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The role of autologous micrografts injection from the scalp tissue in the treatment of COVID-19 associated telogen effluvium: Clinical and trichoscopic evaluation

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Abstract

The clinical presentation of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2 COVID-19) varies from asymptomatic infection to a life-threatening, multi-organ disease. One of these manifestations is telogen effluvium (TE) which is characterized by diffuse hair loss occurring in patients previously infected with SARS-CoV-2 and lasts ~3 months, after which excessive hair loss follows. Hair follicles are known to contain a well-characterized niche for adult stem cells which is the bulge containing epithelial and melanocytic stem cells. Stem cells in the hair bulge, a demarcated structure within the lower permanent portion of hair follicles, can generate the interfollicular epidermis, hair follicle structures, and sebaceous glands. This study aims to evaluate autologous micrografts from scalp tissues as a therapeutic modality in the management of TE caused by COVID-19. Twenty patients of previous COVID-19 infection suffered from TE were included in this study for human follicle stem cells micrograft scalp treatment and they were evaluated after 3 months of treatment and after 6 months. There was significant improvement of the hair thickness and density compared with the start of the treatment and 6 months of follow-up. Autologous micrograft of the scalp showed marked improvement in the treatment of COVID-19 TE.

KEYWORDS
autologous micrografts, COVID-19, telogen effluvium

1 | INTRODUCTION

Coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of "coronavirus disease 2019 (COVID-19)." It has various clinical presentations as pneumonia, acute respiratory distress syndrome, acute liver and/or kidney injury, cardiac complications, pro-thrombotic coagulopathy, neurological syndromes, and may be asymptomatic.[1] SARS-CoV-2 has an affinity to angiotensin-converting enzyme 2 receptors so targeting respiratory epithelial cells and pneumocytes.[2] Symptoms of COVID-19 may be proceeded by various cutaneous manifestations as commonly appearing pruritic erythematous rash and/or patchy exanthematous red rash on the trunk and micro thrombotic presentations as acroischemic lesions or "COVID toe" that may occur in both children and adults. Other dermatologic manifestations of the virus included livedo racemosa, pernio, purpura, onychomadesis, and morbilliform eruption.[3]

Telogen effluvium (TE) is the most common finding associated with COVID-19 infection being characterized by diffuse hair shedding involving the entire scalp. There is abnormal hair cycling with loss of telogen (club) hair. It can be diagnosed by scalp examination, hair pull test, and laboratory investigation to find the cause.[4]

The etiopathogenesis of TE is largely unknown it may be an endocrinal, nutritional, or chronic condition such as thyroid disorder, profound iron deficiency anemia, malnutrition, drugs, and chronic

autoimmune diseases.[5] Also, chronic stress including pregnancy, psychological trauma, illness, hospitalization, surgery, malnutrition, and medications may represent one of the major causes since it is known that it exerts a profound inhibitory effect on hair growth. Patients infected with COVID-19 were under psychosocial and physiologic stress.[6]

Diffuse hair shedding occurs 2–3 months after a stressor. The precipitating event causes premature termination of the anagen phase and subsequent transition to the catagen and telogen phases, resulting in hair shedding. TE is usually self-limited; acute TE typically resolves within 6 months of onset and is nonscarring alopecia.[4]

The body responds to SARS-CoV-2 infection by creating a pro-inflammatory state, which leads to tissue damage and other sequelae. Proinflammatory cytokines are released and anti-coagulation mechanisms are impaired, which may provoke TE via the systemic inflammatory response and/or microthrombi in the hair follicles.[7]

Hair follicles are known to contain a well-characterized niche for adult stem cells: the bulge, which contains epithelial and melanocytic stem cells. Stem cells in the hair bulge, a demarcated structure within the lower permanent portion of hair follicles, can generate the interfollicular epidermis, hair follicle structures, and sebaceous glands. The bulge epithelial stem cells can also be reconstituted in an artificial in vivo system to a new hair follicle.[8]

Considering this, the outcome of this study was to attempt a novel therapeutic modality for the treatment of TE caused by COVID-19 by autologous micrografts injection from the scalp tissue and evaluation of the hair regrowth clinically and trichoscopy to assess the gain for the patients from this treatment modality.

2 | PATIENTS AND METHODS

2.1 | Patients

The current study was conducted from June 2020 to June 2021 on 20 female patients aged between 30 and 45 years old who suffered from increased hair loss after COVID-19 infection, with no history of previous hair loss problems. All patients had polymerase chain reaction (PCR) confirmed COVID-19, the condition did not require hospitalization for these cases only home isolation and medications for COVID19 in the form of azithromycin 500 mg tablet, paracetamol 500 mg tablet, and supportive treatment. Patients with a lack of confirmatory PCR or anti-body testing, presence of signs and symptoms of other causes of hair loss, such as an autoimmune disorder, vitamin deficiency, or hormonal abnormality were excluded from this study.

All patients were subjected to complete history taking and total body examination. The demographic characteristics of the patient, including age, sex, history of the disease, and medications taken, were recorded. General examination and laboratory investigations to exclude any other systemic causes of TE as thyroid dysfunction, malnutrition, and anemia were done.

The trichoscopic examination was done using Dino-lite Premier AM4113T microscope before the beginning of the treatment (T0), after 3 months of treatment (T3), and after 6 months (T6). Trichoscan analysis software automatically calculated the hair density and thickness. Digital photography was done by using (Sony Cyber-shot DSCW690 16.1 MP 10X optical zoom digital camera; Sony, Japan).

This study was approved by the Research Ethical Committee of Tanta University Institutional Review Board, Egypt following the Declaration of Helsinki (2008 version), Code No: 35138. This trial followed the CONSORT guiding principles. All participant patients were informed of the nature, benefits, and potential risks of their participation in the study, they all signed informed consent before starting the study and also for imaging to be published.

3 | METHODS

3.1 | Therapeutic regimen

In the current study, a total of 20 female patients were injected locally in the scalp with a human follicle stem cells (HFSCs) micrograft. Mechanical centrifugation was done for human hair follicle punch biopsy to isolate human adult stem cells without culture. Regenera Activia device was used to prepare human autologous hair follicle suspension from human follicle stem cells and it is used immediately for clinical injection.

The patients were prepared by removing the hair in the area where the biopsies were to be taken by razor and was cleaned by antiseptic (e.g., alcohol 70%). Local anesthesia was administrated at the area behind the ears, and then four-punch biopsies of 2 mm were taken from the area behind the ears in a strict sterile condition. Compression was done for hemostasis, and plaster on the wound was placed during the whole procedure. The biopsies were inserted in sterile Regenera cons® and a specific connector of the device was used to add 1.2 ml saline (NaCl 0.9%) where the biopsies were slightly embedded in it, then the cover on top of the Regenera cons® device was placed. Then it was placed on its receptacle, and placed in the Regenera device for centrifugation at 80 rpm for 2 min. Then the isolated HFSCs solution was injected using a 30-gauge needle at a 4 mm depth in the scalp which was divided into four parts (frontal, parietal, vertex, and occipital); there was no need for local anesthesia in the treated areas. The patients were instructed to take care of the wound in the scalp by putting antibiotic cream and avoiding excessive water exposure.

Patients were evaluated at the beginning of the treatment and follow-up visits were scheduled after 3 and 6 months after treatment. The efficacy of treatment was assessed through the evaluation of changes from baseline in hair density and thickness and global photographic assessment by two dermatologists who were blinded to the procedure of the treatment. High-resolution digital photographs and photo-trichograms at baseline (T0), after 3 months of treatment (T3), and at the 6 months, follow-up (T6) were taken.

3.2 | Evaluation of the outcomes of the treatment

Hair density was measured by using the Dino-lite Premier AM4113T microscope before the beginning of the treatment (T0), after 3 months of treatment (T3), and after 6 months (T6). Trichoscan analysis software automatically calculated the hair thickness and hair density.

Hair thickness was measured at baseline (T0), after 3 months of treatment (T3), and at the 6 months follow-up (T6). The dermoscopic examination also was performed for the remaining scalp to detect any inflammation, redness, and peripilar sign.

The evaluation of treatment was made by assessment of standardized global photographs taken by Sony Cyber-shot camera. The hairs of patients were centered-parted to take each photographic view. All the photos were registered before entering the study (T0), after 3 months of treatment (T3), and at the 6 months follow-up (T6). The degree of improvement was graded by two independent dermatologists who did not participate in the medical care of the patients and who were blinded to the treatment.

3.3 | Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov-Smirnov was used to verify the normality of distribution of variables, analysis of variance (ANOVA) with repeated measures for normally distributed quantitative variables, to compare between more than two periods or stages, and post hoc test (Bonferroni adjusted) for pairwise comparisons. The significance of the obtained results was judged at the 5% level.

4 | RESULTS

The total number of patients conducted in this study was 20 female patients. The demographic data of the patients are shown in Table 1. Their age was between 30 to 45 years old who suffered from severe hair loss after COVID-19 infection within 3 weeks to 3 months.

Clinical examination of the patients revealed no cicatricial alopecia with positive hair pulling test.

Clinical photos were evaluated by two dermatologists who were blinded and were not involved in the treatment of the patients. They were evaluating the clinical photos by no improvement, mild, moderate, and marked improvement. There were 11 patients with marked improvement as shown in Figure 1 and 6 patients with moderate improvement and 3 patients with mild improvement. The procedure wasn't painful and the patients did not complain about any side effects.

Trichoscopic examination of the hair revealed non-cicatricial alopecia with hair volume loss and thinning all over the scalp. Figure 1.

Regarding the evaluation of hair density, it was significantly improved after 6 months of treatment since the mean + *SD* in T0 was 184.1 ± 40.9 and in T3 after 3 months of treatment was 190.4 ± 38.8 and at T6 was 192.9 ± 39.6 as shown in Table 2.

TABLE 1 Distribution of the studied cases according to demographic data ($n = 20$)

	No (%)
Age (years)	
≤40	15 (75%)
>40	5 (25%)
Sex	
Male	0 (0%)
Female	20 (100%)
COVID-19 confirmation diagnosis (PCR)	20 (100%)
COVID-19 hospitalization	
No	20 (100%)
Yes	0 (0%)
Onset related to COVID-19 (days)	
Mean ± *SD*	36.7 ± 4.7
Median (min.–max.)	36 (30–45)
Treatment of COVID-19	
Azithromycin 500 mg	10 (50%)
Panadol 500 mg	9 (45%)
Azithromycin 500 mg, panadol 500 mg	1 (5%)
Physical examination	
Positive telogen hair pulling test	6 (30%)
Diffuse hair thinning	6 (30%)
Positive telogen hair pulling test, diffuse hair thinning	8 (40%)

Regarding the evaluation of hair thickness, it was significantly improved after 6 months of treatment since the mean + *SD* in T0 was 0.06 ± 0.01 and in T6 after 6 months of treatment was 0.08 ± 0.01 as shown in Table 2.

5 | DISCUSSION

TE is an alternation in the hair cycle characterized by excessive telogen hair loss. It has many triggering factors as stress, malnutrition, surgery, pregnancy, thyroid dysfunction, and others leading to generalized hair loss from the entire scalp and if it is prolonged more than 6 months it will be chronic TE.[9]

The pandemic of COVID-19 became one of the stressors that the patients suffered from it and resulted in a different range of diseases including cutaneous manifestations in which TE is one of these manifestations.[4]

This study discusses the evaluation of the management of TE caused by COVID-19 by HFSCs micrografts injection from scalp tissues concerning changes in hair density after 3 months of treatment (T3) and at the 6 months follow-up (T6). All the enrolled patients completed 6 months follow-up.

These results agreed with the study of Gentile et al. who stated that hair thickness, density, and tensile strength significantly improved with the use of HFSC injection in the scalp for the treatment of different types of alopecia.[10]

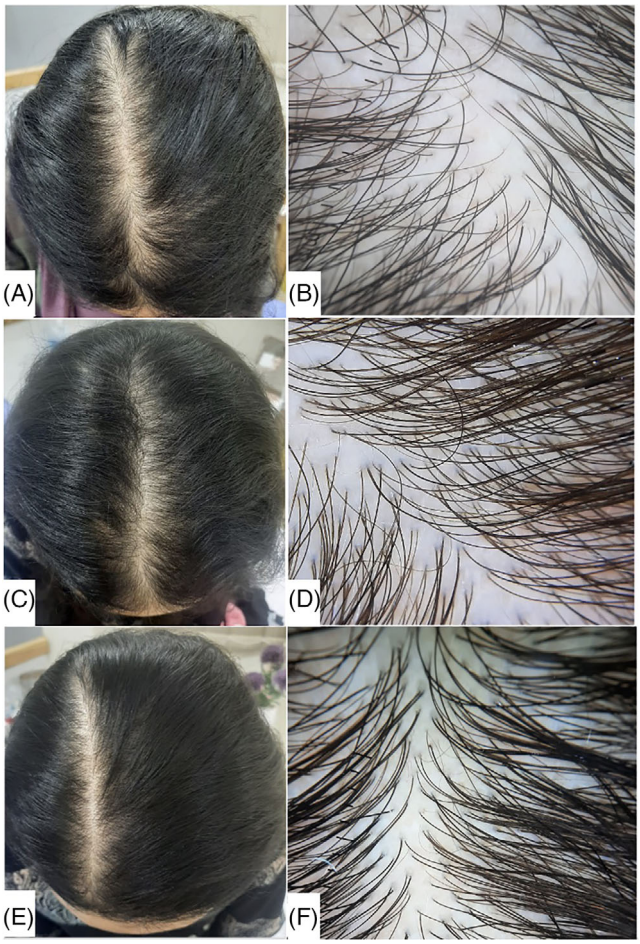

FIGURE 1 A 35 years old female patient with: (A) Hair thinning with reduced density at T0. (B) Trichoscopic examination showing hair thinning at T0. (C) Improvement of hair density and thickness at T3. (D) Trichoscopic examination showing improvement of hair density and thickness at T3. (E) Marked improvement of hair density and thickness at T6. (F) Trichoscopic examination showing marked improvement of hair density and thickness at T6

Fat tissue and scalp tissue could be sources of adult stem cells. The fat tissue contains a great number of mesenchymal stem cells and could be collected using a minimally aggressive procedure as gentle liposuction.[11] Adipose-derived mesenchymal stem cells and stromal vascular fraction cells are vital for the activity of the epidermal stem cells in the scalp, through the release of several growth factors. The vascular endothelial growth factor stimulates hair growth while the platelet derived-growth factor prompts the anagen stage, and insulin-like growth factor-1 controls the hair growth cycle.[11]

In addition, it is likely that the anti-inflammatory and immunomodulatory properties of platelet-rich plasma or dermal and progenitor stem cells, as in the HFSC, may favor hair regrowth.[12]

Yu et al.[13] illustrated that human hair follicles contain a stem cell population that may give rise to various types of cells as neurons, melanocytes, and even smooth muscle cells in the induction medium. Their information demonstrates that Oct4-positive cells, belonging to the family of pluripotent cells of the developing embryo, are available in the human epidermis, and the majority of them are situated in the hair follicles. These cells display promising plasticity in in vivo and ex vivo conditions, making them candidates for both cell engineering as well as cell replacement therapies.[13]

In agreement with Gentile et al.[8] scalp tissue was selected as the source of (HFSCs) micrograft as the scalp is very rich in hair follicles, and it is easily accessible. The stem cells in the bulge of this follicle-rich site are critical ensuring a good therapeutic response.

The biopsies were taken from the area behind the ear as it is a hidden site where no scar tissue -even with the use of a very small 2 mm punch- would present a concern to the patients.

Zari[14] demonstrated the role of autologous cellular micrografts in male and female androgenetic alopecia and concluded that it has promising results in the treatment of AGA. Meanwhile, Gentile et al.[15] clarified the clinical and trichoscopic effects of micrograft scalp infusion in males and females affected by androgenetic alopecia with promising results in their treatment.

At the clinical level in the current study, HFSC was used to treat patients with TE and those patients showed hair regrowth and a positive response to treatment with HFSC. The patients did not complain of any side effects or pain during the procedures.

TABLE 2 Comparison between the three studied periods according to hair density and hair thickness ($n = 20$)

	Baseline	After 3 months of treatment	After 6 months of treatment	F	*p*
Hair density/cm^2					
Mean ± *SD*	184.1 ± 40.9	190.4 ± 38.8	192.9 ± 39.6	21.663*	<0.001*
Median (min.–max.)	198 (106–228.5)	201 (123–238.5)	202 (123–259)		
Sig. bet. periods.	$p_1 < 0.001$*,	$p_2 < 0.001$*	$p_3 = 0.103$		
Hair thickness (mm)					
Mean ± *SD*	0.06 ± 0.01	0.08 ± 0.01	0.08 ± 0.01	36.087*	<0.001*
Median (min.–max.)	0.06 (0.05–0.08)	0.08 (0.06–0.10)	0.08 (0.06–0.10)		
Sig. bet. periods	$p_1 < 0.001$*	$p_2 < 0.001$*	$p_3 = 0.076$		

Note: F: F test (ANOVA) with repeated measures, Sig. bet. periods was done using Post Hoc Test (adjusted Bonferroni). p: *p*-value for comparing between the studied periods. p_1: *p*-value for comparing between Baseline and After 3 months of treatment. p_2: *p*-value for comparing between Baseline and After 6 months of treatment. p_3: *p*-value for comparing between After 3 months of treatment and after 6 months of treatment.
*Statistically significant at $p \leq 0.05$.

6 | LIMITATIONS

The study was conducted on 20 patients. This number of patients is relatively small and may be considered as a limitation of the current study.

7 | CONCLUSION

The results of this study showed that HFSC could be considered as a safe and effective therapeutic method in cases with TE due to the significant improvement of hair density and thickness with minimal side effects. Further long-term studies are recommended to evaluate the prognosis of TE associated with COVID-19 infection.

AUTHOR CONTRIBUTIONS

Soha Abdalla Hawwam: Designed the study and suggested the conception of the work and shared in the conduction, writing, and supervision. Mayada Ismail: Contributed in the clinical work and in the literature review. Esraa E. Elhawary: Contributed in the clinical work, data collection and analysis, writing and critical review and is the corresponding author.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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