

Efficacy Of Adipocytes Derived Stem Cells Conditioned Media (ADSC-CM) In Management Of Androgenetic Alopecia – A Review.

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Abstract:

Androgenetic Alopecia (AA), commonly referred to as male and female pattern baldness, is the most common cause of hair loss today. It affects approximately 50% male and 30-40% female population worldwide across varied ages. In the recent times, there has been a surge of patients asking for treatment of hair loss due to patterned hair loss. Though there has been a multitude of non-surgical treatment options available today, every modality has its own pros and cons. Adipocyte derived stem cells- condition media (ADSC-CM) is the growth factor rich media produced when adipose derived stem cells are cultured. During culturing, the adipocyte derived stem cells constantly release growth factors into the surrounding culture media. The stem cells are subsequently removed, leaving a cell free, growth factor rich solution which has been shown to exhibit regenerative potential similar to treatment using adipose derived stem cells. The Conditioned media of Adipocyte derived stem cells (ADSC-CM), has emerged as a novel and effective noninvasive modality for managing hair loss and hair regrowth due to patterned hair loss. This review paper describes in details about various aspects of AA and the advantages of use of ADSC-CM in treating patients suffering with AA.

Key Words:

Adipocyte Derived Stem cells- conditioned media (ADSC-CM) therapy, Androgenetic Alopecia (AA) , Patterned Hair loss (PHL), treatment of patterned hair loss, growth factor therapy in hair loss, treatment of hair loss.

1. INTRODUCTION:

Androgenetic Alopecia (AA), referred to as male and female pattern baldness, is the most common reason of hair loss for patients visiting a hair restoration physician today. Approximately 50% male and 30-40% female population across varied ages worldwide are affected by AA. Of lately, there has been a surge of patients asking for treatment of hair loss due to patterned hair loss, possibly due to the obligations of being presentable at the social

and professional fronts. Though a multitude of non-surgical treatment options available today, every modality has its own pros and cons. The Conditioned media of Adipocyte derived stem cells (ADSC-CM), has emerged as a novel and effective noninvasive modality for managing hair loss and hair regrowth due to patterned hair loss due its safety, efficacy and non-invasiveness.

2. DISCUSSION:

Alopecia:

Alopecia is a medical condition that leads to temporary or permanent loss of hair from part of scalp or body. This leads to localised or diffused hairless areas on scalp or any other areas of the body. It can affect both males and females regardless of their age. Though studies related to the individual's psychological issues associated with hair loss is limited, there are evidences confirming that the consequences of such hair loss can cause behavioural alterations, leading to serious emotional suffering, and often leading to personal, social, and professional set-backs and that patients with severe hair loss are more likely to experience psychological distress than those with mild hair loss [1]. The Hair society estimates approximately 35 million men and 21 million women suffer from hair loss worldwide.

The rationale behind alopecia or hair loss can be simply enumerated as:

a) Scarring or

b) Non- scarring.

While the Scarring type of alopecia is normally less commonly encountered and is mostly due to the complication of another disease or condition which causes desolation of the involved hair follicles, that includes, but not limited to infections (bacterial or viral), injuries (burns or mechanical trauma), inflammatory skin diseases (discoid lupus erythematosus, lichen planopilaris, or folliculitis decalvans), neoplasia etc, the Non-scarring type is very frequently seen and may be due to genetic pattern (androgenetic alopecia), autoimmune related (alopecia areata), physical & mental stress induced (telogen effluvium), consequence of systemic conditions (anaemia, hypo or hyperthyroidism etc), medications (beta blockers, blood thinners, methotrexate, NSAIDS, antidepressants etc), or chemotherapy (anagen effluvium).

Androgenetic Alopecia (AA) :

Androgenetic Alopecia or patterned baldness is a multifactorial disorder caused by interactions between a variety of genes and environmental factors in predisposed scalps. The environmental factors include but not limited to circulating androgen hormones, hair follicle inflammation etc [2,3]. It is characterized by a progressive loss of visible terminal hair on the scalp via hair follicle miniaturisation [4]. According to International Society of Hair Restoration Surgery, as per 2018 data, genetic pattern hair loss accounted for 84.6% of people who got hair-loss treatment done.

Pathogenesis of AA:

The cross-talk between the mesenchymal dermal papillae cells and the epidermal hair matrix cells, under the influence of androgens, unfurls the secretion of many factors from the dermal papillae. These can have autocrine effect on the dermal papillae itself and paracrine effect on the hair follicle epithelial cells.[5] These factors include growth factors like Insulin like growth factor (IGF-1), basic fibroblast factor (bFGF), vascular endothelial growth factor (VEGF); and cytokines like transforming growth factor beta 1 (TGFbeta 1), interleukin 1 alpha (IL -1alpha) and tumor necrosis factor alpha (TNF alpha)[6-8].

In AA, there is a total turn around in the hair cycle identified as a premature termination of anagen and early entry into catagen followed by telogen. Follicles enter the catagen phase

due to the decreased expression of anagen maintaining factors such as the IGF-1, bFGF and VEGF. Also, an increased expression of cytokines such as the TGF beta 1, IL -1alpha and TNF alpha promotes apoptosis [9]. Recently, a study has shown the upregulation of Dickkopf-1 gene by DHT resulting in inhibition of outer root sheath cells and triggering apoptosis [10].

Pattern of depletion of density: The Male pattern baldness is typically characterised by a definitive retracted / retracting hairline starting from one temporal recess through the frontal line to the other side temporal recess along with a synchronous reduction in density in the vertex. In advanced conditions or grades, the reduction in vertex density leaves a bald area which amplifies to connect to the retracted frontal hairline.

On the other hand, a female pattern baldness is typically a dispersed pattern of reduction in density over the frontal scalp area without a deprivation of hairline.

Modalities of treatment of Androgenetic Alopecia :

Multitude of management options are available today to deal with AA. Every option has its own limitations and neither of them promise to give a long-term enduring result.

AA as a condition per se is primarily a cosmetic deformity. Patients coming in for treatment of this condition have typically very high expectations and hence need to be counselled well regarding the natural course of the condition and the pros and cons of each treatment modality. Patients should be sufficiently explained and educated about the benefits of early treatment and the necessity of prolonged therapy.

The various modalities include:

1. *Surgical Modality-* Hair transplant by FUE and FUT techniques are currently practiced to restore lost hair by redistributing the follicles from androgen insensitive areas (the occipital hair) to areas of scalp that have lost the follicles.

2. *Camouflage technique-* It involves use of hair systems and wigs.

3. *Medicinal management-* Topical minoxidil and oral finasteride are the only two treatments currently approved by the USFDA for androgenetic alopecia in men. However, these only prevent further hair loss and do not effectively reverse the baldness. Moreover, both require unceasing use to maintain the effect.

4. *Low level laser therapy-* Involves use of devices like laser cap or comb with diodes that emit red light (wavelength 630-670 nm) or infrared. It is used as an adjunctive therapy.

5. *Antioxidants and micro nutritional therapy-* Antioxidants counter the reactive oxygen species and low levels of micronutrients compensate the daily requirement, both of which today have strongly been implicated as playing a major role in hair loss.

6. *Growth factors therapy-* Platelet rich plasma (PRP) isolated by centrifuging the autologous whole blood has been successfully used for its growth factors and stimulatory mediators.

Last few years has witnessed a surge in the progress of a new treatment modality in regards to AA. The conditioned media of adipose derived stem cell has been much researched on and could in near future be the primary nonsurgical modality for the treatment of AA.

The conditioned media of Adipose derived stem cells as a promising treatment modality for pattern hair loss:

Adipose derived stem cells (ADSC):

Increasing

number of researches today support a correlation of dermal adipose deposits and proper follicle function and cycling. A study by Hermann et al on mice as experimental animals, reveal of the various malformations in skin structures including hair loss, epidermal hyperplasia and abnormal sebaceous gland function, as associated with the reduction of intradermal adipose tissues [11].

Festa et al. examined the role of intradermal adipocytes on follicular stem cell activity and observed a dynamic process of adipogenesis that parallels the activation of hair follicle stem cells [12]. Additional functional investigations revealed that the production of platelet derived growth factor (PDGF) by immature adipocyte lineage cells is necessary and sufficient to drive follicular stem cell activation. They ultimately established that adipose tissue plays a crucial role in the normal hair cycle [13]. He et al examined the involvement of adipose derived stem cells in the hair cycle and found that CD34+ cells actually participate in the formation of hair follicles, blood vessels, and fat tissue [14].

These and many more studies suggest a powerful association of adipose and adipose derived stem cells with hair growth cycle and hence this potential therapeutic application needs to be investigated further.

Adipose derived stem cells-conditioned media (ADSC-CM):

Various therapies based on adipocytes derived stem cells like cell assisted lipo transfer (CAL) and adipocyte derived stem cells conditioned media (ADSC-CM) have been utilised in many researches and studies for its effects in male and female pattern baldness and initial results appear promising and hence needs further exploration.

ADSC-CM is the growth factor rich media produced when adipose derived stem cells are cultured. During culturing, the adipocyte derived stem cells constantly release growth factors into the surrounding culture media. The stem cells are subsequently removed, leaving a cell free, growth factor rich solution which has been shown to exhibit regenerative potential similar to treatment using adipose derived stem cells [13]. Various culture conditions like hypoxia have shown to alter the growth factor contents and that could enhance the regenerative potential [15].

Preliminary studies were done by Won et al in 2010 to show the hair growth promoting effects of ADSC & ADSC-CM [16]. They did invitro studies, wherein the human dermal papilla cells (hDPCs) and immortalized keratinocytes (HaCaT) were treated with ADSC-CM. They found significant enhanced proliferation of hDPCs by upto 130% at 48hrs. ADSC-CM also activated both Erk and Akt signalling pathways, which indicated the enhancement of survival and proliferation of dermal papilla cells. Phosphatidylinositol 3-kinase (PI3K)/AKT pathway has been shown to controls cell growth, proliferation, survival, mobility and invasion. Mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway has been shown to be responsible for mitogenesis [17]. Significant proliferation of HaCaT cells was also noted. They then investigated the effect of ADSC-CM on the hair shaft elongation by culturing about 370 anagen hair follicles with it and found significant hair elongation by about 40%.

Park et al. in 2010 studied the hair growth promoting effect of ADSC-CM by administering it subcutaneously in C3H/NeH mice [18]. They derived that injecting subcutaneously, ADSC-CM could induce anagen phase and increased hair regeneration. They also concluded that ADSC-CM increased the proliferation of human follicle dermal papilla cells and human epithelial keratinocytes. Furthermore, a hypoxic condition of these conditioned media significantly increased the secretion of growth factors like Insulin like growth factor binding protein -1 & 2 (IGFBP-1 & IGFBP-2), Macrophage colony stimulating factor (M-CSF), M-CSF Receptor (M-CSF R), Platelet derived growth factor receptor beta (PDGF RB), and Vascular endothelial growth factor (VEGF) which control the hair growth and follicle size.

Ultraviolet B irradiated preconditioning was done in preparation of ADSC & ADSC-CM and was compared with preparations without the irradiation and their effect on hair growth in mice by Jeong et al [19]. For groups of the experimental animals with similar telogen were made. The groups included ADSC or ADSC-CM and with or without UVB irradiation. The mice were shaved and the product was injected as per the group. Generally, they noticed that,

hair follicles in all groups were able to transfer from telogen phase to anagen phase, but both the ASC and ADSC-CM groups which had been preconditioned with UVB irradiation demonstrated accelerated conversion and subsequently more hair growth.

Shin et al in 2015 published a retrospective clinical case series in which 27 females with Ludwig's grade 1 female pattern hair loss were treated with ADSC and ADSC-CM [20]. The treatment was done with a protocol of once a week for 12 weeks. Each sitting had application of ADSC-CM along with micro needling by derma roller. Phototrichographic images were captured pre and post treatment to assess the hair density and thickness. An increase of 16.4 % in the mean hair density was noted by the actual counts which escalated from 105.4 hairs/cm² to 122.7 hairs/cm². These results were comparable to those described by the use of topical minoxidil twice daily for 48 weeks at concentrations of 5% and 2% which showed improvement in hair density by 17.3% and 13.8% respectively [21]. An increase in the mean hair thickness by 11.3% was also reported at 12 weeks with an improvement from 57.5 µm to 64.0 µm. This outcome was superior than that of 2% minoxidil use. The treatment was not accompanied with any serious adverse events.

Fukuoka et al. used ADSC-CM to treat 25 subjects [22]. 12 male subjects suffered from androgenetic alopecia, 1 male subject had androgenetic alopecia with alopecia areata and 12 female patients had female pattern baldness. A protocol of application of the protein solution from ADSC-CM by mesotherapy technique such as nappage and papule injections were 4 to 6 times every 3 to 5 weeks. Considerable increase in amount of hair growth was noticed within 34 months with superior improvement in the frontal region of the head.

A follow-up study by Fukuoka and Suga was performed on 22 patients (11males and 11 females) with alopecia [23]. Subjects underwent intradermal injections with 31g needle. During the course of the study, only 6 of all the male patients were advised finasteride, but not the female patients. Treatment was performed at intervals of 3-5 weeks for a total of 6 sessions. 3-4 ml of ADSC-CM was injected in each session with 0.02 ml / cm² in each injection site. Pre and post treatment trichoscopic images were taken for the assessment of changes. They reported a significant improvement in number of hair in the entire population of study. The male subjects averaged an increase of 29 ± 4.1 hairs/cm² while that of female subjects averaged an increase of 15.6 ± 4.2 hairs/cm². No significant difference in increase in number of hair was observed in between male subjects with and without finasteride use. Simultaneously, another group of 10 patients (8 males, 2 females) were treated in a similar fashion with half of the side of scalp being treated with ADSC-CM and the other half with plain saline placebo injections. Surprisingly, increase in hair growth was reported in both sides of the scalp, although the ADSC-CM treated side was significantly higher than the saline only side of the scalp. This suggests that mechanical tissue injury, as here caused by needle, could possibly result in marginal hair growth and that the results of ADSC-CM treatment can help hair regeneration in the whole scalp via local diffusion or circulation and is not entirely localized to the treatment area.

A review by Su-Eon Jin and Jong-Hyuk Sung in 2016 concluded that in animal models, ADSC and ADSC-CM promoted hair growth and that ADSC-CM in vitro, induced proliferation of hair compositing cells. To enhance the hair growth promoting effect, they can be preconditioned with stimulators like Vit C, hypoxia, PDGF and UVB [24].

Fukuoka H et al have described their experience in hair regeneration therapy using ADSC-CM in more than 1000 patients [25]. They administered ADSC-CM intradermally in a quantity of 3-4ml in the entire scalp using a 31g needle in volume of 0.02ml per site, spaced 1cm apart. In most cases, to improve the efficacy of ADSC-CM with antioxidant effects, they combined the injections with vitamin B1 (5 mg), vitamin B6 (2.5-5 mg), vitamin H (1 mg), vitamin C (80-100 mg), vitamin E (5 mg), coenzyme Q10 (10 U) and amino acids by mesotherapy using nappage technique. They have referred this to as Hair regenerative

therapy (HARG). The injections are given once a month and are repeated 6-8 times. Their experience mentions that after 4-5 treatment sessions, patients noticed changes in hair quality and this could be confirmed by the reductions of area of thinning through photograph. They noticed that in AA, hairline improvement follows parietal improvement. Henceforth, with the large series of cases they confirmed the efficacy of the treatment.

3. CONCLUSION:

There has been quite a sizeable amount of studies that has been put in the science of using ADSC-CM as a non-invasive treatment modality for hair loss due to Androgenetic alopecia. This definitely would offer a huge benefit to patients who do not want to go in for surgical hair transplants and especially in females in whom hair transplant is very challenging and who cannot take oral antiandrogens. Last two and half decades hasn't seen any new and validated modalities of hair loss management. Hence, more research needs to be put in this therapy. It could evolve as one of the most effective therapies for hair restoration in Androgenetic alopecia.

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