250.0	−58.1	17	47	30.0	176.5	7	15	8.0	114.3	20	0	−20.0	−100.0
Mean (SD)	230.4 (299.9)	100.5 (128.1)	−129.9 (172.5)	−59.8 (18.1)	36.1 (12.9)	45.5 (9.4)	9.4 (11.6)	41.3 (61.5)	19.4 (9.7)	26.8 (8.0)	7.4 (5.1)	53.1 (45.6)	30.3 (13.0)	19.1 (14.7)	−11.3 (8.9)	−45.2 (39.7)
Unimproved																
7	376.2	389.0	12.8	3.4	25	36	11.0	44.0	20	24	4.0	20.0	30	40	10.0	33.3
8	604.0	595.0	−9.0	−1.5	28	42	14.0	50.0	29	28	−1.0	−3.4	40	55	15.0	37.5
9	345.3	437.0	91.7	26.6	49	50	1.0	2.0	20	20	0.0	0.0	0	15	15.0	NE
Mean (SD)	441.8 (141.3)	473.7 (107.8)	31.8 (53.0)	9.5 (15.0)	34.0 (13.0)	42.7 (7.0)	8.7 (6.8)	32.0 (26.2)	23.0 (5.2)	24.0 (4.0)	1.0 (2.7)	5.5 (12.6)	23.3 (20.8)	36.7 (20.2)	13.3 (2.9)	35.4 (3.0)
All																
Mean (SD)	288.1 (276.9)	202.3 (210.2)	−86.8 (164.6)	−40.9 (36.3)	35.5 (12.3)	44.7 (8.5)	9.2 (10.2)	38.8 (53.0)	20.4 (8.6)	26.0 (7.1)	5.6 (5.4)	40.1 (44.5)	28.5 (14.7)	23.9 (17.3)	−4.5 (13.7)	−29.1 (48.8)
P-value			0.054	0.010			0.017	0.019			0.006	0.006			0.307	0.100

P-value was calculated by the Wilcoxon signed rank test.

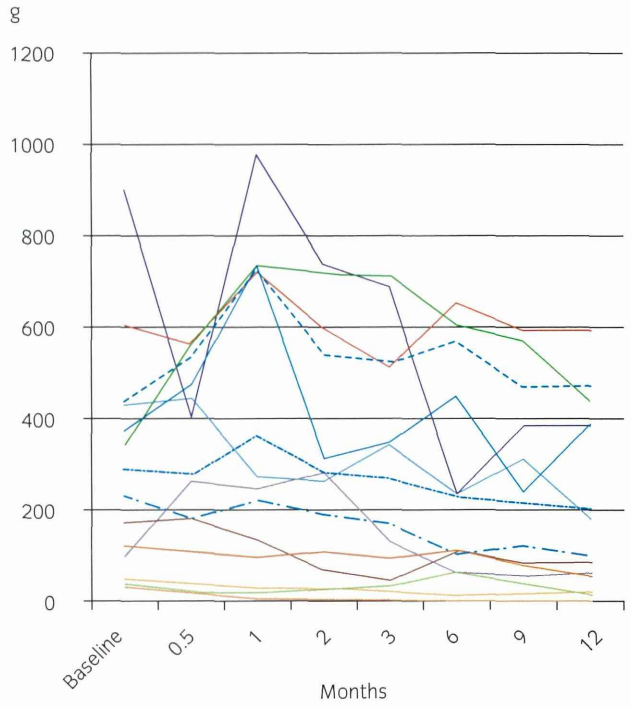

Fig. 2 Changes in daily leakage volume by 24-h pad test. In eight patients, leakage volume decreased progressively over time up to 12 months with a mean reduction rate of 59.8%; however, no change in leakage volume was achieved in three cases. In the eight patients showing decreased leakage volume, urinary incontinence improved immediately after injection, deteriorated approximately 1 month after injection and progressively improved thereafter up to 6–12 months. One patient achieved total continence. —, 1; —, 2; —, 3; —, 4; —, 5; —, 6; —, 7; —, 8; —, 9; —, 10; —, 11; —, All ($n = 11$); - - -, Improved ($n = 8$); - - -, Unimproved ($n = 3$).

patients, changing from 28.5 mL at baseline to 23.9 mL 3 months after treatment. Additionally, no significant change in maximum flow rate was detected.

The outcomes on subjective symptoms and QOL assessed by the ICIQ-SF are summarized in Table 3. In all patients, the frequency of incontinence was significantly improved ($P = 0.016$), whereas the remaining three parameters were not (i.e. $P = 0.311$ for total score, $P = 0.500$ for amount of leakage and $P = 0.645$ for QOL, respectively). The eight patients with improved leakage volume showed improvement in the total score and all subscores of the ICIQ-SF, such as frequency of incontinence, amount of leakage and QOL. However, the three patients who did not show changes in the leakage volume showed no improvement in the parameters of ICIQ-SF (Table 3).

In all patients, enhanced ultrasonography showed a sequential increase in the blood flow to the area where the ADSC were injected (Fig. 4), which was maintained during the entire follow-up period. MRI showed a bulking effect at the site of adipose tissue injection, which persisted even at 3 months after injection.

No significant adverse event occurred during the liposuction and ADSC injection procedures. No severe side-effects, such as pelvic pain, inflammation or de novo urgency, were observed after the operation in all cases during the follow-up period. Serum prostate-specific antigen level did not increase from the

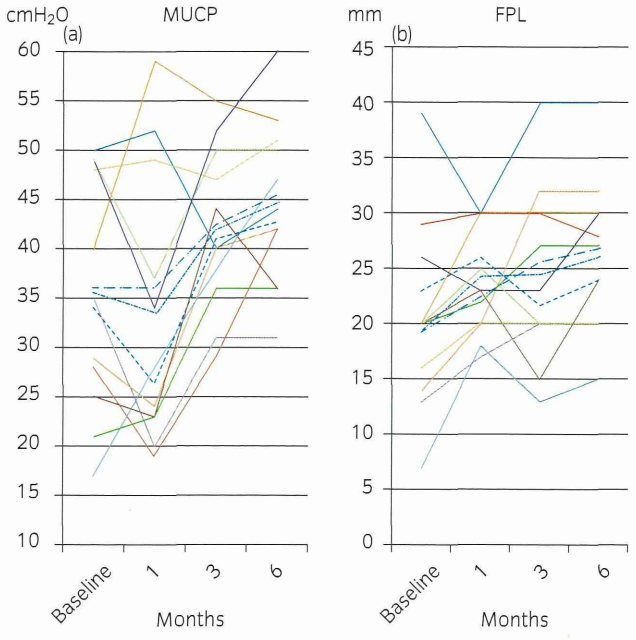

Fig. 3 Changes in (a) MUCP and (b) FPL on urethral pressure profile. (a) Mean MUCP progressively increased both in the patients with improved and those with unimproved leakage volume on the 24-pad test. (b) In contrast, mean FPL increased in patients with improved leakage volume, but not in those with unimproved leakage volume. —, 1; —, 2; —, 3; —, 4; —, 5; —, 6; —, 7; —, 8; —, 9; —, 10; —, 11; - - -, All (n = 11); — —, Improved (n = 8); - - -, Unimproved (n = 3).

baseline level in any of the patients. In four patients (cases 2, 3, 9, 11), mild subcutaneous hemorrhage at the abdomen was a complication of liposuction, which spontaneously disappeared within 1 month.

Discussion

The pathophysiology of male SUI after prostate surgery is urethral sphincter dysfunction caused by a reduction in the volume of skeletal and smooth muscle cells, impaired blood flow, and denervation at the sphincter. Because the treatment of sphincter dysfunction requires an increase in the muscle cell population, the promotion of revascularization and the reconstruction of innervation, regenerative treatment using stem cells could be developed into an ideal treatment modality for this condition. At the experimental level, the treatment of SUI using stem cells derived from the bone marrow, skeletal muscles and adipose tissue has been reported in several studies.[5–11] These studies suggested the potential and promising role of stem cell therapy for the treatment of SUI. In contrast, regenerative treatment of SUI in humans has been reported in a limited number of clinical studies.

A few clinical studies have described the use of autologous adult muscle-derived stem cells for the treatment of female SUI, which has shown promising efficacy and safety.[18,19] Carr and Chancellor carried out a prospective, dose-ranging study to assess the 12-month safety and potential efficacy of autologous muscle-derived cell therapy in 38 female patients with SUI.[19] A muscle biopsy sample was obtained from the quadriceps femoris and cultured to harvest autologous muscle-derived cells. Using a cystoscope-assisted periurethral approach, the cells were injected into the external urethral sphincter. Among 29 patients receiving two treatments, 88.9% of those who received a high-dose injection of muscle-derived cells and 61.5% of those who received low-dose injection showed a 50% or greater reduction in urine leakage in 1-h pad tests. Additionally, 77.8% of the high-dose group and 53.3% of the low-dose group had a 50% or greater reduction in the frequency of SUI.

Because adipose tissue contains abundant multipotent stem cells, therapeutic levels of ADRC can be isolated using the Celution system, as shown in the present study. Clinical studies assessing the application of ADRC have been carried out for breast reconstruction[20] and cardiac infarction.[21] These clinical studies support the feasibility of cell therapy using ADRC. Our group carried out the first in-human study using cell therapy with ADRC for SUI, and we described the short-term results of three cases in a previous report.[14] In the present study, we extended our previous clinical findings by including a larger number of patients and investigating the 1-year outcomes. Although this is a preliminary study, we obtained promising results as described in the present report.

The improvement of urinary incontinence observed in the present study can be explained by several mechanisms. In most cases, SUI improved initially within a week after injection, deteriorated subsequently and progressively improved thereafter. This clinical course suggests the involvement of a specific mechanism in which a bulking effect produced by the injected adipose tissue fraction mixed with ADRC plays an important role. The injected adipose tissue fraction, which was processed to isolate ADRC, contained 30% of lactated Ringer's solution. Absorption of the solution could be responsible for the temporary deterioration in the condition during the initial week. Among the ADRC, the ASC subpopulation might have contributed to the progressive improvement in sphincter function, which was reflected in the increased MUCP and FPL, and the decreased frequency and amount of SUI. The persistent bulking effect indicated the survival and growth of the injected adipose tissue, which could be attributed to the presence of ASC.

ASC can differentiate into mature adipose tissue and possibly into contractile cells. In our preclinical experimental study,[13] cultured rat ASC were injected into the proximal urethra after bilateral transection of the pelvic nerves. The leak point pressure was significantly higher in the rats undergoing ASC injection than in those undergoing injection of collagen or vehicle. Additionally, when GFP expressing cultured ASC were injected into the urethra of female nude rats, alpha smooth muscle actin-positive cells were stained in the merged distribution (70%) with the GFP expressing ASC 12 weeks after injection, suggesting the possible differentiation of ASC into smooth muscle cells. Previous studies on rats showed that cultured ASC injected into the injured urethra differentiated into contractile cells with smooth muscle cell features.[22] We also confirmed in pigs that injected ADRC isolated by the Celution system differentiated into smooth muscle cells (unpubl. data).

Environmental effects caused by the injected ASC could also be responsible for the improvement in SUI. Cultured ASC are known to secrete a large number of angiogenesis-related cytokines.[23] In our experimental study, injection of cultured human ASC into the ischemic hind limb of nude rats produced human hepatocyte growth factor and vascular endothelial growth factor, and improved blood flow (unpubl. data). In the

Table 3 Means and standard deviations on subjective symptoms and QOL assessed by the ICIQ-SF

	Total			Frequency of leakage			Leakage amount			QOL		
	Baseline	12 Months	Change	Baseline	12 Months	Change	Baseline	12 Months	Change	Baseline	12 Months	Change
Improved patients	13.8 (3.7)	11.3 (6.1)	−2.5 (5.8)	4.6 (0.5)	3.4 (1.7)	−1.3 (1.5)	4 (1.1)	3.3 (1.8)	−0.8 (1.5)	5.1 (2.9)	4.6 (3.2)	−0.5 (3.8)
Unimproved patients	19.7 (1.5)	19.7 (1.5)	0.0 (2.6)	5 (0)	4.3 (0.6)	−0.7 (0.6)	5.7 (0.6)	6 (0)	0.3 (0.58)	9 (1.7)	9.3 (1.2)	0.3 (2.5)
All patients	15.4 (4.2)	13.5 (6.5)	−1.8 (5.2)	4.7 (0.5)	3.6 (1.5)	−1.1 (1.3)	4.5 (1.2)	4 (2)	−0.5 (1.4)	6.2 (3.1)	5.9 (3.5)	−0.3 (3.4)

Total score: 0–21, frequency of leakage: 0–5, leakage amount: 0–6, QOL: 0–10.

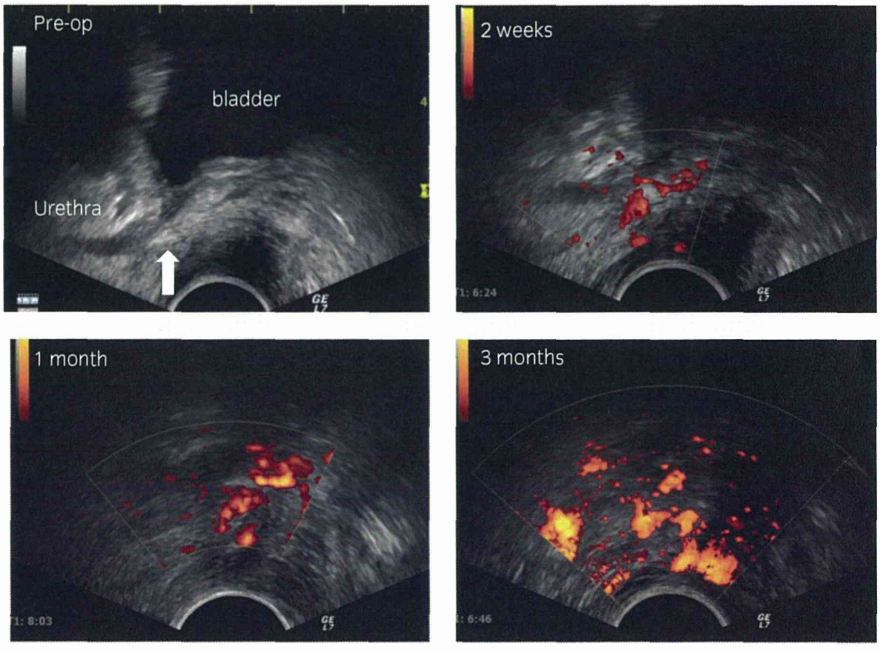

Fig. 4 Contrast-enhanced transrectal ultrasonography to assess the blood flow of the periurethral area after ADRC injection. The bladder and urethra was visualized as a sagittal section. The blood flow around the injected area visualized as orange color was progressively increased after the injection of ADRC up to 3 months in case 1.

present study, increased blood flow to the injected area, which was observed by ultrasonography, was maintained throughout the follow-up period. This increase in blood flow could be related to the promotion of angiogenesis by cytokines secreted by the injected ADRC, and could have positively affected the regeneration of the injected adipose tissue and impaired sphincter function.

The present study had some limitations. This was a preliminary, single-arm, non-comparable study. The sample size was small. The favorable outcomes of the present preliminary study suggest that a phase III trial with a randomized, comparable protocol and an appropriate sample size is required. The lack of improvement in three cases in the present study could not be explained.

In conclusion, periurethral injection of autologous ADRC is a safe and feasible treatment modality for male SUI, and probably for female SUI. Our method has the advantages that the cells used are autologous and do not require culture, and the treatment is carried out in the context of a single surgical procedure.

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Conflict of interest

None declared.

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