



AMERICAN ACADEMY
OF COSMETIC SURGERY

THE AMERICAN JOURNAL of COSMETIC SURGERY

The Latest Advance in Hair Regeneration Therapy Using Proteins Secreted by Adipose-Derived Stem Cells

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ORIGINAL SCIENTIFIC PRESENTATION

The Latest Advance in Hair Regeneration Therapy Using Proteins Secreted by Adipose-Derived Stem Cells

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Introduction: Adipose-derived stem cells (ADSCs) that can be harvested from fat cells are one of the latest breakthroughs in the aesthetic field. In addition, basic studies have reported that ADSC conditioned medium (ADSC-CM) promotes skin and hair regeneration. We validate our novel approach, known as hair regenerative therapy, for hair growth treatment using ADSC-CM.

Materials and Methods: ADSCs were cultured and expanded in hypoxic culture conditions, and ADSC-CM was collected. ADSC-CM includes various cytokines and growth factors that influence hair regrowth, to which we added buflomedyl, cysteine, coenzyme Q10, and vitamins. Protein solution from ADSC-CM was applied 4 to 6 times every 3 to 5 weeks by mesotherapy techniques such as nappage and papule injections. Satisfactory results of hair regenerative therapy in 12 women and 13 men were determined with a visual analog scale.

Results: All patients experienced increased hair growth from the treatments with ADSC-CM. Four treatment sessions performed within 3 to 4 months provided especially good results. Scores on the visual analog scale increased with treatment frequency. Statistical significance was determined by Friedman's 2-way analysis of variance ($P < .01$) and Wilcoxon's signed rank test ($P < .01$).

Discussion: ADSCs secrete cytokines, such as keratinocyte growth factor, vascular endothelial growth factor, platelet-derived growth factor, hepatocyte growth factor. Those cytokines and growth factor are very important for hair growth. Our new therapy with ADSC-CM does not require specialized facilities, such as a cell-processing center, and can be a valuable treatment.

Adipose-derived stem cells (ADSCs) are one of the latest scientific breakthroughs in the field of aesthetic surgery. For many years, doctors have discarded the fat tissue removed during cosmetic surgeries, such as tummy tucks, liposuction, and breast reduction. However, it was recently found that adult stem cells can be isolated from the fat tissues and then used to rejuvenate hair and skin tissues.¹⁻³

Most of the research concerning mesenchymal stem cells (MSCs) has focused on bone marrow mesenchymal stem cells (BMSCs). However, it is now known that MSCs exist in normal adipose tissue. ADSCs are easily isolated from fat tissue harvest by liposuction, and they can differentiate into several types of lineages in culture.⁴ ADSCs are likely to be pluripotent MSCs, which share similar characteristics with BMSCs. ADSCs have paracrine effects on their surrounding environment through the secretion of many growth factors, such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), keratinocyte growth factor (KGF), transforming growth factor (TGF)- β 1, insulin-like growth factor-binding protein (IGF-BP) precursors, fibronectin, and superoxide dismutase (SOD).¹

These proteins secreted by ADSCs exert diverse skin-rejuvenating effects, such as the stimulation of collagen synthesis and fibroblast migration during wound healing.² In addition, ADSC-conditioned medium (ADSC-CM) inhibits melanogenesis in B16 melanoma cells³ and produces skin-whitening effects.⁵ ADSC-derived secretory factors also protect dermal fibroblasts from oxidative stress induced by chemical and ultraviolet B irradiation.⁶⁻⁹ Interestingly, our improved method for harvesting ADSC-CM under hypoxic conditions yields ADSC-CM that appears to promote hair growth.¹⁰ Because conventional treatments for skin aging induce new collagen synthesis via the activation of dermal fibroblasts, we decided to consider ADSCs as a possible

Received for publication February 12, 2012.

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DOI: 10.5992/AJCS-D-12-00015.1

Patient Profiles			
Patient Profiles			(%)
Sex	Men	13	52
	Women	12	48
Age	20~29	2	8
	30~39	7	28
	40~49	10	40
	50~59	3	12
	60~69	3	12
Men:age	20~29	2	8
	30~39	4	16
	40~49	7	28
	50~59	0	0
	60~69	0	0
Women:age	20~29	0	0
	30~39	3	12
	40~49	3	12
	50~59	3	12
	60~69	3	12

tool in antiaging skin therapy. Several studies have found hair growth-stimulating effects of ADSC growth factors in ex vivo animal models; therefore, we performed a clinical study of ADSC-CM for human hair regeneration. We used a trichogram to obtain preliminary data that hair counts in certain areas increased with treatment frequency.¹¹

Most studies of ADSC-based therapies have been in vitro animal model studies with satisfactory results. However, there are safety issues with respect to the direct application of cultured ADSCs to human skin; in particular, this technique might create a risk of cancer. In addition to safety concerns, it is currently very difficult to commercialize ADSCs. Therefore, new approaches are needed to overcome the limitations of cellular therapy. Fortunately, the proteins secreted from ADSCs might have great advantages over cell-based therapy for skin regeneration.¹ Because of its long-term stability, lyophilized ADSC-CM avoids most of the safety issues associated with cell-based therapies. The use of ADSC-CM may also enhance the scalability of production, which would allow for the development of low-cost therapeutics.

A commercial advanced adipose-derived stem cell protein extract (AAPE) was developed by a Korean research team at Prostemics Co, Ltd (Seoul, Korea). This extract contains numerous growth factors and regeneration-promoting proteins. Its main components include PDGF (44.41 ± 2.56 pg/mL), bFGF (131.35

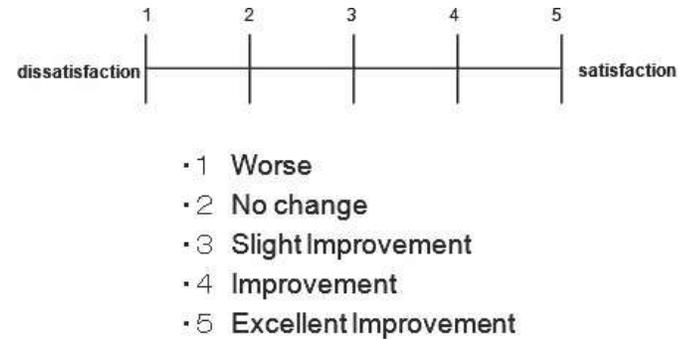


Figure 1. Visual analog scale (VAS). Subjects graded their level of satisfaction with the treatment on a 5-point scale in which 1 = dissatisfaction and 5 = satisfaction. The physician-determined VAS scores were assessed after the fourth treatment.

± 30.31 pg/mL), KGF (86.28 ± 20.33 pg/mL), TGF- β 1 (103.33 ± 1.70 pg/mL), HGF (670.94 ± 86.92 pg/mL), VEGF (809.53 ± 95.98 pg/mL), collagen (921.47 ± 49.65 pg/mL), fibronectin (1466.48 ± 460.21 pg/mL), and SOD in 5 mL saline solution. In the present study, we examined the ability of AAPE injections combined with buflomedyl (0.15 – 0.25 mg), vitamin B₁ (5 mg), vitamin B₆ (2.5 – 5.0 mg), vitamin H (1 mg), vitamin C (80 – 100 mg), vitamin E (5 mg), and coenzyme Q10 (10 U), along with amino acid nappage mesotherapy, to improve the function of mesotherapy with antioxidant effects and induce hair growth.^{12–18} We refer to this combined therapy as hair regenerative therapy (HARG) enhanced by hypoxic ADSC-CM.¹⁰

Materials and Methods

Protein Solution From ADSC-CM

Adipose tissue was voluntarily donated by 5 healthy 20-year-old women and was examined for any possible bacterial and viral infections. After the adipose tissue was collected during elective liposuction, ADSCs isolated from the aspirates were cultured under hypoxic conditions.

Finally, the ADSC-CM was concentrated by centrifugation and freeze-dried as a commercial AAPE (Prostemics Co, Ltd).^{10,11,19–24} This product was examined for possible bacterial and viral infections, such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Escherichia coli*, *Salmonella typhimurium*, *Proteus mirabilis*, *Enterococcus faecalis*, *Bacillus subtilis*, *Bacteroides vulgates*, *Candida albicans*, *Clostridium sporogenes*, *Mycoplasma arthritidis*, *Mycoplasma orale*, *Mycoplasma pulmonis*, *Mycoplasma hyorhinitis*, *Mycoplasma salivarium*, *Mycoplasma fermentans*, *Mycoplasma pneumoniae*, *Mycoplasma bovis*, *Acholeplasma laidlawii*, human immunodeficiency virus, hepatitis B

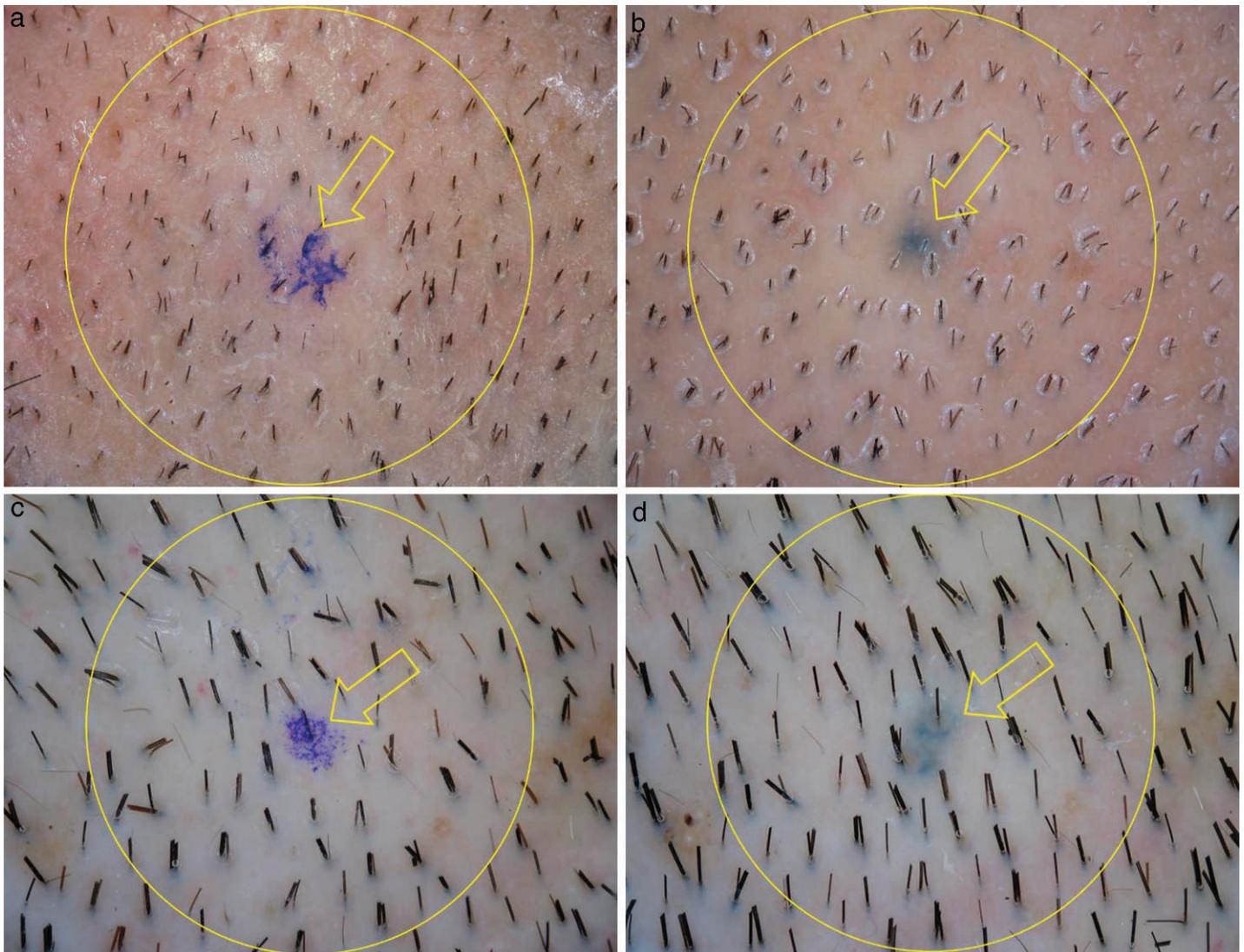


Figure 2. Macro-photographs (trichograms). The number of hairs was counted within a circle with a diameter of 11 mm (area, 95 mm²) centered on the tattoo in the shaved area. That number increased after treatment with adipose-derived stem cell protein extract (AAPE) compared with pretreatment. (a) Pretreatment photograph of a 42-year-old patient without finasteride medication. The number of hairs within the circle area is 154. (b) Photograph of the same patient after 2 sessions of AAPE treatment. The number of hairs within the circle area is 204. (c) Pretreatment photograph of a 45-year-old patient with female alopecia. The number of hairs within the circle area is 97. (d) Photograph of the same patient after 3 sessions of AAPE treatment. The number of hairs within the circle area is 121.

virus, and hepatitis C virus. AAPE was manufactured in accordance with the guidelines of Korean Food and Drug Administration for cell therapy. Informed consent for using AAPE addressed safety and possible risks such as infections.

For the hair regeneration treatments, vitamin B, buflomedyl, cysteine, vitamin H, vitamin C, vitamin E, and coenzyme Q10 were added to AAPE. Buflomedyl and AAPE are not FDA approved by the US Food and Drug Administration. Mesotherapy techniques such as nappage and papule injections with 30G or 32G

needles were used; however, the point-by-point technique was not used. Nappage involved sticking the skin every 3 mm² to penetrate the clear zone of skin (without bleeding) with a 30G needle attached to a solution-filled syringe. Papule injections provided 0.02 to 0.05 mL of AAPE per square centimeter in each intradermal injection for a total volume of 3–4 mL per treatment. Patients received 4 treatment sessions every 3–5 weeks until hair regeneration was observed. The patients received follow-up examinations at 2- to 4-month intervals for at least 1 year after the final treatment session.

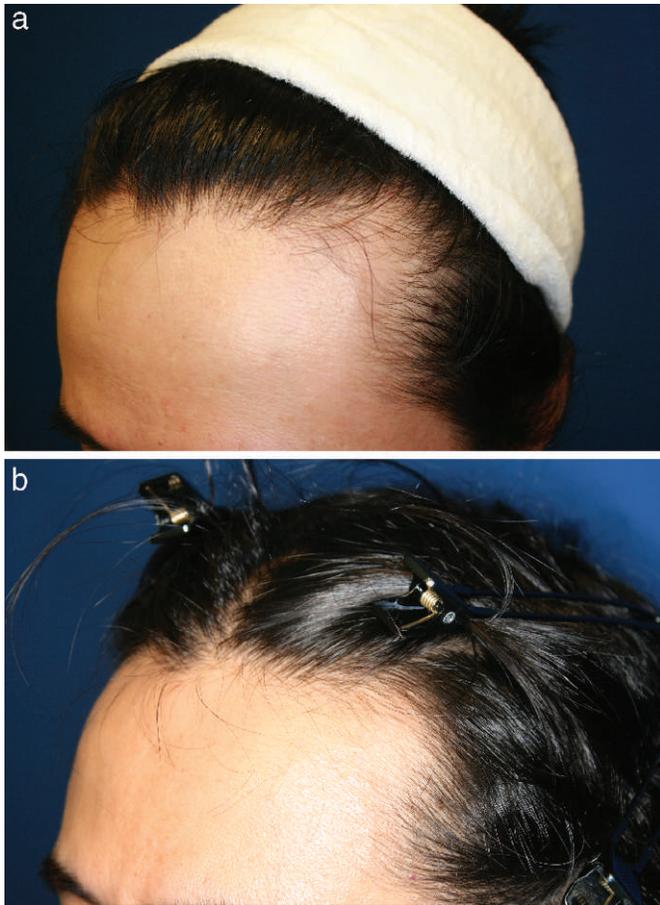


Figure 3. Photographs of a male patient (39 years old) without Finasteride medication. (a) Before treatment. (b) After 3 sessions of stem-cell protein (adipose-derived stem cell protein extract) treatment (5 months after initial treatment). Remarkable hair growth was observed at the hairline after treatment.

Patients

The effect of hair regenerative therapy was evaluated in 25 patients (Table): 12 men with androgenic alopecia, 1 man with androgenic alopecia and alopecia areata, and 12 women with female pattern androgenic alopecia (including 3 women with diffuse alopecia). Finasteride was administered to 5 male patients during the study: 3 had a history of finasteride use before the study and continued the medication, 2 men started finasteride during the study, and 1 man stopped finasteride medication when the study started. No female patients took finasteride or any supplementary medication. These patients agreed to provide self-assessments of treatment satisfaction using a visual analog scale (VAS), which is an arbitrary point scale ranging from 1 (dissatisfaction) to 5 (satisfaction) (Figure 1). Patient self-evaluations were performed after each of the first 4 sessions. Patients evaluated their satisfaction with every treatment

3 to 4 weeks after the previous treatment. Physician-determined scores were assessed for 25 patients after the fourth treatment with the following VAS: 1 = worse, 2 = no change, 3 = slight improvement, 4 = improvement, and 5 = excellent improvement. Physician-determined assessment and patients' satisfaction with the fourth treatment were determined 4–6 weeks after the fourth treatment. Differences with $P < .01$ were taken as statically significant.

Results

Protein solution from ADSC-CM applied during 4 treatment sessions within 3–4 months induced considerable increases in hair growth. Interestingly, protein solution from ASDC-CM promoted hair growth at the frontal region of the head in patients with androgenic alopecia (Figures 2 through 6).

Positive responses regarding treatment were obtained from all patients in the present study. We had previously studied only 1 patient with iatrogenic alopecia and several patients with alopecia areata; however, these patients are not included with the present 25 patients because we do not have the VAS score sheets from the earlier patients. We compared HARG therapy and a meso-cocktail with mesotherapy using a side-by-side comparison (Figure 7). There were no adverse effects, including bacterial infection and granuloma. Hair regrowth was maintained for at least 1.5 years, but this was dependent on patient age. Men older than 60 years had the least maintenance of hair regrowth, followed by men 50–60 years old and women older than 60 years (Figure 6). Men younger than 50 years and women younger than 60 years maintained hair regrowth between 1.5 and 2.5 years.

Friedman's 2-way analysis of variance and Wilcoxon's signed rank test were used to establish statistical significance in the self-assessments of treatment satisfaction performed by 25 patients. Statistical significance was set at $P < .01$. The analyses were performed with commercially available statistical software (Excel, Microsoft, Redmond, Wash; Statcel3 Excel, OMS Publishing Inc, Tokorozawa, Japan).

The mean patient-determined VAS scores were 2.52 after the first session, 2.92 after the second session, 3.40 after the third session, and 3.72 after the fourth session. The mean VAS scores for men were 2.46 after the first session, 2.85 after the second session, 3.38 after the third session, and 3.77 after the fourth session. The mean VAS scores for women were 2.58 after the first session, 3.00 after the second session,

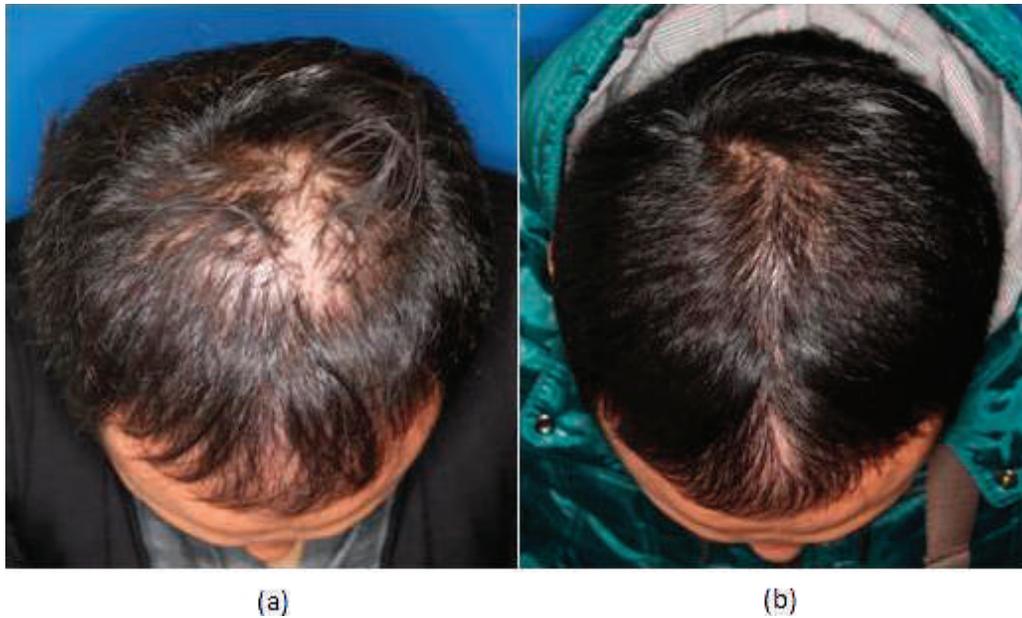


Figure 4. Photographs of a 36-year-old male patient on 0.2 mg/day finasteride for 4 months, starting 2 months after the initial treatment. (a) Before treatment. (b) After 6 sessions of treatment with adipose-derived stem cell protein extract (6 months after initial treatment). Remarkable hair growth was observed after treatment.

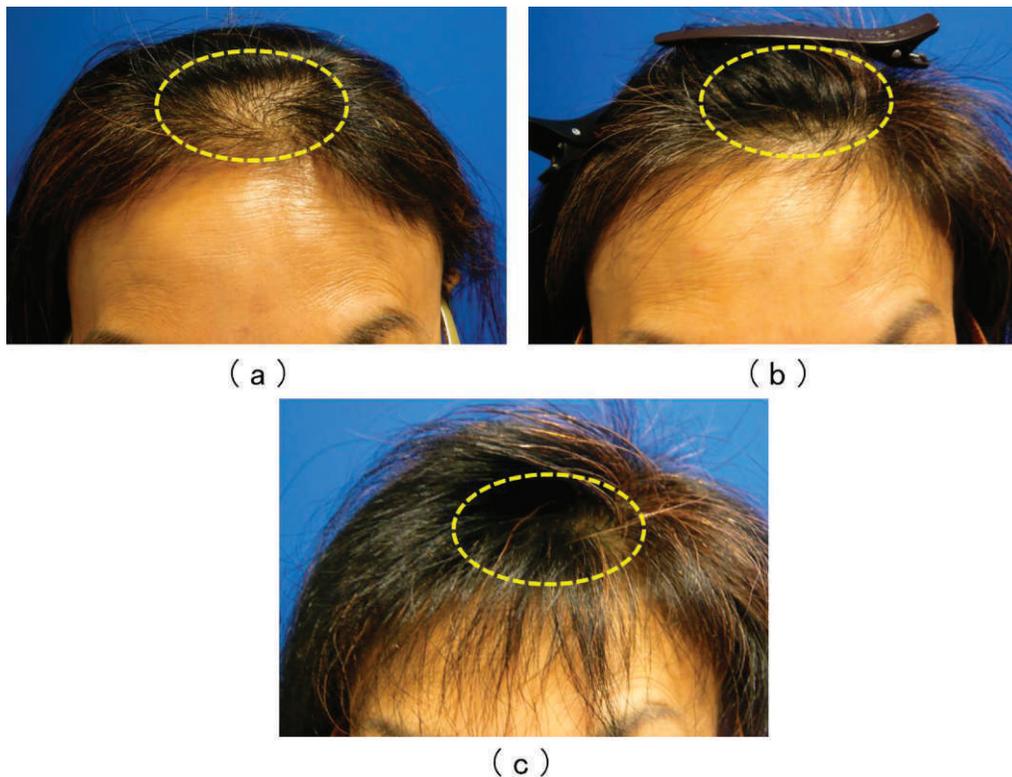


Figure 5. Photographs of a 55-year-old female patient without finasteride medication. (a) Before treatment. (b, c) After 4 sessions of treatment with adipose-derived stem cell protein extract (4 months after initial treatment). Remarkable hair growth was observed at the hairline after treatment.

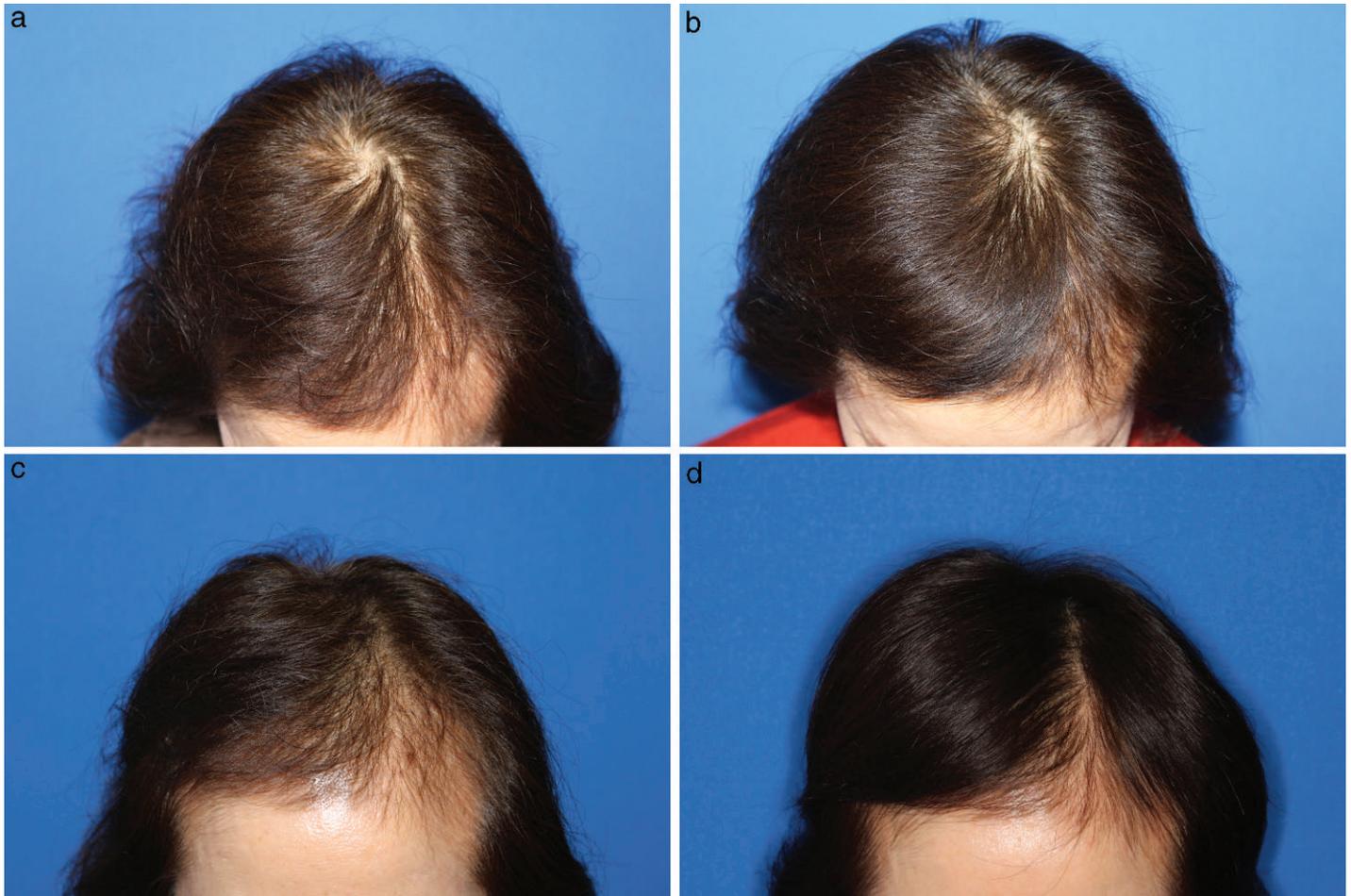


Figure 6. Photographs of a 66-year-old female patient without finasteride medication. (a) Before treatment. (b) After 1 session of treatment with adipose-derived stem cell protein extract (AAPE). Remarkable hair growth was observed only with 1 session. (c) Hairline before treatment. (d) Hairline after 6 sessions of AAPE treatment. Remarkable hair growth was maintained for 17 months after initial treatment.

3.42 after the third session, and 3.67 after the fourth session. The VAS scores increased as the number of treatments increased. The mean patient-determined VAS score after each treatment is plotted in Figure 8. The number of patients who reported a VAS score ≥ 3 increased as the number of treatments increased (Figure 9).

The physician-determined score was assessed after the fourth treatment, and the mean scores were 4.20 for all patients, 4.15 for men, and 4.25 for women (Figure 10). Statistically significant differences were determined by Friedman's 2-way analysis of variance ($P < .01$) and Wilcoxon's signed rank test ($P < .01$). Statistically significant improvements in VAS scores were observed from the first treatment ($P < .01$). There were statistically significant differences between the physician-determined assessment scores and patient satisfaction scores (t test, $P < .01$).

Discussion

Human adipose tissues that contain ADSCs are easily obtained by suction-assisted lipectomy. Because of their pluripotent nature, stem cells may provide therapies for many symptoms and diseases. The clinical potential of MSCs has been illustrated with tissue engineering studies, and MSCs are sometimes regarded as a substantial therapy for clinical cases of some diseases. For example, in an intracranial hemorrhage mouse model, transplantation of MSCs reduced acute cerebral inflammation and chronic brain degeneration and promoted long-term functional recovery.⁹ In a model of hepatic failure, conditioned medium from MSCs provided trophic support to the injured tissue by inhibiting cell death and stimulating regeneration.⁹ These effects have also been observed in cosmetic applications.

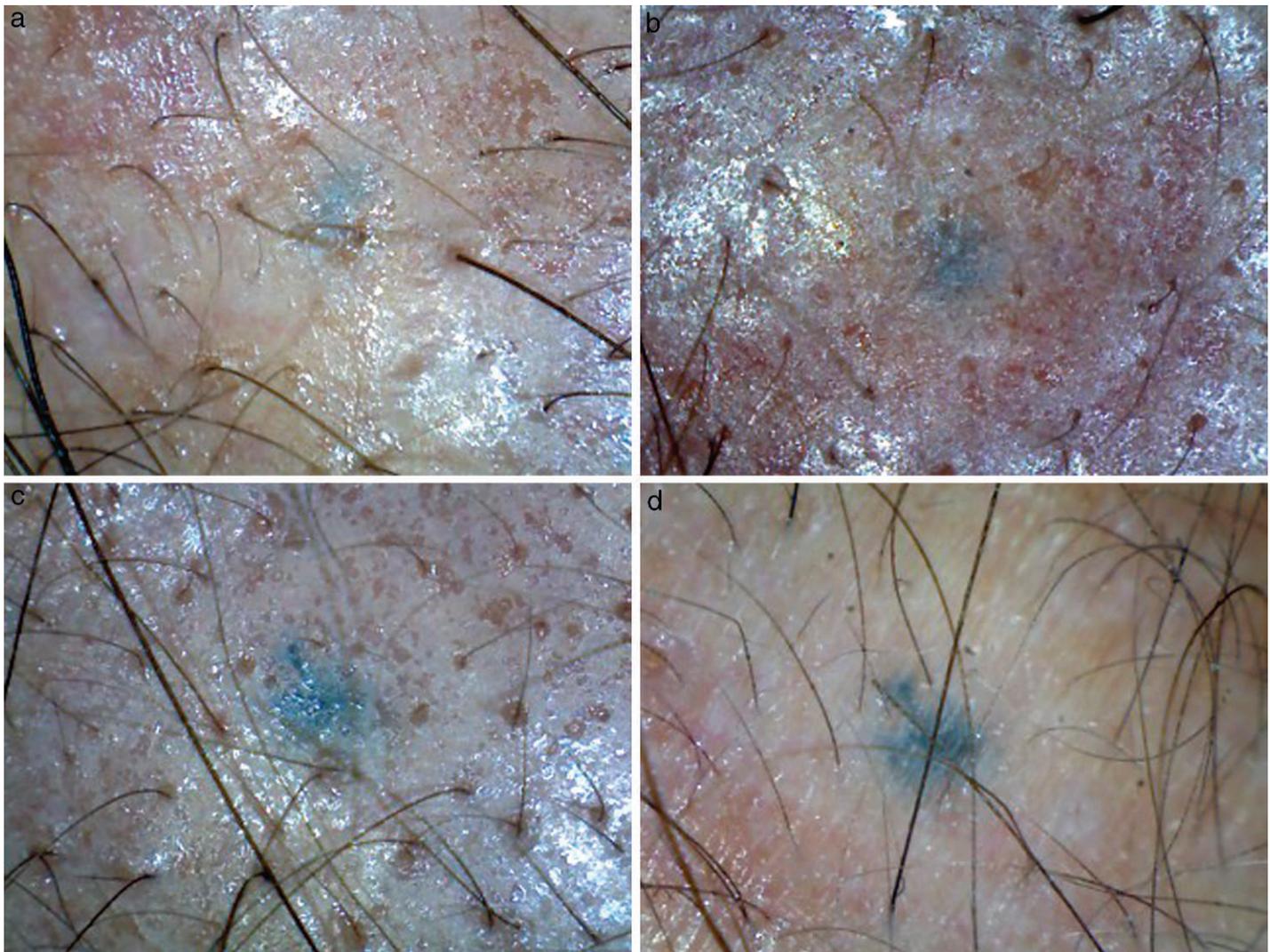


Figure 7. (a) Pretreatment photograph of a 68-year-old patient with androgenic alopecia on the hairline, showing the nontreatment side (left side) of the side-by-side treatment without finasteride medication. The number of hairs is 32 within a specific photographed area. (b) Photograph of the same patient after 4 sessions of treatment on the nontreatment side. The number of hairs is now 27 within the specific area. (c) Pretreatment photograph of the same patient, showing the treatment side (right side) of the side-by-side treatment. The number of hairs is 29 within a specific photographed area. (d) Photograph of the same patient after 4 sessions of treatment with adipose-derived stem cell protein extract. The number of hairs is 53 within the specific area.

ADSCs have potent antioxidant activity and protect human dermal fibroblasts (HDFs) from oxidative injury by inhibiting apoptosis. ADSCs are good candidates for the control and prevention of skin damage from free radicals in various skin conditions.²¹ ADSCs were found to be superior to HDFs in promoting HDF proliferation and upregulating type I collagen secretion.²² ADSCs secretory factors protect dermal fibroblasts from oxidative stress induced by chemical and ultraviolet B irradiation.^{3,6-9} When combined with traditional treatment modalities, stem cells appear to have dramatic antiwrinkle, skin-whitening, and skin-tightening effects, mediated by significant increases

in collagen synthesis and dermal thickness, improvements in the inflammatory reactions of blood vessels, and inhibition of melanin synthesis.^{2,22}

Granulation after mesotherapy for alopecia has previously been reported.²⁴ Granulomas may form after injection of some growth factors. The doses of growth factors in AAPE are within the physiological range. We consider that HARG therapy causes no granuloma formation because the promoting factors are colocalized with the inhibitory factors.

Growth factors are important in hair follicle development. PDGF isoforms induce and maintain

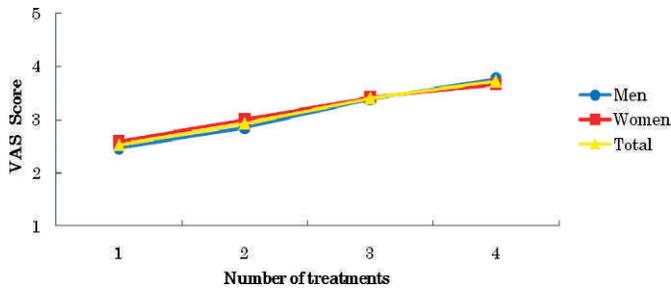


Figure 8. Patient satisfaction measured by the visual analog scale (VAS). The mean VAS score determined by the patients increased with the number of treatments ($P < .01$). Men are shown in blue, women are shown in red, and the total patient group is shown in yellow.

the anagen phase in murine hair follicles²⁵ and promote the hair stem cells to hair mother cells.²⁶ In addition, VEGF controls hair growth and follicle size by angiogenesis in a VEGF transgenic mouse model.²⁷ HGF alters cyclic hair growth and stimulates hair follicle growth,^{28,29} and IGF upregulates hair follicle growth by stimulating the proliferation of follicle cells through the signaling pathways of its receptors.^{30,31} IGF-BP modulates the actions of IGF-I in hair regeneration.³²⁻³⁴ KGF-2 significantly stimulates human hair follicle cells.^{35,36}

Patient satisfaction was lower with mesotherapy treatment than with HARG therapy. Some patients moved from mesotherapy treatment to HARG therapy with stem cell protein. The stem cell proteins are the most essential components of this hair regrowth therapy. Treatment using only the vitamin mixture was not more effective than the stem cell protein treatment in our recent double-blind test. However, we expected that the addition of vitamins would be beneficial for hair growth effects such as antioxidant effects.¹⁵⁻¹⁹

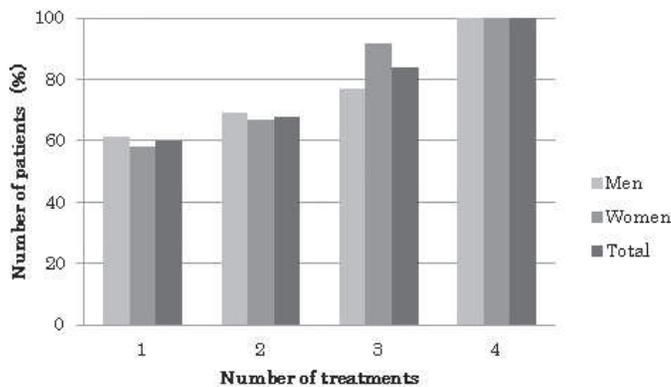


Figure 9. Number of patients who rated their satisfaction with a score of 3 or higher. All patients rated their satisfaction with a score of 3 or higher after the fourth treatment.

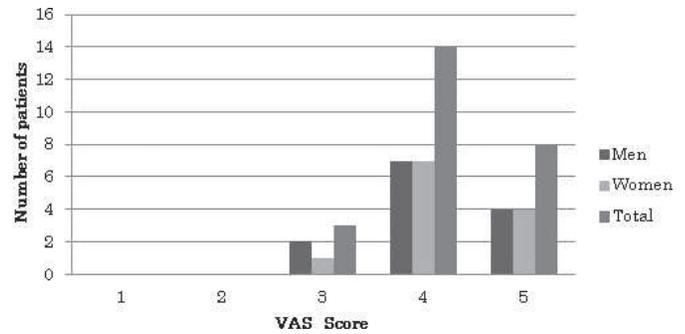


Figure 10. Physician-determined Visual Analog Scale (VAS) scores after the fourth treatment. The average VAS score was 4.20.

HARG therapy is a great alternative for hair rejuvenation in patients who are unwilling or unsuitable to undergo traditional hair rejuvenation surgery (eg, many women are inappropriate candidates for surgical hair transplantation). Thin and short hair show prominent changes in length and thickness after therapy. As patients feel changes in their hair after the first and second treatments, their satisfaction scores are relatively high. New hair appears on the head after several treatments. Patient satisfaction increases as the number of treatments increases. There was a significant difference between physician-determined assessment scores and patient satisfaction scores. This result indicates that doctors evaluate hair growth by vellus growth, whereas patients appraise hair growth by perception, such as feeling the increased density of hair. Objective and consistent means of evaluation are needed.

Conclusion

ADSC proteins are commercially available and do not require specialized equipment, such as a cell-processing center. These proteins can be routinely applied by a well-trained medical practitioner. We demonstrated that HARG therapy was effective for hair growth and is a potential alternative for hair regeneration in patients who are unwilling or unsuitable to undergo traditional surgical hair transplantation.

Acknowledgments

The authors thank Professor Ryuzaburo Tanino, MD, PhD (Tohoku University Tokyo Hospital, Tokyo, Japan) and Professor Kiyonori Harii, MD, PhD (Kyorin University, Tokyo, Japan) for reading our manuscript and Professor Byung-Soon Park, MD, PhD (Leaders Clinic and Seoul National University, Seoul, Korea) and Prostemics Co, Ltd (Seoul, Korea) for giving us product information about adipose-derived stem cell protein extract.

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