Review Article

# The Role of Adipose Tissue in Hair Regeneration: A Potential Tool for Management?

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## Abstract

Human adipose tissue (AT) is a rich and easily harvestable source of stem cells and various growth factors (GFs). It has been widely used hitherto for facial rejuvenation and volumization. Increasing evidence shows that dermal adipocytes are intricately associated with hair follicles (HFs) and may be necessary to drive follicular stem cell activation. Early published data have shown encouraging preliminary results for the use of adipocytes and their stem cells as a treatment option for hair growth. The aim of this review study is to analyze published literature on the effect of fat on hair growth and to summarize the current evidence.

**Keywords:** Adipose derived stem cells, adipose tissue, alopecia, fat, fat graft, hair, hair growth, hair regeneration, micrograft, nanofat, stromal vascular fraction

**Key Messages:** Several recent studies document the benefit of autologous fat (AF) transfer in hair growth. Physicians need to be aware of the potential of this emerging treatment.

## Introduction

Various treatments for hair loss include drug therapy, hair transplant surgery, low-level light therapy, platelet-rich plasma (PRP) therapy, microneedling, artificial hair implants, and others.[1-5] Each of these treatment options has its own advantages and shortcomings, and thus there is always a search for new and alternative therapies. In recent times, the role of AT in the hair growth cycle has been explored. A number of recent publications have supported the hypothesis that AT, which is a complex and biologically active tissue, can be a source of stem cells and GFs that can influence and stimulate hair growth.

## Interactions between Adipose Cells and Normal Hair Cycle

HFs are closely associated with subcutaneous fat in several ways. Usually, HFs encompassed by subcutaneous fat cells and the dermis shape an interfollicular dermal macro-environment, which is imperative for maintaining the best possible growth of bulge and follicle cells.[6,7] The AT appears to experience comparative changes in the HF cycle. Physiologically, fat tissue encompassing HFs have been found to increase from telogen to anagen.[7] Adipocytes emit BMP2 during the late anagen to the middle of the telogen stage, which supports the resting state of hair follicle stem cells (HFSCs) in the niche; however, the emission of BMP2 is lessened toward the late telogen stage, which bolsters the activation of HFSCs. Adipocytes, thus, have a critical role in extending the anagen stage.[8] Likewise, correspondence between fat tissue and the epithelium is continuous and vital. Transformations hindering the hair cycle have been found to restrain adipogenesis, which suggests that epithelial cells send signals actuating the expansion of the adipocytes.[9]

## Adipose-Derived Stem Cells and Possible Role in Hair Growth

The AT contains numerous cells, including adipocytes, adipose-derived stem cells (ADSCs), endothelial cells,

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fibroblasts, mural cells, and leukocytes [Figure 1].[10] The ADSCs have self-renewable capacity and display multi-lineage potential.[11,12] The number of pluripotent cells contained in a cubic centimeter of AT is 100 to 1,000 times larger than the number of stem cells contained in the bone marrow.[13] Hence, ADSCs have shown potential in regenerative medicine.[14] The ADSCs also secrete various GFs that have been shown to promote hair growth. These GFs include vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), platelet-derived growth factor (PDGF), keratinocyte growth factor (KGF), and fibroblast growth factor-1 and 2(FGF-1, FGF-2) [Table 1].[15-20] The ADSCs-derived proteins improve hair growth and protect human dermal papilla cells against cytotoxic injury caused by androgen and reactive oxygen species. Moreover, the conditioned media of ADSC (ADSC-CM) induces the anagen phase and promotes hair growth in mice, and it enhances the elongation of hair shafts in *ex vivo* human hair organ cultures. The ADSC-CM promotes hair growth *in vitro*, *ex vivo*, and *in vivo*.[21]

The various biomolecular GFs that have a role in hair growth and their actions are as follows[22]:

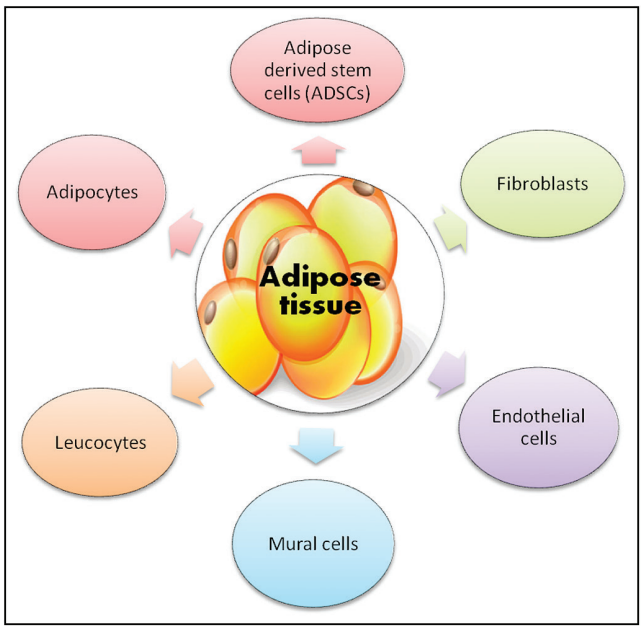


**Figure 1:** Flowchart showing composition of adipose tissue

- HGF and HGF activators (discharged by dermal papilla cells (DPCs)) enhance the proliferation of follicular epithelial cells.
- Epidermal growth factor (EGF) improves the activity and growth of follicle outer-root sheath cells by activation of Wnt/β-catenin flagging.
- Basic-FGF improves the advancement of HFs.
- Interleukein-6 (IL-6) is involved in WIHN through STAT3 enactment.
- VEGF improves perifollicular angiogenesis.
- Transforming growth factor-β (TGF-β) stimulates the signaling pathways that manage the hair cycle.
- IGF-1 improves the migration, survival, and proliferation of HF cells.
- IGF binding protein-1 to -6 (IGFBP) manages the IGF-1 effect and its connection with extracellular matrix proteins at the HF level.
- BMP maintains the DPC phenotype (fundamental for stimulation of HFSCs).
- BMPR1a maintains the proper identity of the DPCs.
- Macrophage-colony stimulating factor (M-CSF) is involved in wound-induced hair growth.
- M-CSF receptor (M-CSFR) is involved in wound-induced hair growth.
- PDGF and PDGF receptor (PDGFR-β/-α64) upregulate the genes associated with HF separation, induction, and control of anagen. PDGF and its receptors are fundamental for follicular improvement.
- Wnt3a is involved in HF advancement through β-catenin flagging.
- PGE2 stimulates anagen in HF.
- PGF2α and analogs enhance change from telogen to anagen.
- PGE2 or hindrance of PGD2 or PGD2 receptor D2/GPR4477 enhances follicle regeneration.

## Stromal Vascular Fraction

The stromal vascular fraction (SVF) is a heterogeneous population of stem/stromal cells isolated from the perivascular and extracellular matrix of adipose tissue complex (ATC). The SVF is suitable for use in regenerative surgery due to its lack of immunogenic properties, its simplicity of extraction, its multipotential characteristics, the simplicity of separating it into

**Table 1: Mechanism of action of major GFs released by ADSCs in promoting hair growth**

| Growth factors | Mechanism of hair stimulation |
|---|---|
| VEGF | Improves perifollicular vascularization, resulting in increased size of HFs and shafts.[15] |
| HGF | Delays transition from anagen to telogen, has mild anagen inducible property, promotes HF growth, and elongates the hair length.[16] |
| PDGF | Induces and maintains anagen phase of hair cycle.[17] |
| IGF-I | Prolongs resting phase of hair cycle and delays initiation of new anagen phase. Promotes follicular proliferation and differentiation.[18] |
| KGF (FGF-10) | Stimulates proliferation and differentiation of early progenitor cells within HFs. Induces anagen phase in resting HFs.[19,20] |
| FGF-1, FGF-2 | Induces anagen phase in resting HFs.[20] |

different cell lines, and its significant potential for angiogenesis. The SVF is commonly divided into cellular SVF (cSVF) and tissue SVF (tSVF). Cellular SVF is obtained from ATC by collagenase digestion, incubation/isolation, and pelletization by centrifugation. However, enzymatic disaggregation may alter the relevant biological characteristics of AT and hence in many countries, the isolation of cellular elements is most often limited to controlled clinical trials and subject to regulatory review. Several alternative, nonenzymatic methods of AT processing have been developed to obtain an autologous tSVF, which is easier, quicker, has minimal manipulation of cells, and, hence, bypasses regulatory approval and can be adopted in a clinical setting. These nonenzymatic methods use mechanical or physical forces to loosen the structural integrity of the AT extracellular matrix and periadventitial structures. Emulsification (nanofat), condensation, microfat, and mini-microfat are some examples of such mechanical processes. Commercial kits are also available for such extraction.[23]

Several recent scientific publications that are analyzed later have projected ADSCs as the next biological treatment, as the next PRP therapy. Several companies have marketed various products for purified fat preparations. Although this treatment is not as yet an established form of treatment, there are several reviews and early original articles that talk of its possible role in hair loss management.

## Analysis of Studies on Adipose Tissue as a Treatment for Hair Regeneration [Summaries on Tables 2 and 3]

We searched Pub Med, Science Direct, Researchgate, Europe PMC, and Google Scholar for all articles with the following search terms: adipose tissue AND hair growth, fat grafting or nanofat AND alopecia, ADSC AND alopecia, SVF AND alopecia. The exclusion criteria were non-English language publications, animal studies, and those studies where AT was not used as a treatment for hair loss. This left us with 21 articles. We have analyzed these studies and presented their review.

Fat has been used in several ways for hair regeneration: AF transfer, nanofat, ADSCs, SVF, and micrografts of adipose tissue derived follicular stem cells. These have been tried not only in androgenetic alopecia (AGA), but also in other forms of alopecia such as alopecia areata (AA) and scarring alopecia. It has also been tried after the hair transplantation procedure. Each of these different aspects is dealt with in the analysis of the following studies.

## Studies Using Autologous fat

Fat transfer is an established treatment for atrophic scar, post-injury scars, scleroderma etc. Incidental hair growth has been observed on and around such scars, alopecic patches, and also AGA, treated with AF in various studies.

Nilforoushzadeh *et al.* reported a study including nine adults (five women, four men) with AGA who were injected with autologous AT in a single session. Hair regeneration was assessed via measurement of hair diameter and density using trichogram. Hair pull test was also done. There was a significant increase in hair diameter and density and a significant decrease in hair pull test in all patients at three and six months after the treatment.[24]

Nilforoushzadeh *et al.* also reported a case of scarring alopecia after trauma that responded to AF transfer, resulting in increased hair growth at the alopecic patch.[25]

Tedesco M published a case report on fat transfer in a 41-year-old female patient with 25 years of recurrent folliculitis decalvans not responding to conventional therapies. Two sessions were conducted at an interval of five months. Patient did not develop new folliculitis after treatment and were able to discontinue the antibiotic therapy. Hair regrowth was observed in the peripheral area affected by the disease.[26]

Dini M *et al.* reported a case of a 25-year-old woman with AA of the left eyebrow with atrophy caused by an intralesional steroid. After one session of autologous fat transplantation (AFT), not only was there an expected improvement in the area of atrophy but also hair regrowth was observed in the alopecic lesion three months after the fat transfer.[27]

Cho SB *et al.* reported a case of a 26-year-old woman with alopecia secondary to localized scleroderma that presented as an atrophic alopecic patch on the frontal scalp along with linear skin depression of the forehead. Two sessions of AFT at a three months interval was performed. In addition to improvement in the atrophy and depression, regrowth of terminal hairs was observed on the alopecic patch at three months, which had further grown thicker and longer after the second AFT.[28]

## Studies Using Nanofat

Nanofat is a form of mechanically emulsified SVF first described by Tonnard *et al.* in 2013.[29] Vestitia *et al.* described a study using nanofat for AGA in 12 male patients. The authors prepared nanofat using the Tonnard protocol, and a single session of nanofat injection was given. Each treated area showed an increase in the number and thickness of hairs.[30]

## Studies Using Micrografts of Adipose Tissue Derived Follicle Stem Cells

In a study reported by Pietro Gentile, 33 patients (23 males, 10 females) with AGA were injected with an autologous solution of micrografts from scalp tissue containing

**Table 2: Summary of clinical studies using adipose tissue and its extracts for hair growth**

| Author, year | Type of alopecia | Patient number | Type of study | Product used | Treatment duration | Treatment protocol |
|---|---|---|---|---|---|---|
| **Using AF** | | | | | | |
| Nilforouzadeh *et al.* 2020[24] | AGA | 9 | Prospective clinical trial | AF | Single session | Injection of adipose tissue 1.0 ml/cm$^2$ of scalp |
| Nilforoushzadeh *et al.* 2019[25] | Traumatic alopecia of scalp | 1 | Case report | AF | Three sessions at 0, 3, and 9 months | First session, liposuction and injection of 40ml of purified fat; second session, injection of 20ml of frozen fat; third session, liposuction and injection of purified fat. Volume injected 1ml/cm$^2$ of scalp. |
| Tedesco M. 2018[26] | Folliculitis decalvans | 1 | Case report | AF | Single session | Injection of fat 0.2 ml/cm2 over an alopecic patch of 10×10 cm |
| Dini M *et al.* 2014[27] | Alopecia areata of eyebrow | 1 | Case report | AF | Single session | Injection of 0.5 ml of purified fat |
| Cho SB *et al.* 2010[28] | Localized scleroderma with depressed alopecic patch at frontal scalp | 1 | Case report | AF | 2 sessions 3 months apart | Injection of 2 ml of fat droplets in first session. In second session, 1 ml injection using frozen fat. |
| Using nanofat | | | | | | |
| Vestitia *et al.* 2017[30] | AGA | 12 | Prospective clinical trial | Autologous nanofat | Single session | Injected at alopecic areas (details not given) |
| Using micrografts of adipose tissue-derived follicle stem cells | | | | | | |
| Gentile P, 2019[31] | AGA | 33 | Prospective clinical trial | Autologous micrografts of adipose tissue | Three injections at a 45 days interval | Injection of 1.1ml of micrografts suspension at 5 mm depth. Volume used 0.2 ml/cm$^2$ |
| Using ADSCs | | | | | | |
| Kuka *et al.* 2020[32] | AGA | 71 | Prospective, randomized, multicenter device trial | ADRC-enriched autologous fat grafts | Single session | Subcutaneous injection of 0.1 mL/cm$^2$ of Puregraft purified autologous fat followed by 0.1 mL/cm$^2$ of ADRCs (available in 2 different doses) in intervention group |
| Tak *et al.* 2020[33] | AGA | 38 | Prospective randomized, double-blind, vehicle-controlled clinical trial | ADSC-CE | 16 weeks | Twice daily self-application of topical solution up to 16 weeks |
| Ozturk *et al.* 2020[34] | AGA | 20 | Prospective clinical trial | SVF prepared by beautycell device (bitorend company) | Single session | Intradermal injection of 5 ml of SVF over whole scalp (25 injections of 0.2ml in each area). Followed by microneedling with 2 mm dermapen. |
| Lee *et al.* 2020[35] | AGA | 30 | Prospective, double-blinded, randomized, and placebo-controlled trial | Commercially available ADSC-CM product SCM2-Black3 (Anterogen, Co. Ltd, Seoul, Korea) | 12 weeks | Non-ablative Erbium-glass fractional laser treatment at first visit followed by topical application of ADSC-CM once per week for 12 weeks. Also, weekly single-pass self-application of 0.24mm microneedle stamps. |
| Narita *et al.* 2019[36] | AGA and female-PHL | 40 | Prospective clinical trial | AAPE (Prostemics, Seoul, Korea), a commercialized ADSC-CM product cultured under hypoxic conditions | Once a month for six sessions | Intradermal injections of AAPE (one vial of AAPE dissolved in 4 ml of saline) |
| Butt *et al.* 2019[37] | AGA | 22 | Prospective, randomized clinical trial | SVF obtained via liposuction and processing of AF, and PRP | Two sessions, four weeks apart | Intradermal injection of SVF mixed with PRP (3 mL at 20 µL/100 000 cells) at 0.5 cm interval |

**Table 2: Continued**

| Author, year | Type of alopecia | Patient number | Type of study | Product used | Treatment duration | Treatment protocol |
|---|---|---|---|---|---|---|
| Stevens *et al.* 2018[38] | AGA | 10 | Prospective clinical study | SVF obtained via liposuction and processing of AF, and PRP | Single session | A total of 5 mL of PRP and 1 mL of SVF was combined in one syringe. Intradermal injection of small droplets of 0.01 mL, 0.4 cm apart over an area of 100 $cm^2$. |
| Shin *et al.*, 2017[39] | Female -PHL | 27 | Retrospective observational study | AAPE™ | 12 weeks (once per week) | Scalp area first cleansed with a micro-needle roller followed by application of ADSC-CM once/week for 12 consecutive weeks. |
| Fukuoka *et al.* 2012[40] | Male-and female-PHL | 25 | Prospective observational study | AAPE® [HARG® enhanced by hypoxic ADSC-CM] | Four sessions every three to five weeks until hair regeneration seen | Mesotherapy techniques such as nappage and papule injections used. In nappage technique, every 3 $mm^2$ area of skin was injected. In papule technique, intradermal injections of 0.02 to 0.05 $ml/cm^2$ of AAPE given with a total volume of 3–4 ml per treatment. |
| Fukuoka *et al.* 2015[41] | Alopecia (type not specified) | 22 (Another group of 10 patients for half-side comparison study) | Prospective observational study | AAPE® | Six treatment sessions every three to five weeks | Intradermal injections of 0.02 $ml/cm^2$ of solution. Total volume of 3–4 ml per session. |
| Fukuoka *et al.* 2017[42] | Male- and female-PHL | 21 (Another group of 10 patients for half-side comparison study) | Prospective observational study | AAPE® [HARG®) enhanced by hypoxic ADSC-CM] | Once a month for six to eight sessions [≥10 times in some patients] | Mesotherapy techniques such as nappage and papule injections were used. In papule technique, intradermal injections of 0.02 $ml/cm^2$ of AAPE given with a total volume of 3–4 ml/treatment. Nappage technique was not described in this article. |
| Perez meza *et al.* 2017[43] | Male- and female-PHL | Nine (only six for 24 weeks follow-up) | Prospective observational study | Mixture of purified autologous fat graft (processed via Puregraft system) and ADRCs (processed via Keratem Celution system) obtained via liposuction | Single session | Needle-puncture incisions first made followed by subcutaneous injection of this mixture (1$ml/cm^2$) in a fanlike patterned movement via cannula. |
| Anderi *et al.* 2018[44] | Alopecia areata (scalp) | 20 | Retrospective observational study | Autologous ADSVCs | Single session | Injection at a depth of 4 mm, 0.2 $ml/cm^2$ with a total of 5 ml in 25 spots |
| Zanzottera *et al.* 2014[45] | Hair transplant surgery with application of ADSC | 3 | Case series | Cellular suspension obtained from discarded adipose tissue of scalp strips used for hair transplantation (via Rigenera system) | Single session | Subcutaneous injection of cell suspension on recipient area on the frontal region of scalp. Drops of cell suspension also applied on recipient site, both before and after hair graft insertion. |

Human Intra- and Extra- Dermal Adipose Tissue-Derived Hair Follicle Stem Cells (HD-AFSCs). This solution was obtained from mechanical fragmentation and centrifugation of scalp biopsy using "Gentile protocol." Three injections were administered at a 45 days interval. The author reported an improvement in hair density at 23 and 44 weeks after the last injections, with a mean increase of 33%±7.5% and 27%±3.5%, respectively, on photo-trichogram. On histological analysis of scalp biopsies done at 11 months from the last injections, there was expansion in the number of hair follicles per $mm^2$ compared with baseline (1.4 ± 0.27 vs 0.46 ± 0.15, respectively; $P < 0.05$).[31]

## Studies Using Adipose Derived Stem Cells (ADSCs)

The ADSC has attracted a lot of attention and a number of studies about its role in hair loss have been published, which are discussed later.

Kuka *et al.* reported a clinical trial of 71 patients (17 females and 54 males) with AGA using adipose-derived regenerative cell (ADRC) enriched AF grafts. Lipoaspirate obtained from patients were processed in the Puregraft System to remove the impurities, and in the Kerastem Celution System to isolate and concentrate ADRCs. Patients were divided into four groups: 16 with Puregraft

**Table 3: Continue...Summary of clinical studies using adipose tissue and its extracts for hair growth**

| Author, year | Method used to evaluate hair growth | Follow up | Outcome measures | Results |
|---|---|---|---|---|
| **Using AF** | | | | |
| Nilforouzadeh *et al.* 2020[24] | Trichogram (hair number, diameter), hair pull test | Three and six months | Hair number, diameter | Significant increase in hair number and diameter; and significant decrease in hair pull test. |
| Niforoushzadeh *et al.* 2019[25] | Physician visual assessment | At three and six months after the last injection | Hair growth | Hair regrowth seen |
| Tedesco M. 2018[26] | Clinical and dermoscopic assessment | Five months | Hair growth, folliculitis, pain, or burning sensation | Hair regrowth at peripheral area affected by the disease, no new folliculitis, no pain or burning |
| Dini M *et al.* 2014[27] | Physician visual assessment | Three months | Hair growth | Hair regrowth seen at three months of fat injection |
| Cho SB *et al.* 2010[28] | Physician visual assessment | Upto six months | Hair growth | Hair regrowth seen |
| Using nanofat | | | | |
| Vestita *et al.* 2017[30] | Trichogram examination and patient VAS scores | One, three, six, and 12 months after treatment | Hair number, thickness | Increase in hair number and thickness, and patient satisfaction |
| Using micrografts of adipose tissue-derived follicle stem cells | | | | |
| Gentile P. 2019[31] | Phototrichoscopy, histological analysis via scalp biopsy | At 23 and 44 weeks after the last injection | Hair density and hair follicles/mm$^2$ on histological analysis | Improvement of hair density and expansion of hair follicles/mm$^2$ on histologic evaluation |
| Using ADSCs | | | | |
| Kuka *et al.* 2020[32] | Macrophotograpphy, global photography | Six, 24, and 52 weeks | Hair count and width | Low-dose ADRC group reported an increase in hair count at 24 weeks. No statistically significant change in hair width at any groups. |
| Tak *et al.* 2020[33] | Phototrichogram | 16 weeks | Hair count and diameter | Significant improvement in hair count and diameter |
| Ozturk *et al.* 2020[34] | Macroscopic and trichoscopic examination | Three months | Hair density and diameter | Increase in hair density and diameter in the majority of patients in the temporoparietal and vertex region |
| Lee *et al.* 2020[35] | Clinical photograph, phototrichogram | Four, eight, and 12 weeks | Hair density, global improvement scores (GIS) compared by clinical photographs, investigator's improvement score (IIS) measured by questionnaire | Significant increase in hair density and GIS. No significant difference in IIS. |
| Narita *et al.* 2019[36] | Trichogram, histological evaluation via punch biopsy of scalp | Two, four, and six months | Hair density, anagen hair rate | Hair density and anagen hair rate increased significantly |
| Butt *et al.* 2019[37] | Trichoscan, photographs, pull test | Six months after the last injection | Hair density, pull test, and physician and patient global assessment scores | Increase in hair density, reduction in pull test, and improvement in patient and physician assessment scores were much more in the SVP-PRP group compared with the PRP group. |
| Stevens *et al.* 2018[38] | Ultra high-resolution photography (Fotofinder) | Six and 12 weeks post-injection | Hair density | Significant increase in hair density at both six and 12 weeks post-injection |
| Shin *et al.* 2017[39] | Phototrichography | 12 weeks (for all 27 patients) [nine patients for six months and one patient for one year] | Hair density and thickness | Statistically significant increase in hair density and thickness |
| Fukuoka *et al.* 2012[40] | Trichogram images | Upto 2.5 years | Physician- as well as patient-determined VAS scores | Statistically significant improvement in physician-determined VAS scores. Improvement in patient-determined VAS scores. |
| Fukuoka and Suga. 2015[41] | Trichogram images | Upto one year | Hair count | Significant increase in hair count |
| Fukuoka H *et al.* 2017[42] | Trichogram images | Upto one year | Hair count | Significant increase in hair count |

**Table 3: Continued**

| Author, year | Method used to evaluate hair growth | Follow up | Outcome measures | Results |
|---|---|---|---|---|
| Perez-Meza *et al.* 2017[43] | Macrophotographic and global photographic images | Six months (one patient for eight months) | Hair count, anagen and telogen %, and cumulative thickness | Significant increase in hair count. No change in anagen/telogen %, or cumulative thickness |
| Anderi R *et al.* 2018[44] | Trichogram images | Upto six months | Hair diameter and density, hair pull test | Significant improvement in hair diameter and density. Significant decrease in hair pull test. |
| Zanzottera F *et al.* 2014[45] | Photographs | Upto one month after surgery | Hair growth, wound healing, and patient's perception of pain by via VAS scores | Faster healing of the micro-wound and continuous growth of the transplanted hair even two months after the procedure. |

fat and $1.0 \times 10^6$ ADRCs/cm$^2$ scalp (high-dose ADRC group), 22 with Puregraft fat and $0.5 \times 10^6$ ADRCs/cm$^2$ scalp (low-dose ADRC group), 24 with Puregraft fat alone, and nine with saline control. Injection of purified fat with low-dose ADRC demonstrated superior results compared with other groups. The low-dose ADRC subgroup reported an increase in terminal hair count at all weeks (6, 12, 24, and 52 weeks), with maximum hair count seen at week 24. The group treated with fat and high-dose ADRC did not respond. At the 24-week evaluation of all patients, there were no statistical differences in terminal hair counts or width between any of the treatment groups.[32]

Tak *et al.* reported a clinical trial in 38 patients (29 men, nine women) with AGA treated with topical adipose-derived stem cell constituent extract [ADSC-CE; T-Stem Co. Ltd (Changwon-si, Republic of Korea)]. Patients were divided into two groups, an intervention group (IG), with twice-daily self-application of the ADSC-CE topical solution and a control group (CG). Patients were evaluated at week eight and 16. There was a significant increase in hair count and thickness in the IG compared with the CG at 16 weeks. The overall change in hair count was 28.1% in IG vs 7.1% in CG. Improvement of hair diameter was 14.2% in IG vs 6.3% in CG.[33]

In a report from Turkey, 20 patients (14 males, six females) with AGA were injected with SVF prepared by beautycell device (Bitorend company). Three months later, improvement was noted in hair density and diameter. Hair density in the temporoparietal region improved by 10–20% in 75% of patients, whereas there was no improvement in 25% of patients. In the vertex, there was a 10% increase in hair density in 75% of patients and a 20% increase in 25% of patients. In the temporoparietal region, hair thickness increased by 25% in all patients. In the vertex, there was no change in hair thickness in 50% of patients, whereas it increased by 10–30% in the remaining 50% of patients.[34]

Lee *et al.* studied the effect of topically administered ADSC-CM on AGA after nonablative fractional laser treatment in 30 patients (15 men, 15 women). They used commercially available ADSC-CM product SCM2-Black3 (Anterogen, Co. Ltd, Seoul, Korea). Assessment was done by phototrichograms and clinical digital photographs. The ADSC-CM group had significantly higher final hair densities compared with the placebo group. The authors concluded that the application of ADSC-CM after nonablative fractional laser treatment accelerated an increase in hair density and volume in patients with AGA.[35]

In a study done by Narita et al, 40 patients (21 men, 19 women) with AGA and female-PHL were treated with an intradermal injection of ADSC-CM every month for six months. They used advanced adipose-derived stem cell protein extract (AAPE), Prostemics Co, Ltd, Seoul, South Korea, which is a commercialized ADSC-CM product cultured under hypoxic conditions. Assessment via trichoscopy showed a significant increase in hair density and anagen hair rate.[36]

Butt *et al.* analyzed the efficacy of use of SVF in 11 patients with AGA. Patients were divided into two groups: PRP group (only PRP) and SVF-PRP group (mixture of SVF and PRP). Autologous AT was processed to obtain SVF in all patients. Patients were injected twice, four weeks apart, and evaluation was done at six months after the last injection. Mean hair density increased by 21.5% in the PRP group and by 51.6% in the SVF-PRP group. A reduction in pull test was seen in both groups, with a more significant reduction in the SVF-PRP group. There was also significant improvement in the physician and patient assessment scores in the SVF-PRP group.[37]

Stevens *et al.* also reported a study evaluating the effect of SVF in combination with PRP [platelet-rich stroma (PRS)] in 10 male patients with AGA. All patients were treated with a single injection of autologous PRS. There was a significant increase in hair density at six weeks and 12 weeks posttreatment.[38] Since there was no control group in this study, the efficacy of SVF over PRP cannot be ascertained.

Shin *et al.* performed a retrospective observational study in 27 patients with female pattern hair loss (PHL) treated with ADSC-CM. They used commercial ADSC-CM product AAPE™ (Prostemics Co, Ltd, Seoul, South Korea). AAPE™ has been shown to contain numerous cytokines, including VEGF, HGF, basic FGF, KGF, and PDGF. After 12 weeks of treatment, the mean hair density increased by 16.4%; the mean hair thickness

increased by 11.3%. These improvements were statistically significant.[39]

Fukuoka H *et al.* published three studies in which they evaluated the hair regenerative effects of AAPE in patients with male- and female-PHL.[40-42]

In their first study conducted in 2012, Fukuoka *et al.* evaluated 25 patients (13 men and 12 women) with male- and female-PHL. In this study, AAPE injections were combined with buflomedyl, vitamin B1, vitamin B6, vitamin H, vitamin C, vitamin E, coenzyme Q10, and amino acids. This combined therapy was referred to as hair regenerative therapy (HARG) enhanced by hypoxic ADSC-CM. Mesotherapy techniques such as nappage and papule injections were used to administer the therapy. Patients received four treatment sessions every three to five weeks until hair regeneration was observed. Patients were followed up at a two to four months interval for at least one year after the final treatment session. Statistically significant improvements in physician-determined VAS scores were observed from the first treatment ($P < 0.1$). Patient-determined VAS scores also increased as the number of treatments increased.[40] However, this study lacked an objective and consistent means of evaluation.

In their next study conducted in 2015, Fukuoka *et al.* treated two groups of patients with ADSC-CM (AAPE®) with a somewhat complex design. In the first group, 22 patients (11 men and 11 women) with alopecia (type of alopecia not mentioned) were given intradermal injections of ADSC-CM. Finasteride was also administered to six out of 11 male patients. In the second group of 10 patients (eight men and two women), a half-side comparison study was performed. They received ADSC-CM treatment on the left side and placebo treatment (saline injection) on the right. Patients of both groups received treatment every three to five weeks for a total of six sessions and were examined with trichogram both before and after completing treatment. In the first group of 22 patients, the number of hairs increased significantly after treatment in both males and females. The mean increase in the number of hairs was 29 ± 4.1 in male patients and 15.6 ± 4.2 in female patients. Also in the first group, among six out of 11 male patients, the addition of finasteride made no significant difference in the number of hairs. In the half-side comparison group, the number of hairs increased significantly after treatment on both the left (ADSC-CM) and right (placebo) sides, but the increase was significantly higher on the ADSC-CM treated side than on the placebo side.[41]

In a third study conducted in 2017 by Fukuoka *et al.*, 21 patients (16 males and five females) with male- and female-PHL were evaluated. Intradermal AAPE injections were given once a month and were repeated six to eight times. On evaluation by trichogram, the number of hairs at three months of treatment increased significantly in comparison to that before treatment (141.3±31.4 vs. 109.8±43.5, respectively; $P < 0.01$).[42]

Thus, these three studies by the same author suggested that ADSC-CM was effective in inducing hair growth. However, although the authors performed three studies over five years, they seem to have recruited different patients in each study, and hence the follow-up period was not long in any of the studies.

Perez-Meza *et al.* performed an observational study on nine patients (eight men, one women) with female- and male-PHL using a mixture of purified fat and SVF. Fat aspirated by liposuction was divided into two aliquots. Processing by Puregraft system™ (Puregraft LLC, Solana Beach, CA, USA) was used to obtain a purified AF graft in the first aliquot, whereas Kerastem Celution System™ was used to obtain a suspension of ADRCs (also known as SVF) in the second aliquot. Hair count, anagen percentage, telogen percentage, and cumulative thickness were calculated at six months. A mean increase of 31 hairs/cm$^2$ of scalp (23% relative percentage increase) was documented in five patients with proper follow-up. However, no statistically significant change was noted in cumulative thickness or percentage of hairs in the anagen or telogen phase.[43]

Besides male- and female-PHL, the use of ADSCs has been attempted in other pathological alopecias also, such as AA. In a retrospective study of 20 patients (11 men, nine women) with scalp AA, conducted by Anderi et al, autologous adipose-derived stromal vascular cells were injected in a single session treatment. After six months of treatment, the hair diameter increased significantly in 19 out of 20 patients (from 60.5 ± 1.8 μm to 80.8 ± 2.4 μm at 6 months). There was an average of 32% improvement in hair diameter, with greater improvement in females as compared with males.[44]

Treatment with ADSCs has been reported in patients undergoing hair transplantation as well. Zanzottera F *et al.* reported a case series of three patients who underwent hair restoration surgery along with the application of ADSCs and growth factors. The ADSC was obtained from the hypodermis and AT discarded from the donor strip of scalp, and it was processed using Rigenera system. Rigenera device is a standardized sample preparation system for the automated mechanical disaggregation of the cell population and it yields a cellular suspension composed of erythrocytes, epithelial cells, ADSCs, and immature adipocytes. The cell suspension was injected subcutaneously on the recipient area on the frontal region of the scalp. The patients were evaluated after five days, two weeks, and one month based on photographs and the patients' impressions. The authors reported that there was continuous growth of the transplanted hair as early as two months after the procedure, with shortening of the dormant phase.[45] However, there was no comparative

group and hence it was difficult to draw a definite conclusion.

Thus, a number of studies have been published on this topic, which indicate a potential benefit. Summaries of all these studies are given in Tables 2 and 3 including a description of treatment protocol, the method of evaluation of hair growth, treatment duration, and follow-up period.

## Discussion

The main goal of this review was to evaluate the logic and effectiveness of AT in hair regeneration. The review includes studies of male and female-PHL, AA, hair transplant surgery, folliculitis decalvans, traumatic alopecia, and localized scleroderma. All the studies showed improved outcomes with AT treatments. However, there was significant variation in the methods of preparation of ADSCs and fat from harvested AT. Till now, there is no universal protocol for fat grafting and the various methods of fat harvesting, processing, and reinjection can affect results, which leads to difficulty in comparing results from various studies. Most of these studies also had a small sample size, variable control groups, and different durations and outcome measures; lacked long-term data; and were either case reports, small case series, or pilot studies. Hence, the level of evidence is lower than randomized controlled trials (RCTs). However, such low-quality studies and lack of a higher level of evidence are true of all new treatment modalities.

Overall, based on above data, it can be said that AT and ADSCs may represent a new and promising therapy for hair regeneration and physicians need to be aware of developments in this field. However, the therapy is still in the experimental mode and as such cannot be a part of routine management of hair loss yet. The therapy needs further larger studies with high-quality large RCTs so that standardized and effective protocols can be made. In the future, as we gather more clinical evidence with new emerging trials, AT may be considered as a promising treatment option in the field of hair regeneration.

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### Conflicts of interest

There are no conflicts of interest.

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