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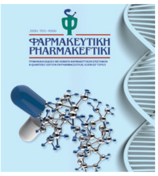

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Investigating DNA methylation patterns in hair samples of patients with COVID-19-related acute telogen effluvium

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ABSTRACT

This study has investigated the association between acute telogen effluvium and global DNA methylation in female patients recovering from coronavirus disease 2019 (COVID-19). In a cross-sectional case-control design, 100 participants were enrolled: 50 women presenting with post-COVID-19 hair loss and 50 age-matched healthy controls. Samples were obtained from patients attending consultant physician clinics at the Hilla Teaching Hospital and the Al-Imam Al-Sadeq Teaching Hospital between November 2022 and May 2023. Hair specimens were collected, DNA was extracted, and global methylation levels were quantified using liquid chromatography–mass spectrometry. A correlation was observed between age and the likelihood of hair loss; however, no statistically significant differences in DNA methylation levels were detected between the study groups. These findings suggest that while age may influence susceptibility to post-COVID-19 telogen effluvium, global DNA methylation does not appear to play a major role. Further research is warranted in order to elucidate the contribution of epigenetic mechanisms in post-viral hair loss syndromes.

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1. Introduction

The outbreak of the coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to a range of chronic sequelae[1,2], including hair loss – specifically, acute telogen effluvium (ATE). ATE has been observed in individuals exposed to multiple stressors, including viral infections, and is frequently reported to occur following COVID-19. Emerging evidence implicates epigenetic modifications, particularly DNA methylation (DNAm), in the pathophysiology of ATE. DNAm refers to the enzymatic addition of a methyl group to cytosine residues within DNA, thereby modulating gene expression without altering the underlying nucleotide sequence[3].

Epigenetics encompass heritable changes in gene expression that occur independently of alterations in DNA sequence. DNAm is a key epigenetic mechanism, wherein DNA methyltransferases (DNMTs) catalyse the covalent attachment of a methyl group to the 5′-carbon of cytosine residues, typically resulting in transcriptional silencing[4]. The viral perturbation of DNAm may disrupt immune regulation and contribute to host pathology[5]. For example, aberrant DNAm patterns in the angiotensin-converting enzyme 2 (ACE2) promoter have been shown to influence ACE2 expression; a critical determinant of SARS-CoV-2 cellular entry[6]. Notably, SARS-CoV-2 has been identified as a potent modulator of DNAm, with methylation changes persisting well beyond the acute phase of infection[3]. DNAm alterations in leukocytes have been shown to remain dysregulated for up to 12 months post-recovery, suggesting a role in the sustained immune dysregulation observed in post-acute COVID-19 syndrome.

This study aimed at investigating the relationship between hair loss and DNAm, specifically the ratio of 5-methylcytosine to adenine, in female Iraqi patients recovering from COVID-19.

2. Methodology

This study was conducted at the Department of Biochemistry, College of Pharmacy, University of Babylon, Hillah, Iraq. A total of 100 female participants aged 17–45 years were enrolled, comprising two groups: 50 women diagnosed with ATE following COVID-19 and 50 healthy volunteers (controls) without a history of hair loss. Participants were recruited from consultant physician clinics at the Hilla Teaching Hospital and the Al-Imam Al-Sadeq Teaching Hospital between November 2022 and May 2023. Hair samples were collected for DNA extraction, and global DNAm levels were quantified by using liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). The analysis focused on the ratio of 5-methylcytosine to adenine as a proxy for DNAm activity. Spectrometric measurements were performed using the AB Sciex Triple Quadrupole 4500 System.

Ethical approval was obtained from the Babil Health Directorate (protocol number: BHD, CR-BC, 11-5-2022; approval date: 22 May 2022). Written informed consent was obtained from all participants in accordance with the principles of the Declaration of Helsinki. Statistical analyses were conducted using SPSS version 24.0. Data normality was assessed by using the Shapiro–Wilk and Kolmogorov–Smirnov tests. Normally distributed continuous variables are presented as mean ± standard deviation. Group comparisons were performed by using independent-samples *t*-tests or Mann–Whitney U tests, as appropriate. Statistical significance was defined as $p<0.05$.

3. Results and Discussion

A significant correlation was observed between age and the likelihood of post-COVID-19 hair loss (Table 1). The mean ± standard deviation of the recorded DNAm levels was 0.22 ± 0.02 in the patient group and 0.27 ± 0.03 in the control group ($p=0.35$; Table 1). Although variations in DNAm were noted, the difference was not statistically significant, thereby underscoring the complexity of epigenetic contributions to ATE in post-COVID-19 female patients. These findings suggest that while age may influence susceptibility to ATE, global DNAm does not appear to be a primary driver. The lack of statistical significance may reflect limitations in sample size or variability in DNA yield from hair specimens. Moreover, differences in sample integrity and DNA quality could have influenced methylation quantification.

Previous studies have demonstrated that COVID-19 can induce DNAm changes at CpG sites involved in immune regulation[7]. Inflammatory cytokines released during infection may alter DNMT

Table 1. Characteristics of the study participants; values expressed as mean ± standard deviation.

Variable	**Control**	**COVID-19 patients**	***p*-value**
Age (years)	31.9 ± 8.3	27.6 ± 8.6	0.011
5-methylcytosine intensity / adenine intensity ratio	0.27 ± 0.3	0.22 ± 0.2	0.35

activity, particularly during myeloid cell differentiation. COVID-19 patients exhibit hypomethylation of interferon-inducible genes compared to healthy individuals[8], potentially contributing to immune dysregulation and exacerbation of conditions such as ATE. It is important to note that most DNAm studies in COVID-19 patients rely on bulk tissue analyses, which may obscure cell type-specific methylation patterns due to limitations in single-cell sequencing technologies and associated costs[9]. Understanding these cellular-level alterations is essential for elucidating the mechanisms underlying ATE and other post-COVID-19 sequelae.

This study reinforces the need for further investigation into epigenetic factors that may influence long-term health outcomes following COVID-19. Insights into DNAm-mediated immune memory could inform novel therapeutic and vaccination strategies against SARS-CoV-2[10]. Epigenetic interventions may help restore immune homeostasis, mitigate hair loss symptoms, and enhance vaccine efficacy. Future research should explore the clinical utility of epigenetic modulators. Agents targeting DNAm pathways may support immune recovery and improve responses to COVID-19 vaccines[10]. Moreover, differential DNAm patterns between acute and convalescent phases may guide the development of immune-based therapies.

Finally, targeting inflammation may also alleviate ATE symptoms in recovered COVID-19 patients, who appear particularly susceptible[8]. An integrated approach combining immunomodulation and epigenetic therapy warrants urgent exploration.

Although this study advances understanding of DNAm and hair loss in post-COVID-19 females, further research is needed in order to identify specific genes and pathways implicated in ATE, with the goal of developing targeted interventions to reverse post-viral hair loss.

4. Conclusion

This study underscores the multifaceted relationship between DNAm and ATE in women recovering from COVID-19. While age was significantly associated with hair loss, no significant differences in global DNAm levels were observed between COVID-19 patients and controls. Although epigenetic mechanisms remain a promising avenue for therapeutic intervention, further studies are required in order to delineate their role in post-COVID-19 hair loss.

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Conflicts of interest

None exist.

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