Immunoglobulin E and Serum Interleukin-13 and Bacteria in Patients with Alopecia Areata

Anfal Frman[1].Ayad M Gaidan[2]

[1]*Iraq, College of Science, Tikrit Universit. Email: anfal.frman@st.tu.edu.iq*
[2]*Iraq, College of Science, Tikrit Universit. Email: Ayad.muqdad@tu.edu.iq*

KEYWORDS
Alopecia areata (AA), Immunoglobulin E ,IgE, Interleukin-13 , IL-13,Bacteri

ABSTRACT

Alopecia areata (AA) is a form of hair loss that does not result in permanent scars. The etiopathology of it is not completely understood. To evaluate the serum concentration of immunoglobulin E (IgE) and interleukin-13 (IL-13) in patients diagnosed with AA and determine the bacterial strain present in individuals with infections. The study comprised a sample of 60 women afflicted with alopecia areata and 30 women who were in good health, serving as controls.The levels of IgE and IL-13 in the serum were evaluated using an enzyme-linked immunosorbent assay test(ELISA). The microorganisms were identified by conventional techniques and verified using Vitek technology. for IgE showed highly significant differences (p value < 0.1) Between patients and the control group, Regarding IL-13, the results showed significant differences (p value < 0.05), Between patients and the control group, Regarding age As for IgE, there is no significant difference between patients in the three groups (p value > 0.05), but it is different from the control (p value < 0.05).IL-13 There are significant differences (p value < 0.05). Among adults, the level of interleukin is higher than that of middle and young people. The weight-related results demonstrated significant variability across patients (p value < 0.05), with obese individuals exhibiting higher levels of IGE and IL-13 compared to those of medium and underweight. Regarding, In relation to bacteria, the percentages were as stated S.epedermidis (50.98%) , (S.aureus33.33%) mixed , S.aureus + S.epedermidis , (9.8%) E.coli (1.96%) Pseudomonas aeruginosa(1.96 %) , Granulicatella elegans (1.96%) .Total is IgE and IL-13 increased in patients with alopecia areata, Regarding bacteria, we need other studies to prove their role in alopecia areata.

1. Introduction

Alopecia, often known as hair loss, occurs when the germinal matrix cells responsible for hair growth are unable to get nutrients from the dermal follicle papilla cells. This leads to improper hair growth and subsequent hair loss.[1]. Female hair loss is more prevalent than male hair loss due to the influence of sex hormones on the biological hair cycle. Fluctuations in hormone levels can be detected during menstruation, pregnancy, the use of contraceptives, and menopause. These factors undoubtedly impact the hair cycle's equilibrium by disturbing its inherent synchronisation. [2]. Immune alopecia includes (AA) and cicatricial alopecias alopecia areata) and non-immune alopecia includes Androgenetic alopecia (AGA) (due to the androgen hormone), Telogen effluvium (due to psychological stress, iron deficiency, childbirth, and weight loss) Trichotillomania (due to a psychological condition in which patients repeatedly pull their hair) Traction alopecia due to hairstyles[3].A typical, robust hair follicle undergoes a growth phase that lasts for several years before it is eventually replaced. The process consists of four primary developmental phases: anagen, catagen, telogen, and exogen. [4]. The anagen phase refers to the period during which the hair follicle is actively undergoing growth. It is typical for hair follicles to go through transient phases of non-growth when an individual undergoes brief periods of stress or illness. If the level of stress is not excessively high, the anagen phase persists for a period of 3-5 years until the club hair is fully developed.In a healthy scalp, the majority of hairs are in the anagen phase, Only 6-8% of hairs that have finished the anagen phase and are in the process of transitioning back to anagen remain. As soon as the anagen phase concludes, the catagen phase commences, lasting for roughly 10-13 days. In this phase, the hair follicle undergoes a transformation and becomes a dormant follicle, which is referred to as a telogen follicle. The telogen phase, which is the resting phase of the hair growth cycle, can persist for a maximum duration of three months. During this phase, the follicle discharges the hair strand (also known as shedding) and initiates the formation of a fresh hair strand. The process of hair strand detachment and the subsequent regeneration of the hair follicle is referred to as the exogen phase. [5]. At the end of the exogen phase, the anagen phase

starts once again.On average, around 100 hairs are lost each day. However, during the initial phases of hair loss disorders, this number is considerably greater since the regular hair development cycle is disrupted. The primary issue is a disruption to the anagen phase. [6].Alopecia areata (AA) is a long-lasting, complex, genetically influenced, and diverse condition that impacts the development of hair follicles in vulnerable individuals, leading to temporary and non-permanent hair loss that is difficult to anticipate[7]. Alopecia areata is a prevalent kind of hair loss in humans, characterized by an immunological response.Alopecia areata is the second most common form of non-scarring hair loss, following male and female pattern hair loss.There are various types of hair loss, which might include localized patches of hair loss or more widespread and complete loss of hair throughout all areas of the body with hair. The most prevalent kind of alopecia is patchy hair loss that specifically affects the scalp. Alopecia areata impacts approximately 2% of the overall population at some stage in their lifespan. [8]. Tyrosinase, as well as tyrosinase-related protein 1/2 (TRP1/2), are crucial enzymes involved in melanogenesis in melanocytes. These enzymes have been proposed as autoantigens in AA and are immunologically shielded from autoimmune responses during the anagen phase.[9-11]. The targeted hair follicles (HFs) are those in the anagen phase, actively producing melanin. These HFs have immunological tolerance due to various factors, such as the absence of major histocompatibility complex (MHC) class I in the proximal outer root sheath (ORS) and matrix cells, which is known as HF immune privilege (HF-IP). NKG2D-positive CD8-positive T cells are considered to be effector cells in the development of AA, and these cytotoxic T cells generate substantial quantities of interferon (IFN)-γ, which leads to the breakdown of HF-IP. IFN- γ is currently recognized as the primary cytokine responsible for triggering AA, making it classified as a type 1 inflammatory disease. Atopic dermatitis (AD) is a significant comorbidity of AA, characterized by type 2 inflammation. Nevertheless, our understanding of the immunological components of AA in connection to AD remains limited. A recent study found a notable rise in the levels of both type 1 and type 2 cytokines, including IL-13[12].

Interleukin-13 is a multifunctional cytokine involved in immune system regulation. Shares both functional and structural resemblances with interleukin-4. IL-13 functions as a signalling molecule that has a role in immune system processes, particularly in the initiation of allergic responses. Discovered in 1989, the proinflammatory cytokine IL-13 exhibits a wide range of effects. IL-13 plays a crucial role in regulating immunoglobulins (Ig), , anti-parasitic responses, inflammation, fibrogenesis, and allergic reactions. IL-13 can also be secreted as a precursor by granulocytes such as mast cells ,basophils, , or eosinophils, with IgE playing a significant part in this process. [13]. Immunoglobulin E, also known as IgE, is one of the five categories of immunoglobulins, alongside IgM, IgG, IgD, and IgA. IgE possesses a distinct chemical composition and serves several physiological roles, including defense against parasite infections, modulation of autoimmune processes, and safeguarding against venomous substances. Type I hypersensitivity reactions occur when mast and basophils are activated, leading to the production of Th2 responses[14].The human skin and hair follicles are acknowledged as locations where microorganisms colonize. The microbiota have a role in controlling the immune system of the host by interacting with immune cells, affecting the balance of the body and inflammation. Bacteria exert influence on immune responses by regulating the local inflammatory environment, the disruption of which can lead to the development of chronic inflammatory illnesses. The presence of changes in the microbiome of hair follicles in some inflammatory skin conditions indicates a potential connection between the development or continuation of these conditions and an imbalance in the microbial community. While the hair follicle infundibulum is a site of significant immunological interactions, the bulge and bulb regions are considered immune-privileged niches. Maintaining immune privilege is crucial for the growth and regeneration of hair. Inflammatory hair disorders such as primary cicatricial alopecia and alopecia areata are characterized by the collapse of immune privilege and the presence of inflammation[15]. The purpose of this study was to assess the levels of immunoglobulin E (IgE) and interleukin 13 (IL-13) in the blood serum of women diagnosed with AA, as well as identify the specific bacterial strain found in these women.

2. Materilas and Methods

After obtaining the approval of the Ethics Committee in the Department of Life Sciences at the College of Science, Tikrit University, and obtaining the approval of the Salah al-Din Health Department, consent was taken from all participants in the study, where 60 samples were collected from women with alopecia areata aged (15-50) who were They were diagnosed clinically by specialist doctors in the dermatology consultant at Tikrit Teaching Hospital from October 2023 to January 2024. The private information of each patient was recorded using a special questionnaire form. Then, blood samples were collected from the patients, and 30 control blood samples were collected from uninfected women aged (15-50). 3 ml of blood was taken and left to clot, after which the samples were centrifuged. The separated serum was stored at -20°C until examined. ELISA kits were used to evaluate the levels of total IL-13 and IgE(Bioassay Korea Company). For the purpose of diagnosing the bacteria present in the scalp of patients, swabs were taken from the scalp using a sterile cotton swab and then cultured on basic media (blood and macconkey agar) and then on diagnostic media. Biochemical tests were performed and Vitek technology was also used to confirm Diagnosis.

Statistical Analysis

The results were analyzed statistically by applying the statistical program MINITAB, VER-17, and the T-TEST and ANOVA tests were applied to determine the statistical differences between the groups included in the study. Duncan's multinomial test was also applied to determine the differences between the arithmetic means of the groups included in the test at a probability level of 0.05.

3. Results

for IgE showed highly significant differences (p value < 0.1) as it appears from the table that the average concentration in patients was 671, and in healthy people the average concentration was 536.Regarding IL-13, the results showed significant differences (p value < 0.05), as it appears from the table that the average concentration for patients was 44.2, and for controls, the average concentration was 55.7.

Table 1: Comparison between patients and control group regarding mean values of serum IgE and IL-13

Group	**Number**	**IgE mean ± SD**	**IL-13 mean ± SD**
P	60	671 ±46.3	44.2 ±9.6
C	30	536 ± 36.7	35.7 ± 6.3
p.value		0.014**	0.035*
test was used t-test IgE: Immunoglobulin E, IL-13: Interleukin-13, SD: Standard deviation			

Regarding age, the results showed statistically significant differences (P value < 0.05). Between patients and healthy people.As for IgE, there is no significant difference between patients in the three groups (p value > 0.05), but it is different from the control (p value < 0.05).IL-13 There are significant differences (p value < 0.05). Among adults, the level of interleukin is higher than that of middle and young people.

Table 2 :Association between IgE and IL-13 levels and the Age

Group	**Age**	**Number**	**IgE mean ± SD**	**IL-13 mean ± SD**
P	10-25	32	664.4±60.9a	45.29±9.78b
	26-40	24	676.8±42.2a	40.78±6.53b

	41-55	4	694±33.2a	55.6±7.3a
C		30	535.7±56.5b	35.74±6.33c
P-VALUE			0.036*	0.045*
Tests that were used Duncan's and F-test, SD: Standard deviation The Duncan test gave the highest value in the arithmetic mean (a), and if the next value is statistically different from it, we give it (b). The Duncan test says that similar letters mean that there is no significant difference between them.				

Regarding weight, the IgE level among those who suffer from obesity is higher than the average and those who are underweight, and there is no significant difference between them, and all of them have an IgE level higher than the control (p value < 0.05).IL_13 among those who suffer from obesity is higher than the average and those who are underweight, there is no significant difference between them, and all of them have an Il-13 level higher than the control.

Table3: Association between IgE and IL-13 levels and the Weight

Group	**WEIGHT**	**Number**	**IgE mean ± SD**	**IL-13 mean ± SD**
p	Fat	4	895±29.7a	68.3±9.8a
	Average	34	649.4±19.87b	41.83±6.15b
	underweight	22	664.4±29.23b	43.43±7.57b
c			535.7±23.65c	35.74±6.33c
P-VALUE			0.022*	0.010**
Tests that were used Duncan's and F-test, SD: Standard deviation The Duncan test gave the highest value in the arithmetic mean (a), and if the next value is statistically different from it, we give it (b). The Duncan test says that similar letters mean that there is no significant difference between them.				

Regarding bacteria Out of 60 people, 51 bacteria were isolated from them, and they were as follows

Bacteria	Number of isolates	Percentage
S.epedermidis	26	50.98
S.aureus	17	33.33
S.aureus+S.epedermidis	5	9.8
E.coli	1	1.96
Pseudomonas aeruginosa	1	1.96
granulicatella elegans	1	1.96

Discussion

Previous studies have examined the correlation between blood IgE levels and AA, yielding inconsistent findings.These results agreed with[16-18] Results varied with[19].The precise mechanism underlying the increase of IgE in AA remains unknown. Several cytokines regulate the synthesis of IgE. IL-7, IL-4 , IL-9, IL-6, and IL-13 promote the synthesis of IgE. On the other hand, IFN-γ and IL-10 suppress the production of IgE antibodies. The presence of high levels of IgE in instances of AA may be

attributed to an elevation in tumor necrosis factor (TNF)-α, which is recognized for its significant involvement in the development of AA. TNF-α is produced in epidermal keratinocytes, along with various other cytokines[20]. It is a highly effective inhibitor of cell growth[21] TNF-α can increase IgE levels by producing a micro-environment that is abundant in Th2 cytokines, specifically IL-4 and IL-13, which stimulate the process of IgE class switching[22].Furthermore, it has been discovered that individuals with AA possess remarkably elevated levels of B cell activating factor (BAFF), which is a member of the TNF family and is produced by cells of the myeloid lineage[23]. The production of BAFF is believed to be induced by IFN-γ, which is known to be elevated in individuals with severe AA. CD40 over-expression may also contribute to the rise of IgE levels in patients with AA. This molecule belongs to a family of surface molecules that are similar to the receptor for nerve growth factor. It is found on B cells[24, 25]. Proposed that the activation of CD40 alone could augment the generation of IgE from cells that produce IgE in vivo. CD40 was also detected in the hair structures, specifically in the dermal papilla of AA lesions, which supports the idea that it may contribute to increased levels of serum IgE in certain AA patients[26].Genetic linkage provides more support for the hypothesis that increased IgE levels in individuals of African ancestry (AA) may have another underlying cause. Several genetic loci and specific genes have been linked to the cause of allergy diseases[27]. The prevalence of atopic illnesses in patients with AA ranges from 1% to 52%[28].Studies have shown that AA tends to progress more severely when accompanied by atopy, starting at an earlier age and lasting for a longer period of time. Additionally, it has been found that AA does not respond well to treatment in these cases[29].The discovery of a correlation between atopy and the 11q13 chromosomal locus was made by[30]. For IL-13, the results agreed with[31, 32]. Results varied with[17, 33].L-3/IL14 induces the development of allergic dermatitis by facilitating the differentiation of Th2 cells, impairing the activities of the skin barrier, and encouraging the generation of IgE antibodies. IL-4/IL-13 diminishes the functions of the epidermal barrier via controlling the expression of the filaggrin gene in keratinocytes, resulting in heightened vulnerability to infection. [34]. Additionally, an elevated level of Th2 cell activity is linked to a reduction in the activity of Th1 cell cytokines, which are essential for combating infections and promoting cell proliferation. [35, 36]. Nevertheless, AA has lately been associated with atopy, which refers to Th2 cell-mediated illnesses. IL-13, the primary agent of Th2 cells, exhibited a notable increase in both AA and AD skin lesions. [37]. In addition to the epidemiological and molecular connections between AA and AD, research has identified a robust genetic correlation between IL-4/IL-13 and AA [38].Regarding age , As for IgE, there are no significant differences between patients with regard to their ages between the three groups, but there is a difference from the control. This result agreed with[39-41]. This result differed with[17, 33].Each allergen shows a certain trend with age[42].As for interleukin 13, the results showed that there were statistically significant differences among adults, as the level of interleukin was higher than among the middle group and young people. These results differed with[36], These results agreed with[43].Alopecia areata affects individuals of all age groups and its prevalence grows with age, reaching 80% at the age of 40 and 40% at the age of 20[44].Individuals aged 18 to 44 have the highest annual prevalence of AA[45]. Any approach to the age group included in our study. [46] reached a conclusion. Alopecia areata is not influenced by age; nevertheless, a study conducted by [47] revealed that the incidence of alopecia areata tends to rise as individuals grow older.. Recent research conducted by[48] has demonstrated that age does not have an impact on alopecia areata. Opinions have varied because of the diverse causes of alopecia areata that have been examined. Age can influence certain causes, whereas others are not influenced by age.Concerning weight ,The weight-related findings revealed a notable disparity across patients, with individuals who were obese exhibiting a larger percentage of IGE and IL-13 compared to those with average and low body weight.For IgE This result agreed with[49, 50] Obesity can be included in the list of factors that are linked to elevated IgE concentrations[50] Additional research is required to examine the processes that are responsible for this connection For interleukin 13 These results agreed with[51, 52]and[53] He found that there is a clear correlation between the growth of fat mass and the overproduction of IL-13. This conclusion is backed by the fact that hypertrophic and hyperplasic adipocytes enhance their capacity to synthesise IL-13 Multiple studies have indicated that there is a greater occurrence of obesity in individuals with

AA[54, 55] Obesity is marked by chronic inflammation at low levels. In obese individuals, the adipose tissues contain enlarged adipocytes that produce a large amount of inflammatory adipokines, such as leptin. Additionally, there is an excessive presence of inflammatory M1 macrophages, CD8+ and CD4+ T cells that produce IFN-γ, and Th17 cells in the adipose tissues of obese subjects. Furthermore, the synthesis of anti-inflammatory adipokines, such as Tregs, adiponectin, andM2 macrophages, is reduced in the adipose tissues of individuals who are obese. The adipose tissues can release inflammatory cytokines and adipokines, which can then circulate in the bloodstream and reach peripheral sites. Specifically, IFNγ has the potential to cause type 1 autoimmune disorders and stimulate the production of MHC class I/II in hair follicles, hence initiating AA[56].Regarding bacteria, These results agreed with the study conducted by[57] which shown a notable rise in the prevalence of Staphylococcus aureus among individuals with alopecia areata. These results agreed with[58] which appeared to include nearly identical species, albeit in varying amounts. The findings of[59] corroborated the isolation of Pseudomonas aeruginosa and E. coli bacteria, which were found to be associated with alopecia areata. The findings of[60] contrasted with the present data, since they demonstrated a reduction in the Staphylococcus family among individuals with alopecia areata. Staphylococcus epidermidis and Staphylococcus aureus, both belong to the genus Staphylococcus, are frequently seen on the skin[61] S. epidermidis typically inhabits the human epidermis, however it has the potential to induce severe illnesses in certain individuals.Similarly, the microbiota Staphylococcus aureus, which is frequently responsible for skin and systemic infections, can be present in the skin of approximately 10e20% of healthy adults without causing harm, acting as a benign commensal.However, around 90% of individuals with atopic dermatitis (AD) have S. aureus bacteria on their skin lesions, and this higher presence of bacteria is linked to worsening of the condition. Patients with AD have a dysbiotic microbiome present in their skin. Nevertheless, the process via which the typical skin microbiota shifts from a balanced condition to dysbiosis, as well as the role of the abnormal microbiota in the development of AD, is not yet fully understood[62].The study conducted by [63]. investigated the colonisation and adhesion of E. coli and P. aeruginosa on hair shafts. Researchers discovered that E. coli exclusively occupied the periphery of the cuticle scales, whereas P. aeruginosa formed a biofilm. The bacteria Pseudomonas aeruginosa and E. coli were identified and associated with alopecia areata by [59] . Therefore, in theory, in addition to staphylococci, bacteria like E. coli P. aeruginosa and can be transmitted through human hair, potentially leading to illnesses. Therefore, studying the interaction between bacteria and human hair is of conceptual significance and can provide light on potential novel functions of hair shafts in the intricate interplay between skin and bacteria[63].Moreover, hair shafts are continuously exposed to the surroundings and might serve as a potential habitat for bacteria because of their grooved cuticle surface and elongated, slender form. Nevertheless, the bacterial adhesion and colonization of hair have not been assessed[63].

The reference is from[64] They presented, for the first time, the alteration in microbiota in individuals with alopecia areata in comparison to healthy. Abundant scientific literature supports a robust correlation between skin illnesses and microbial imbalance.[65]. The understanding of the specific involvement of bacteria in the development of various forms of alopecia is still in its nascent stage. [15].The bacteria residing in healthy hair follicles closely resemble the microbiota found in the normal skin.[66]. The phylum Proteobacteria is characterised by its high abundance, while the phylum Firmicutes includes the genera Staphylococcus and Streptococcus. Within the phylum Actinobacteria, the families Propionibacteriaceae and Corynebacteriaceae are particularly notable. [67, 68] These microorganisms present in healthy hair follicles stimulate the production of cytokines that contribute to initiating and maintaining the immune response, prevent the colonization of pathogens. [69], and influence tissue repair and reduce Inflammation[70]. However, there is doubt regarding the impact of the imbalance in the microorganisms residing in the hair follicles on the immunological milieu and the hair follicles' growth and regeneration cycle[60].This study does not definitively determine if bacteria directly cause alopecia or if they occur as a result of it. The presence of bacterial and immunological chemicals, as well as alterations in microorganisms within the hair follicles, can impact the inflammatory processes and modulation of immune responses in the skin. There is peribulbar irritation

present. Furthermore, hair follicles are particularly susceptible to harm while in the growth phase. The growth of hair is contingent upon a robust and resilient intellectual property (IP) surrounding the bulb. [71, 72]. Therefore, the epithelium around the bulge may be exposed to external stimuli (bacterial products, metabolites, bacteria) or internal pro-inflammatory such as immune system signals that It is provoked by bacteria. As a result, hair follicle microorganisms may be an effective factor in causing alopecia areata. Patients with alopecia areata have been observed to have a greater incidence of atopic dermatitis. [73]. The functioning of T-cells Th2 and Th17 plays a crucial role in the development of atopic dermatitis. This functionality can be affected by the skin microbiota. [74]. Polak-Witka et al. proposed the hypothesis that dysbacteriosis in alopecia areata and atopic dermatitis may impair the integrity of hair follicles and disrupt the skin barrier function in atopic dermatitis, potentially allowing bacterial antigens to penetrate deeper into the hair follicles. Moreover, the compromised integrity of the skin's protective barrier in atopic dermatitis may facilitate the infiltration of bacterial antigens into the deeper regions of the hair follicle. [69].Granulicatella elegans Recognised as a constituent of the indigenous microbial community in the human oral cavity and urogenital and intestinal tracts. Although rarely implicated in disease, they have been found to be responsible for isolated cases of central nervous system infections, keratitis, endophthalmitis, sinusitis, otitis, prostatitis, cholangitis, arthritis, osteomyelitis and lumbar spine infection, but the most frequently reported syndromes due to Abiotrophia and Granulicatella species are known to be bacteremia, septicemia and endocarditis[75] . In addition, there are a few reports of involvement of these as pathogens in brain and pancreatic abscesses, as well as in osteomyelitis and wound infections[76]. We assert that we are the first discoverers of this bacteria on the scalp, and further investigations are required to substantiate its potential to induce skin ailments such as alopecia areata.

Conclusions

This study provides evidence that people with alopecia areata experience a rise in total (IgE) and (IL-13).There is compelling evidence indicating an imbalance in the microbiome of individuals with alopecia areata; nevertheless, its causality has not been definitively established. The etiology of these changes remains uncertain, as it is unclear whether they are the fundamental etiological factor or a subsequent manifestation of the disease. Nevertheless, existing research indicates that bacteria may have a role in the development of the disease. Alopecia areata.

Reference

[1] D. H. Marks *et al.*, "The medical and psychosocial associations of alopecia: recognizing hair loss as more than a cosmetic concern," *American journal of clinical dermatology*, vol. 20, pp. 195-200, 2019.

[2] Y. J. Bhat, I. Latif, and I. Hassan, "Female pattern hair loss—An update," *Indian Dermatology Online Journal*, vol. 11, no. 4, pp. 493-501, 2020.

[3] L. Malki *et al.*, "Variant PADI3 in central centrifugal cicatricial alopecia," *New England Journal of Medicine*, vol. 380, no. 9, pp. 833-841, 2019.

[4] D. Wall, N. Meah, N. Fagan, K. York, and R. Sinclair, "Advances in hair growth," *Faculty reviews*, vol. 11, 2022.

[5] K. S. Houschyar *et al.*, "Molecular mechanisms of hair growth and regeneration: current understanding and novel paradigms," *Dermatology*, vol. 236, no. 4, pp. 271-280, 2020.

[6] N. Sadgrove, S. Batra, D. Barreto, and J. Rapaport, "An updated etiology of hair loss and the new cosmeceutical paradigm in therapy: Clearing 'the big eight strikes'," *Cosmetics*, vol. 10, no. 4, p. 106, 2023.

[7] S. D. Jadeja and D. J. Tobin, "Autoantigen discovery in the hair loss disorder, alopecia areata: implication of post-translational modifications," *Frontiers in Immunology*, vol. 13, p. 890027, 2022.

[8] C. H. Pratt, L. E. King, A. G. Messenger, A. M. Christiano, and J. P. Sundberg, "Alopecia areata (Primer)," *Nature Reviews: Disease Primers*, vol. 3, no. 1, 2017.

[9] A. Gilhar, B. Assy, R. Shalaginov, S. Serafimovich, M. Landau, and R. S. Kalish, "Melanocyte-associated T cell epitopes can function as autoantigens for transfer of alopecia areata to human scalp explants on Prkdcscid mice," *Journal of*

investigative dermatology, vol. 117, no. 6, pp. 1357-1362, 2001.

[10] K. McElwee *et al.*, "What causes alopecia areata? Section Editors: Ralf Paus, Manchester/Lübeck and Raymond Cho, San Francisco," *Experimental dermatology*, vol. 22, no. 9, pp. 609-626, 2013.

[11] R. Paus, A. Slominski, and B. Czarnetzki, "Is alopecia areata an autoimmune-response against melanogenesis-related proteins, exposed by abnormal MHC class I expression in the anagen hair bulb?," *The Yale journal of biology and medicine*, vol. 66, no. 6, p. 541, 1993.

[12] T. Ito, R. Kageyama, S. Nakazawa, and T. Honda, "Understanding the significance of cytokines and chemokines in the pathogenesis of alopecia areata," *Experimental Dermatology*, vol. 29, no. 8, pp. 726-732, 2020.

[13] E. Roeb, "Interleukin-13 (IL-13)—A Pleiotropic Cytokine Involved in Wound Healing and Fibrosis," *International Journal of Molecular Sciences*, vol. 24, no. 16, p. 12884, 2023.

[14] I. Sanz, S. A. Jenks, and K. S. Cashman, "Structure and Derivation of Autoantibodies," in *Dubois' Lupus Erythematosus and Related Syndromes*: Elsevier, 2019, pp. 340-354.

[15] A. Constantinou, V. Kanti, K. Polak-Witka, U. Blume-Peytavi, G. M. Spyrou, and A. Vogt, "The Potential Relevance of the Microbiome to Hair Physiology and Regeneration: The Emerging Role of Metagenomics," *Biomedicines*, vol. 9, no. 3, p. 236, 2021. [Online]. Available: https://www.mdpi.com/2227-9059/9/3/236.

[16] E. A. Attia, D. El Shennawy, and A. Sefin, "Serum interleukin-4 and total immunoglobulin E in nonatopic alopecia areata patients and HLA-DRB1 typing," *Dermatology research and practice*, vol. 2010, 2010.

[17] S. Li *et al.*, "Allergy to dust mites may contribute to early onset and severity of alopecia areata," *Clinical and experimental dermatology*, vol. 40, no. 2, pp. 171-176, 2015.

[18] Y. Zhao, B. Zhang, S. Caulloo, X. Chen, Y. Li, and X. Zhang, "Diffuse alopecia areata is associated with intense inflammatory infiltration and CD8+ T cells in hair loss regions and an increase in serum IgE level," *Indian Journal of Dermatology, Venereology and Leprology*, vol. 78, p. 709, 2012.

[19] Y. Tokura, K. Sugita, K. Kabashima, T. Ito, and H. Yagi, "Alopecia universalis associated with impaired interleukin-4 production and low serum IgE level," *Journal of the American Academy of Dermatology*, vol. 57, no. 2, pp. S22-S25, 2007.

[20] J. Ansel *et al.*, "Cytokine modulation of keratinocyte cytokines," *Journal of Investigative Dermatology*, vol. 94, no. 6, pp. s101-s107, 1990.

[21] F. W. Symington, "Lymphotoxin, tumor necrosis factor, and gamma interferon are cytostatic for normal human keratinocytes," *Journal of investigative dermatology*, vol. 92, no. 6, pp. 798-805, 1989.

[22] J. Altin, C. Shen, and A. Liston, "Understanding the genetic regulation of IgE production," *Blood reviews*, vol. 24, no. 4-5, pp. 163-169, 2010.

[23] Y. Kuwano *et al.*, "Serum BAFF and APRIL levels in patients with alopecia areata," *Journal of dermatological science*, vol. 50, no. 3, pp. 236-239, 2008.

[24] J. B. Splawski, S. M. Fu, and P. E. Lipsky, "Immunoregulatory role of CD40 in human B cell differentiation," *Journal of immunology (Baltimore, Md.: 1950)*, vol. 150, no. 4, pp. 1276-1285, 1993.

[25] L. Zhang, A. Weetman, P. Friedmann, and D. Oliveira, "HLA associations with alopecia areata," *Tissue antigens*, vol. 38, no. 3, pp. 89-91, 1991.

[26] M. Sato-Kawamura, S. Aiba, and H. Tagami, "Strong expression of CD40, CD54 and HLA-DR antigen and lack of evidence for direct cellular cytotoxicity are unique immunohistopathological features in alopecia areata," *Archives of dermatological research*, vol. 294, pp. 536-543, 2003.

[27] W. Cookson, "Genetics and genomics of asthma and allergic diseases," *Immunological reviews*, vol. 190, no. 1, pp. 195-206, 2002.

[28] S. Kaur, V. K. Sharma, L. Kumar, and B. Kumar, "Atopy and alopecia areata in North Indians," *Indian Journal of Dermatology, Venereology and Leprology*, vol. 68, p. 267, 2002.

[29] W. V. Shellow, J. E. EDWARDS, and J. Y. KOO, "Profile of alopecia areata: a questionnaire analysis of patient and family," *International journal of dermatology*, vol. 31, no. 3, pp. 186-189, 1992.

[30] R. Young *et al.*, "Confirmation of genetic linkage between atopic IgE responses and chromosome 11q13," *Journal of medical genetics*, vol. 29, no. 4, pp. 236-238, 1992.

[31] M. Tembhre and V. Sharma, "T-helper and regulatory T-cell cytokines in the peripheral blood of patients with active alopecia areata," *British Journal of Dermatology*, vol. 169, no. 3, pp. 543-548, 2013.

[32] T. Song *et al.*, "An integrated model of alopecia areata biomarkers highlights both TH1 and TH2 upregulation," *Journal of Allergy and Clinical Immunology*, vol. 142, no. 5, pp. 1631-1634. e13, 2018.

[33] M. Kerkhof, A. Dubois, D. Postma, J. Schouten, and J. De Monchy, "Role and interpretation of total serum IgE measurements in the diagnosis of allergic airway disease in adults," *Allergy*, vol. 58, no. 9, pp. 905-911, 2003.

[34] M. D. Howell *et al.*, "Cytokine modulation of atopic dermatitis filaggrin skin expression," *Journal of Allergy and Clinical Immunology*, vol. 124, no. 3, pp. R7-R12, 2009.

[35] A. Wollenberg, S. Wetzel, W. H. Burgdorf, and J. Haas, "Viral infections in atopic dermatitis: pathogenic aspects and clinical management," *Journal of Allergy and Clinical Immunology*, vol. 112, no. 4, pp. 667-674, 2003.

[36] K. Kaminishi, Y. Soma, Y. Kawa, and M. Mizoguchi, "Flow cytometric analysis of IL-4, IL-13 and IFN-γ expression in peripheral blood mononuclear cells and detection of circulating IL-13 in patients with atopic dermatitis provide evidence for the involvement of type 2 cytokines in the disease," *Journal of dermatological science*, vol. 29, no. 1, pp. 19-25, 2002.

[37] M. Suárez-Fariñas *et al.*, "Alopecia areata profiling shows TH1, TH2, and IL-23 cytokine activation without parallel TH17/TH22 skewing," *Journal of Allergy and Clinical Immunology*, vol. 136, no. 5, pp. 1277-1287, 2015.

[38] R. C. Betz *et al.*, "Genome-wide meta-analysis in alopecia areata resolves HLA associations and reveals two new susceptibility loci," *Nature communications*, vol. 6, no. 1, p. 5966, 2015.

[39] G. Di Lorenzo *et al.*, "A study of age-related IgE pathophysiological changes," *Mechanisms of ageing and development*, vol. 124, no. 4, pp. 445-448, 2003.

[40] O. A. Bakry, R. M. A. El Shazly, M. A. Basha, and H. Mostafa, "Total serum immunoglobulin E in patients with alopecia areata," *Indian dermatology online journal*, vol. 5, no. 2, pp. 122-127, 2014.

[41] N. A. Elsherif, S. A. El-Dibany, and A. S. Greiw, "Study of total serum immunoglobulin E level and prevalence of atopy in alopecia areata patients," *Iranian Journal of Dermatology*, vol. 24, no. 2, pp. 80-84, 2021.

[42] M. De Amici and G. Ciprandi, "The age impact on serum total and allergen-specific IgE," *Allergy, asthma & immunology research*, vol. 5, no. 3, p. 170, 2013.

[43] M. S. Jebur and A. M. Saud, "Serum levels of total IgE and interleukin-13 in a sample of allergic asthma patients in Baghdad," *Iraqi Journal of Science*, pp. 3208-3214, 2020.

[44] A. C. Villasante Fricke and M. Miteva, "Epidemiology and burden of alopecia areata: a systematic review," *Clinical, cosmetic and investigational dermatology*, pp. 397-403, 2015.

[45] A. Mostaghimi *et al.*, "Trends in prevalence and incidence of alopecia areata, alopecia totalis, and alopecia universalis among adults and children in a US employer-sponsored insured population," *JAMA dermatology*, vol. 159, no. 4, pp. 411-418, 2023.

[46] K. H. Safavi, S. A. Muller, V. J. Suman, A. N. Moshell, and L. J. Melton III, "Incidence of alopecia areata in Olmsted County, Minnesota, 1975 through 1989," in *Mayo Clinic Proceedings*, 1995, vol. 70, no. 7: Elsevier, pp. 628-633.

[47] S. A. Mirzoyev, A. G. Schrum, M. D. Davis, and R. R. Torgerson, "Lifetime incidence risk of Alopecia Areata estimated at 2.1 percent by Rochester Epidemiology Project, 1990–2009," *The Journal of investigative dermatology*, vol. 134, no. 4, p. 1141, 2014.

[48] M. A. Aljabali and L. Kuts, "Serum levels of IL-2 and IL-17A are related to clinical type and severity of alopecia areata," *Wiad Lek*, vol. 75, pp. 263-267, 2022.

[49] M. Garozzo *et al.*, "RELATION OF BODY MASS INDEX WITH IgE LEVELS, ALLERGIC SENSITIZATION AND LUNG FUNCTION IN ASTHMATIC CHILDREN: OUR EXPERIENCE AND REVISION OF LITERATURE," *Journal of Biological Regulators and Homeostatic Agents*, vol. 29, no. 2 Suppl 1, pp. 89-95, 2015.

[50] I. Carballo *et al.*, "Factors influencing total serum IgE in adults: the role of obesity and related metabolic disorders,"

International Archives of Allergy and Immunology, vol. 182, no. 3, pp. 220-228, 2021.

[51] S. Matsui *et al.*, "Interleukin-13 and its signaling pathway is associated with obesity-related colorectal tumorigenesis," *Cancer science*, vol. 110, no. 7, pp. 2156-2165, 2019.

[52] T. K. Nestvold, E. W. Nielsen, J. K. Ludviksen, H. Fure, A. Landsem, and K. T. Lappegård, "Lifestyle changes followed by bariatric surgery lower inflammatory markers and the cardiovascular risk factors C3 and C4," *Metabolic syndrome and related disorders*, vol. 13, no. 1, pp. 29-35, 2015.

[53] C. P. Martínez-Reyes *et al.*, "Serum levels of interleukin-13 increase in subjects with insulin resistance but do not correlate with markers of low-grade systemic inflammation," *Journal of diabetes research*, vol. 2018, 2018.

[54] R. R. Conic, S. Chu, N. Tamashunas, G. Damiani, and W. Bergfeld, "Prevalence of cardiac and metabolic diseases among patients with alopecia areata," *Journal of the European Academy of Dermatology & Venereology*, vol. 35, no. 2, 2021.

[55] H. R. Bae *et al.*, "IFNγ is a key link between obesity and Th1-mediated autoimmune diseases," *International journal of molecular sciences*, vol. 22, no. 1, p. 208, 2020.

[56] T. Hagino *et al.*, "Dietary habits in Japanese patients with alopecia areata," *Clinical, Cosmetic and Investigational Dermatology*, pp. 1579-1591, 2021.

[57] E. Wang, J. S.-S. Lee, and T. H. Hee, "Is Propionibacterium acnes associated with hair casts and alopecia?," *International journal of trichology*, vol. 4, no. 2, pp. 93-97, 2012.

[58] M. A. Abdala, S. Abdel, S. M. Ahmed, and I. E. M. T. Eldin, "Isolation and Identification of Some Microorganisms that cause Abnormal Hair Loss (Baldness)," *International Journal of Science and Research (IJSR) Vol*, vol. 6, pp. 1973-1982, 2015.

[59] M. Morales-Sánchez, M. Domínguez-Gómez, F. Jurado-Santa Cruz, and M. Peralta-Pedrero, "Immunization and bacterial pathogens in the oropharynx as risk factors for alopecia areata," *Actas Dermo-Sifiliográficas (English Edition)*, vol. 101, no. 5, pp. 437-443, 2010.

[60] P. Sánchez-Pellicer, L. Navarro-Moratalla, E. Núñez-Delegido, J. Agüera-Santos, and V. Navarro-López, "How our microbiome influences the pathogenesis of alopecia Areata," *Genes*, vol. 13, no. 10, p. 1860, 2022.

[61] M. Otto, "Staphylococcus epidermidis—the'accidental'pathogen," *Nature reviews microbiology*, vol. 7, no. 8, pp. 555-567, 2009.

[62] Y. Yamazaki, Y. Nakamura, and G. Núñez, "Role of the microbiota in skin immunity and atopic dermatitis," *Allergology International*, vol. 66, no. 4, pp. 539-544, 2017.

[63] S. K. Kerk, H. Y. Lai, S. K. Sze, K. W. Ng, A. Schmidtchen, and S. S. Adav, "Bacteria display differential growth and adhesion characteristics on human hair shafts," *Frontiers in microbiology*, vol. 9, p. 393407, 2018.

[64] D. Pinto, E. Sorbellini, B. Marzani, M. Rucco, G. Giuliani, and F. Rinaldi, "Scalp bacterial shift in Alopecia areata," *PLoS One*, vol. 14, no. 4, p. e0215206, 2019.

[65] E. J. Won, H. H. Jang, H. Park, and S. J. Kim, "A potential predictive role of the scalp microbiome profiling in patients with alopecia areata: Staphylococcus caprae, Corynebacterium, and Cutibacterium species," *Microorganisms*, vol. 10, no. 5, p. 864, 2022.

[66] A. L. Byrd, Y. Belkaid, and J. A. Segre, "The human skin microbiome," *Nature Reviews Microbiology*, vol. 16, no. 3, pp. 143-155, 2018.

[67] M. Lousada *et al.*, "Exploring the human hair follicle microbiome," *British Journal of Dermatology*, vol. 184, no. 5, pp. 802-815, 2021.

[68] J. B. Hall *et al.*, "Isolation and identification of the follicular microbiome: implications for acne research," *Journal of Investigative Dermatology*, vol. 138, no. 9, pp. 2033-2040, 2018.

[69] K. Polak-Witka, L. Rudnicka, U. Blume-Peytavi, and A. Vogt, "The role of the microbiome in scalp hair follicle biology and disease," *Experimental Dermatology*, vol. 29, no. 3, pp. 286-294, 2020.

[70] Y. Lai *et al.*, "Commensal bacteria regulate Toll-like receptor 3–dependent inflammation after skin injury," *Nature medicine*, vol. 15, no. 12, pp. 1377-1382, 2009.

[71] P. Suchonwanit, C. Kositkuljorn, and C. Pomsoong, "Alopecia areata: an autoimmune disease of multiple players," *ImmunoTargets and therapy*, pp. 299-312, 2021.

[72] M. Bertolini, K. McElwee, A. Gilhar, S. Bulfone-Paus, and R. Paus, "Hair follicle immune privilege and its collapse in alopecia areata," *Experimental dermatology*, vol. 29, no. 8, pp. 703-725, 2020.

[73] G. C. Mohan and J. I. Silverberg, "Association of vitiligo and alopecia areata with atopic dermatitis: a systematic review and meta-analysis," *JAMA dermatology*, vol. 151, no. 5, pp. 522-528, 2015.

[74] S. M. Edslev, T. Agner, and P. S. Andersen, "Skin microbiome in atopic dermatitis," *Acta Dermato-Venereologica*, vol. 100, no. 12, 2020.

[75] C. Albano *et al.*, "Granulicatella spp., a Causative Agent of Infective Endocarditis in Children," *Pathogens*, vol. 11, no. 12, p. 1431, 2022.

[76] R. E. Dumm, A. Wing, A. Richterman, J. Jacob, L. J. Glaser, and K. G. Rodino, "The Brief Case: A Variant on a Classic—Abiotrophia defectiva Endocarditis with Discitis," *Journal of clinical microbiology*, vol. 59, no. 10, pp. 10.1128/jcm. 03093-20, 2021.