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Unveiling the Truth Behind Psoriasis and Atopic Dermatitis

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Abstract

Psoriasis and atopic dermatitis are serious and inflammatory responses to their skin health. Hence, there are different subdivisions on psoriasis and atopic dermatitis, including the definition, history, classification, aetiology, pathophysiology, and treatment for strategising and managing both skin disorders. However, the pursuit of knowledge in taking care of skin health is still ongoing until now to make such a discovery. Thus, prevention may lessen the burden of healing in time. It is not too late to improve and motivate themselves in reaching out for their health concerns.

Keywords: *Psoriasis, atopic dermatitis, aetiology, pathophysiology*

The formation of the human skin

The skin consists of many glands in the human body. It acts as a protective barrier to survive in an external environment. The skin also enables the body heat to regulate so that it can survive under extreme conditions. Besides that, it also prevents microbes from entering the barrier causing several infections (Hicklin, 2020). Then, it holds body fluids in to prevent dehydration (Hicklin, 2020).

The outermost layer of skin is tiny cells named keratinocytes (Hicklin, 2020). The formation of the cells from the innermost layer of the skin enables the skin to build the whole troop of shield protection (Hicklin, 2020). It shows that these cells had the mechanism to move all the way to make their way to the upper surface of the organ. These cells also release some components that unleash the outermost layer of the skin (Hicklin, 2020). Afterward, the flattened cells form a layer of dead skin in the region which seems to be hardened as a fortress to seal the protective barrier of the human body. The coarse and dry surface also requires moisture-like droplets called keratohyalin granules (KGs) made up of a protein, filaggrin (Hicklin, 2020). However, the gene variants or mutations of the protein in the human skin cause uncertainties to the skin condition and may lead to dryness and flakiness at the same time. Hence, any defectives of the filaggrin resulted in a lack of the KGs making the skin more vulnerable to dermatitis problems, such as atopic dermatitis and psoriasis.

Skin is the outermost layer most frequently touched by their bare hands. As the practitioner attempts to diagnose a patient with psoriasis, it is upraised and grey in the scaly texture of the surface with some discolouration of the pigmentation (IvyPanda, 2020). According to IvyPanda (2020) and Menter (2016), due to immune system dysfunction, plaque psoriasis is where there are patches of redness and scaly skin texture that results in severe itchiness. Menter (2016) added that the manifestation of the skin condition may complicate the diagnosis. IvyPanda (2020) and Menter (2016) further studied that it would not be necessary to include underlying factors and genetic nature that may be associated with the skin health condition. IvyPanda (2020) found similar descriptions of signs and symptoms of atopic dermatitis. A wound-like skin referred to by IvyPanda (2020) and Sherazi et al. (2016) to indicate flares on the skin. Thus, further investigation by IvyPanda (2020) and Sherazi et al. (2016) to sift through atopic dermatitis. Another skin condition discovered by IvyPanda (2020) involving uncontrollable growth and pigmentation on the skin known as Tinea Versicolor. In other words, skin flora tends to proliferate as the skin condition worsens (IvyPanda, 2020 and Gantz & Allen, 2016). Thus, IvyPanda (2020) and Gantz & Allen (2016) summarised that the presence of spores as the skin disorder persists may result in yeast infection that can also be preventable.

The Importance of Studying Psoriasis and Atopic Dermatitis

Both Atopic Dermatitis (AD) and psoriasis are considered by Chovatiya and Silverberg (2019) to be categorised as a global health concern and they are chronic inflammatory skin

diseases with a significant cutaneous and as an indication of poor health-related quality of life. Chovatiya and Silverberg (2019) also added that both skin diseases are caused by a complex combination of immune dysregulation, skin-barrier disruption, genetic factors, and environmental influences. This may lead to other complications. As for AD, the complications are associated with mental problems, such as depression, anxiety, attention-deficit hyperactivity disorder, sleep dysregulation, and other atopic diseases, including asthma, hay fever, cardiovascular disease, stroke, and obesity (Chovatiya & Silverberg, 2019; Silverberg et al., 2012; Silverberg, 2015; Sherry & Silverberg, 2015; Silverberg et al., 2015; Sherry et al., 2016; Silverberg & Simpson, 2013; Strom et al., 2016). On the other hand, psoriasis is associated with rheumatologic (psoriasis arthritis), cardiovascular, metabolic, hepatic, and psychiatric disease (Chovatiya & Silverberg, 2019; Gelfand et al., 2006; Ludwig et al., 2007; Gisondi et al., 2018; Kim et al., 2010). Kim et al. (2019) found newer therapeutic strategies for improving the skin barrier function and targetting polarised immune pathways found in AD. That is to increase more precision medicine approaches to the prevention and treatment of AD (Kim et al. 2019). Thus, early prevention may put a halt to the progression of eczema into allergic airway disease (Thomsen, 2014). Therefore, Chovatiya and Silverberg (2019), Fuxench et al., 2019, Silverberg (2017), Gelfand et al. (2004), and DeKorte et al. (2004) found both AD and psoriasis are strongly associated with poor health-related quality of life, high direct and indirect costs of care, and societal cost as an indication of needing an immediate intervention.

Definition of Psoriasis

Psoriasis is a skin condition in different sensitive areas around the body. These include sensitive body parts, such as the scalp, elbows, knees, trunk (MAYO CLINIC, 2022), buttocks, and genitals (Armstrong, 2017). Then, Raharja et al. (2021) added that psoriasis presents in multiple forms, including plaque, flexural, guttate, pustular, and erythrodermic. It is very worrying since the numbers keep escalating across the globe. Psoriasis affects 2% to 4% of the global population (Armstrong, 2017). So, be ready because, at any age, psoriasis may occur (Armstrong, 2017). Most of the peak time for psoriasis is between 20 to 30 and 50 to 60 (Armstrong, 2017). Most of them are non-Hispanic whites (Armstrong, 2017). Things get tough as family history is one of the contributors to psoriasis (Armstrong, 2017). Other factors are infection, smoking, and certain medications (Armstrong, 2017). Psoriasis may also have complications, including psoriatic arthritis, a progressive joint disease that limits movement if left untreated (Armstrong, 2017). In the future, if the condition worsens, this will increase their risk of developing high blood pressure, diabetes, heart attacks, strokes, obesity, and depression (Armstrong, 2017). MAYO CLINIC (2022) added that psoriasis is a common, prolonged skin health condition, and incurable. Thus, Raharja et al. (2021) mentioned the inflammatory skin disease is associated with psoriatic arthropathy, psychological, cardiovascular and hepatic diseases. However, the MAYO CLINIC (2022) mentioned that there are treatments available for managing the symptoms including lifestyle habits and coping strategies suggested for a life-long soothing skin. Other complications or comorbidities that coexisted with psoriasis are psoriatic arthritis, changes in skin pigmentation, eye disorders (conjunctivitis, blepharitis, and uveitis), obesity, type 2 diabetes, high blood pressure, cardiovascular disease, autoimmune illnesses (celiac disease, sclerosis, and Crohn's disease), and psychological problems (MAYO CLINIC, 2022).

History of Psoriasis

Psoriasis is a historical skin health condition that attempts to infect humans and non-human primates (Ashton, 2021). According to Ashton (2021), the ancient Hindu medical texts found 3000 years ago recorded various skin conditions encountered during that time, such as Khusta and leprosy (Ashton, 2021). However, psoriasis has its identification nowadays (Ashton, 2021). Psoriasis is a Greek word for psora, lepra, and leichen (Ashton, 2021). On the other hand, Ashton (2021) found psora to be itchiness. Lepra is the layer of skin called epidermis and lepo to scale (Ashton, 2021). Until then, in 1809, Robert Willan (1757- 1812) contributed his discovery of psoriasis by identifying different manifestations of it, including guttate (small red, dotty patches), scalp, and palmar lesions (Ashton, 2021). He discovered psoriasis spreading across the knees, elbows, fingers, and toenails (Ashton, 2021). Ashton (2021) found Dr. Robert Willan to use the term lepra vulgaris instead of psoriasis interchangeably with the word leprosy. It would not last long until Ashton (2021) referred to a physician named Ferdinand von Hebra (1816- 1880) posted at the Vienna General Hospital suggested separating the term psoriasis from leprosy to break down any confusion between the two. In the 20th century, Ashton (2021) mentioned different types and sub-types of psoriasis. Before that, for the record, Ashton (2021) added Leo von Zumbusch in 1910 and prescribed a generalised pustular psoriasis which describes the spreading of reddening skin that can be painful and tender. Then, there are some appearances of small pustules on the surface of the skin that develop into large blisters within hourly time (Ashton, 2021). Ashton (2021) stated the condition was followed by fatigue and fever. However, Ashton (2021) also added that the most recent discovery shows psoriasis to be not a skin health condition but a chronic immune disease followed by systemic inflammation. The infection is not on the skin only but also on joints and other bodily systems (Ashton, 2021).

Aetiology Pathways of Psoriasis

Psoriasis is described by MAYO CLINIC (2022) as having an immune problem with the fast growth of the skin far from usual. The cause of psoriasis remains unattended since MAYO CLINIC (2022) discovered that it is an immune system problem and the fighting cells might accidentally mistake it for healthy skin as the infected one. However, MAYO CLINIC (2022) found that genetic and environmental factors may relate to the story of having psoriasis. MAYO CLINIC (2022) also added it is not contagious as it cannot be transmitted to another person. As mentioned by MAYO CLINIC (2022), the main environmental triggers of psoriasis, such as strep throat or skin infections, cold and dry weather conditions, injury to the skin due to scratching or sun burning, smoking or second-hand

smoke, heavy alcohol intake, undergoing medications, and sudden and rapid withdrawal of oral or injected corticosteroids. Genetics plays a crucial role among patients with early onset younger than 40 years old (Raharja et al., 2021). Hence, Raharja et al. (2021) and Nick et al. (2020) mentioned the causal genes for psoriasis are antigen presentation of human leukocyte antigen c (HLA-C and ERAP1), nuclear factor kappa B (TNIP1), type 1 interferon pathway (RNF113 and IFIH1), interleukin (IL)-23/Th17 axis (IL23R, IL12B, and TYK2), and skin barrier function (LCE3). Raharja et al. (2021) and Schon and Erpenbeck (2018) added the complex interplay of T-cells, dendritic cells, and keratinocytes is behind the curtains the whole time, leaving the IL-23/Th17 axis as the immune activation driver, chronic inflammation, and keratinocyte proliferation.

Pathophysiology of Psoriasis

Chovatiya and Silverberg (2019) added the pathophysiology of psoriasis to dysregulated immune activity and genetic factors. Based on Chovatiya and Silverberg (2019) and Lebwohl (2003), psoriasis occurs as there is trauma (Koebner phenomena), medication (beta-blocker, ACE-inhibitor, and lithium), and or infection, such as group A streptococcus involved at the initial stage. Chovatiya and Silverberg (2019) explained the binding of antimicrobial peptides (AMPs) to the keratinocyte's DNA and RNA had triggered the initiation of psoriasis. Then, the plasmacytoid dendritic cells (pDCs) are suited for viral pathogens (Chovatiya and Silverberg, 2019). As mentioned by Chovatiya and Silverberg (2019) and Morizane et al. (2012), keratinocyte functions in the innate immunity system produce pro-inflammatory cytokines as a response to AMP-nucleic acid complexes, such as type 1 interferons, IFNs, tumour necrosis factor-alpha, interleukins, 1 and 6. Further, Chovatiya and Silverberg (2019) added the excretions of pro-inflammatory cytokines, such as tumour necrosis factor-alpha, interleukins of 12 and 23 may also secrete Th1, Th17, and Th22 cells.

The adaptive immune system triggers the self-sustaining, maintenance phase of inflammation in psoriasis (Chovatiya & Silverberg, 2019 & Uyemura et al., 1993). According to Chovatiya and Silverberg (2019), Th-17 is a stand-out epithelial cell that protects the layers of skin from being invaded by the pathogens present at the outermost boundary. Th-17 tends to produce interleukin-17 (IL-17), one of the pre-determined causes of psoriasis (Chovatiya & Silverberg, 2019). Generally, Chovatiya and Silverberg (2019) identified TNF-alpha, IL-17, and IL-23 as the activators of plaque psoriasis, but other triggers create pathways to variants of psoriasis. IL-1, IL-8, and IL-36 are immunity disruptors in developing pustular psoriasis (Chovatiya and Silverberg, 2019; Johnston et al., 2017; Tauber et al., 2016). Besides that, guttate psoriasis is another predisposed variant of psoriasis escalated by the T-cell receptors that permit the accumulation of streptococcal superantigen and molecular mimicry of keratin proteins (Chovatiya and Silverberg, 2019; McFadden et al., 1991; Leung et al., 1995).

There seems to be a genetic component inherited by first and second-degree relatives compared to the general population, and even monozygotic twins had a two to threefold higher risk of developing psoriasis compared to dizygotic twins (Chovatiya & Silverberg, 2019; Farber & Nall, 1974; Farber et al., 1974; Lonnberg et al., 2013). HLA-Cw6 is a susceptible allele to a predisposed factor that influences the development of psoriasis among white Caucasian and Chinese populations (Chovatiya & Silverberg, 2019; Nair et al., 2006; Fan et al., 2008). A more solid confinement to the mystery is the family history (Chovatiya & Silverberg, 2019; Nair et al., 2006; Allen et al., 2005).

Classifications of Psoriasis

Psoriasis is detectable as there is a patchy rash or scaling of the body (MAYO CLINIC, 2022). MAYO CLINIC (2022) added the colouration of the rashes depends on the skin pigmentation which varies from one person to another. Among children, MAYO CLINIC (2022) managed to identify the small scaling spots that appear on the skin. The dryness of the skin makes it even more appealing with cracked skin that may bleed once in a while due to the thin layers of skin (MAYO CLINIC, 2022). The mechanical reactions, including itching, burning, and soreness might also affect the patient (MAYO CLINIC, 2022). According to the MAYO CLINIC (2022), the itchiness and dryness of the skin due to psoriasis are accompanied by the continuation of cyclic rashes which may last for weeks or months and then, recover on their own.

The classification of psoriasis is directive and distinctive depending on the severity of the rashness and itchiness spots (MAYO CLINIC, 2022). Plaque psoriasis as studied by MAYO CLINIC (2022) and Raharja et al. (2021) was known to be one of the most common types of psoriasis which appears scaly on the elbows, knees, lower back, and scalp. Thus, the MAYO CLINIC (2022) mentioned the healing patches of the skin may have to do with the healing colours of the skin. Raharja et al. (2021) studied another case involving flexural psoriasis-affected areas, such as the axillae, sub-mammary, and genital areas. Another case reported by MAYO CLINIC (2022) stated nail psoriasis with losing nail bed and abnormal nail growth and discolouration. Raharja et al. (2021) reported up to 50% of the patients may affected by nail psoriasis in the form of nail pitting (indentation in the nails), onycholysis (separation of nail bed from nail bed), oil spots (discolouration of the nailbed), dystrophy, and subungual hyperkeratosis. On the other hand, guttate psoriasis manifests in the trunk, arms, and legs due to bacterial infections so as, strep throat (MAYO CLINIC, 2022) but does not necessarily precede with it (Raharja et al., 2021). The folding parts of the body were also infected by psoriasis, known as inverse psoriasis due to friction and sweating which can be found in the form of fungal infections (MAYO CLINIC, 2022). Pustular psoriasis as indicated by MAYO CLINIC (2022) and Raharja et al. (2021) is widespread on the back of the hand or soles. MAYO CLINIC (2022) then, added the least common type of psoriasis referred to as erythrodermic psoriasis which covers the whole body with red, scaly patches with a peeling rash that is itching and burning at the same time. Raharja et al. (2021) found erythrodermic psoriasis to be a life-

threatening due to a potential causes of hypothermia, risk of infection, acute kidney injury, and high-ouput cardiac failure.

Tokura & Hayano (2022) mentioned the classification and categorisation of clinical diagnoses and individual subgroups according to the clinical features and widely implemented biomarkers. For further verification, other criteria were referred to as well, such as phenotype (clinical signs), skin barrier status (protective or not), serum Immunoglobulin E (IgE) levels, associated comorbidities, ethnicity (European American versus Asian), age, gender, and disease severity.

Risk Factors of Psoriasis

Psoriasis can be inherited by familial history and genetic factors (MAYO CLINIC, 2022). That is, having both parents infected by psoriasis may increase the chances of developing psoriasis (MAYO CLINIC, 2022). MAYO CLINIC (2022) also reported the severity of having psoriasis can be increased with tobacco consumption. Both males and females can develop psoriasis with earlier onset for females with a family history of psoriasis (Raharja et al., 2021). According to Raharja et al. (2021) and Parisi et al. (2020), psoriasis mostly infects high-income countries and older generations. The assessment of psoriasis evaluated by Raharja et al. (2021) involves body surface area (BSA) and the severity of erythema, induration, and scaling. The Psoriasis Area Severity Index (PASI) and Physician Global Assessment Scale also coexisted with an outcome measure, Dermatology Life Quality Index (DLQI) (Raharja et al., 2021; Finlay & Khan, 1994; Feldman & Krueger, 2005).

Therapeutic Strategies and Treatments of Psoriasis

Overall, Raharja et al. (2021) found topical agents (vitamin D analogues and corticosteroids), phototherapy (narrowband ultraviolet B radiation (NB-UVB) and psoralen and ultraviolet A radiation (PUVA)), standard systemic (methotrexate, ciclosporin, and acitretin), biologic (tumour necrosis factor (TNF), interleukin (IL)-17 and IL-23 inhibitors) or small molecules inhibitor (dimethyl fumarate and apremilast) therapies to be the enlisted treatments recommended by dermatologists for psoriasis. Back in the day, psoriasis could be controlled and managed with limited topical preparations of anthralin (also known as dithranol), which produces a line of fighting agents, such as IL-5 and nitric oxide (Chovatiya & Silverberg, 2019; McGill et al., 2005; Arbiser et al., 2006). However, topical corticosteroids (TCS) are highly recommended for psoriasis (Chovatiya & Silverberg, 2019). Another alternative way to treat psoriasis is to apply topical calcineurin inhibitors (TCIs), tacrolimus, and pimecrolimus on localised and infected body patches, such as facial, genital, and intertriginous areas (Chovatiya & Silverberg, 2019 and Wang & Lin, 2014). Chovatiya and Silverberg (2019) also mentioned the effectiveness of using tazarotene in treating psoriasis.

The second line of therapy for psoriasis is phototherapy using narrowband ultraviolet B radiation (NB-UVB) and psoralen with ultraviolet A radiation (PUVA) and inhibited with conventional systemic agents, such as methotrexate, ciclosporin, and acitretin (Raharja et al., 2021). According to Raharja et al. (2021), the safer option is NB-UVB due to the lesser risk of skin cancer.

Systemic immunosuppressants, such as methotrexate, the first approved systemic therapy, and cyclosporine A in treating moderate to severe psoriasis (Chovatiya & Silverberg, 2019). Then, acitretin as an oral second-generation retinoid efficacious for pustular psoriasis and erythrodermic psoriasis as a substitute for phototherapy (Chovatiya & Silverberg, 2019 and Sbidian et al., 2011). Chovatiya and Silverberg (2019) found acitretin to be similar to tazarotene bound to retinoic acid receptor (RAR) to regulate transcription of genes for epidermal proliferation, keratinocyte differentiation, and immune cell production of cytokines.

The Food and Drugs Association (FDA) approved apremilast as the best treatment for moderate-to-severe psoriasis in 2014 (Chovatiya and Silverberg, 2019). According to Chovatiya and Silverberg (2019), Reich et al. (2017), Bissonnette et al. (2018), Papp et al. (2015), Paul et al. (2015), patients with moderate-to-severe plaque or palmoplantar psoriasis treated with apremilast had significant improvement in Psoriasis Area and Severity Index (PASI) of 50% or more reduction from baseline, PASI-75, and static investigates global assessment (sIGA) at week 16 in a multiple phase III double-blind study.

Chovatiya and Silverberg (2019) identified tumour necrosis factor-alpha as the first generation of biological medication for psoriasis at the stage of moderate-to-severe psoriasis for over a decade. Raharja et al. (2021) added biologics are monoclonal antibodies or soluble receptors that naturally lock on proinflammatory cytokines. Since tumour necrosis factor-alpha is involved in innate and adaptive immune systems, it sets off as a center stage to fight pathogens (Chovatiya and Silverberg, 2019). Thus, Chovatiya and Silverberg (2019) highly recommended immunotherapy since it is safe and efficacious for healing psoriasis.

Ustekinumab was a requested treatment approved by the FDA in treating psoriasis in 2009 (Chovatiya & Silverberg, 2019). From Th-17 to Th-1 cells, they are prominent controllers in ensuring the severity of psoriasis, such as the p40 subunit used to target localised psoriasis (Chovatiya and Silverberg, 2019). Thus, Chovatiya and Silverberg (2019) and Gordon et al. (2012) reported the overall infection rate is lower after being treated with ustekinumab compared to tumour necrosis factor-alpha.

IL-17 is one of the significant cytokines produced by Th17 cells and is responsible for activating the inflammatory responses during the chronic phase of psoriasis (Chovatiya & Silverberg, 2019). However, the association between Th17 cells and inflammatory bowel disease (IBD) is still under investigation (Chovatiya & Silverberg, 2019; Hueber et al., 2012). Raharja et al. (2021) and Hay et al. (2017) also found the Global Burden of Disease Study estimated that psoriasis to be around 5.6 million all-age disability-adjusted life-years (DALYs) in 2016 and at least three-fold of inflammatory bowel disease.

According to Chovatiya and Silverberg (2019) and Lee et al. (2004), IL-23 is well-recognised as a more specific target for psoriasis therapy. IL-23 inhibitors surpassed tumour necrosis factor-alpha inhibitors and ustekinumab (Chovatiya and Silverberg, 2019). Thus, Chovatiya and Silverberg (2019) mentioned the effectiveness of IL-23 in tolerating upper respiratory infection, gastroenteritis, and herpes simplex virus called tinea.

Th17 and Th1 cytokines are the basis for the pathogenesis of psoriasis produced by Janus Kinase inhibitors (JAK) (Chovatiya & Silverberg, 2019). Oral tofacitinib is an FDA-approved therapy for psoriatic arthritis (Chovatiya and Silverberg, 2019; Mease et al., 2017; Gladman et al., 2017). However, systemic tofacitinib is associated with several infectious atopic eczema (AE) as observed in several trials, and in 2015, the FDA studied the lack of safety studies on oral tofacitinib (Chovatiya & Silverberg, 2019). Thus, there is ongoing research on small molecules blocking tyrosine kinase 2 in the JAK approved in the line of therapy for psoriasis (Raharja et al., 2021).

Definition of Atopic Dermatitis

According to Thomsen (2014), Atopy can be defined as the inherited tendency to produce immunoglobulin E (IgE) antibodies as responses to pollen, house dust mites, and food allergens. Dermatitis is a Greek origin word derived from "derma", the skin, and "itis" can be referred to as inflammation (Thomsen, 2014). However, Thomsen (2014) found atopic dermatitis to be indefinite since about half of the patients had allergic sensitisation and immunoglobulin E (IgE). Generally speaking, NIH (2017) found AD also known as atopic eczema which is characterised by the inflammation of the skin (dermatitis). The signs and symptoms begin to show at an early age (NIH, 2017 and Thomsen, 2014) but eventually recover during adulthood (NIH, 2017). However, NIH (2017) reported that some people are infected with AD even during and after adulthood. AD is the most chronic inflammatory skin disease (Kim et al. 2019 and Kim & Leung, 2018). Kim et al. (2019) and Silverberg (2017) reported the U.S. prevalence of AD to be 11.3- 12.7% and 6.9- 7.6% in children and adults, respectively. Based on NIH (2017), it was estimated that 10 to 20 percent of children may develop AD as compared to 5 to 10 percent of adults. The dry and reddened skin patches seem to appear on any part of the body causing rashes to form in a different pattern at any age (NIH, 2017). There are also diagnostic tools available for detecting AD which is based on the Hanifin and Rajka criteria and the American Academy of Dermatology Consensus Criteria (Kim et al. 2019, Hanifin & Rajka, 1980, and Eichenfield, 2004). The security index of having an AD can be assessed using Scoring Atopic Dermatitis or the Eczema Area and Severity Index (Kim et al. 2019 and Schmitt et al. 2013). Thus, NIH (2017) added if the skin condition becomes severe by the mechanical reaction of scratching, it may cause the oozing and crusting of the rashes to continue to thicken and harden (lichenification) the skin. This may awaken the patient due to itchiness of the skin which interrupts their comfort during sleep.

The word atopic is in association with the word allergies (NIH, 2017). Not only that, NIH (2017) examined some of the patients who develop asthma or hay fever later in life with 70%, and the remaining 30% are food allergies. It all started with atopic dermatitis followed by allergies, hay fever, and finally, asthma (NIH, 2017). According to NIH (2017) inflammatory diseases, including inflammatory bowel disease, rheumatoid arthritis, and even hair loss due to malfunctioning immune reaction called alopecia areata. In terms of psychiatry, attention-deficit/ hyperactivity disorder (ADHD) or depression is prevalent among those with AD (NIH, 2017). Kim et al. (2019) studied filaggrin (FLG), transglutaminases, keratins, and intercellular proteins are responsible for epidermal function. Defects in these proteins permeate allergens and microbial invasion into the skin (Kim et al., 2019, Egawa & Kabashima, 2016; Schleimer & Berdnikovs, 2017; Strid et al., 2004). Then, the skin barrier dysfunction itself resembled atopic events as well as AD (Kim et al., 2019; Lowe et al. 2018; Dharmage et al., 2014). Kim et al. (2019), Thyssen & Kezic (2014), Egawa & Kabashima (2018), Howell et al. (2009), and Leonardi et al. (2007) found that immune dysregulation, such as the activation of type 2 immune responses, results in impairment of the epidermal barrier.

NIH (2017) also reported there is a subset of patients who have a prolonged condition with AD because they are vulnerable to bacteria and fungi, known as immunodeficiency. Other than that, they may experience a number of signs and symptoms pertaining to skin abnormalities and immunodeficiency (NIH, 2017). NIH (2017) identified them as Netherton syndrome, immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, severe dermatitis, multiple allergies, and metabolic wasting (SAM) syndrome which affect the skin and other bodily functions.

History of Atopic Dermatitis

In history between 1950 and 2000, there was the so-called global health concern over the "allergic epidemic" (Thomsen, 2014). Thomsen (2014) reported the highest prevalence accounted for by the UK and New Zealand populations.

Avicenna (980- 1037) himself compiles and clarifies atopic dermatitis inside one of his medical texts entitled "The Canon of Medicine" (Jaworek & Wojas-Pelc, 2017). According to Jaworek and Wojas-Pelc (2017), itchiness is the main hallmark of atopic dermatitis. Jaworek and Wojas-Pelc (2017) also studied atopic dermatitis and found it to be one of the greatest plagues of modern medicine. Further, a chronic recurrent dermatosis coexists with another atopic dermatitis, such as allergic rhinitis, biochemical asthma, and food allergy (Jaworek & Wojas-Pelc, 2017). Confusion still stirs on the actual meaning of skin disorders, such as eczema. For instance, the subtypes of eczema received quite an attention from dermatologists. Prurigo is a term put into thought by Jadassohn in 1896 (Taieb et al., 2006 & Jadassohn, 1930). Then, Sir Malcolm Morris 1912, the president of the Dermatology Section at the Royal Society of Medicine: At the International Medical Congress in London in 1881 where Mr. Morrant Baker referred to three

cases as identified by Kaposi and Hebra and Unna as types of prurigo of Hebra which received further recognition in the dermatology field across the globe (Taieb et al., 2006 & Anonymous, 1912).

The first text depicted atopic dermatitis is present in the scientific tract on skin diseases (De morbis cutaneis) as written by an Italian physician, Girolamo Mercuriale (1530- 1606), and published in 1572 (Jaworek & Wojas- Pelc, 2017). Atopic dermatitis is achores- exudative and pruritic skin lesions among breastfed infants (Jaworek & Wojas-Pelc, 2017 & Taieb et al., 2006). For further explanation, Francois Boissier de Sauvages 1763 on the role of lactation in the development of cutaneous lesions was also referred to as AD and named tinea lactea (Jaworek & Wojas-Pelc, 2017). Then, Jaworek and Wojas-Pelc (2017) and Taneja et al. (2016) mentioned a French dermatologist, Jean-Louis Alibert (1768- 1837) on AD or infantile seborrhoeic dermatitis in 1806 affecting children's skin (teigne muqueuse, achor muqueuse). For years, dermatologists found neurodermatitis synonymous with the disease entity currently identified as AD (Jaworek & Wojas-Pelc, 2017 & Taieb et al., 2006).

Based on the Willanist approach in the last two centuries, an objective description of the elementary lesions called vesicles (herpes, eczema), papules (strophulus, lichen, and prurigo) and excluding the subjectivity approach in having the first and primary symptom (Taieb et al. 2006 & Besnier, 1892) if now identified as atopic eczema/ dermatitis. As time goes by, Willan, Bateman, and other dermatologists are on a quest to explore a new way of looking at skin disorders. According to Taieb et al. (2006) and Willan & Bateman (1813), skin disorders should be classified based on the primary lesion. Thus, eczema is a vesicular condition, and most cases are due to sunburn or toxic chemicals (Taieb et al., 2006). As mentioned before, prurigo, on the other hand, is a pustular condition of the scalp (Taieb et al., 2006). Surprisingly, porrigo larvalis (like a mask) is similar to the old milky crust and modern atopic eczema/ dermatitis (Taieb et al., 2006).

Therefore, lichen, prurigo, and eczema encompassed clinical precursors of modern atopic eczema/ dermatitis (Taieb et al., 2006). Taieb et al. (2006) found that Jadassohn strategies himself by clearly defining clinical subsets and progressing into pathogenesis. Classifications rely on clinical grounds assisted by the association with constitutional traits, especially asthmatic patients (Taieb et al., 2006). The name "constitutional eczema" termed and coined by Robert Degos, a French dermatologist second half of the twentieth-century term "neurodermatitis" had been dominated by the Germans during the same period, "atopic eczema" is a depiction used by the British Dermatologist the whole time (Taieb et al., 2006).
In 1923, Arthur Fernandez Coca (1875-1959) and Robert A. Cooke (1880-1960) collaboration with Edward Perry from Columbia University discovered the coined term atopy from the Greek word atopos, out of place and strange to describe allergic rhinitis, urticaria, and asthma (Jaworek & Wojas-Pelc, 2017, Coca & Cooke, 1923; Sybilski, 2006). Hence, the division phases based on age were proposed, including 0-2 years, 2-12 years, and atopic dermatitis in adults until today had been popularised (Jaworek & Wojas-Pelc, 2017; Hill & Sulzberger, 1935). Howard Maibach was known to have a better division of dermatological diseases according before corticosteroids and after corticosteroids (Jaworek & Wojas-Pelc, 2017; Sulzberger, 1952; Jaworek & Wojas-Pelc, 2017).

Aetiology Pathways of Having Atopic Dermatitis

However, NIH (2017) added there is a lack of understanding of what causes AD. Rarely, NIH (2017) specified a gene called CARD 11 to be responsible for proteins that permeate the signal pathways in developing and functioning lymphocytes, the immune system cells. Therefore, the protein produced from the CARD 11 gene is dysfunctional (NIH, 2017). NIH (2017) found lymphocytes known as T cells also did not develop and function properly in addition to their vulnerability to bacteria and fungi. Having a weakened immune system, NIH (2017) reported an unusual event of recurrent infections.

Come to think again. NIH (2017) discovered some possible causes due to the combination of genetic and environmental influences by modifying the genetic variations for a small and diminishing risk of developing an AD. Thomsen (2014) added many genes had been associated with AD by encoding epidermal structural proteins and genes encoding the main components of the immune system. Another gene that comes to mind is the FLG gene. As mentioned by Thomsen (2014), there is a strong association between AD and mutations in the FLG gene. It can also be the strongest risk factor to be associated with AD (Thomsen, 2014). Some alterations in the gene mutations are more likely to occur among 20 to 30 percent of people with AD compared to 8 to 10 percent of the general population without AD (NIH, 2017).

Further, the shortage of profilaggrin-related proteins may affect the permeability and protectivity of the skin barrier and may contribute to the development of AD (NIH, 2017). The skin moisturising effect may also be affected by the dryness of the skin due to excess water loss (NIH, 2017). In other words, the disruption in the gene activity and regulation process of protein production may contribute to the increasing number of allergens to penetrate through the skin surfacing layer (NIH, 2017).

Pathophysiology of Atopic Dermatitis

The France Foundation (2022) found Atopic Dermatitis (AD) to be characterised by barrier dysfunction, inflammation, and pruritus. Further, Kim et al. (2019) also stated the three main areas of the pathophysiology of AD, including epidermal lipid profiles, neuroimmune interactions, and microbial dysbiosis. The first stop is the immunological hypothesis stating that the imbalance of T cells, such as T helper cell types, 1, 2, 17, and 22, and also regulator T cells are the primary suspects of having AD (Thomsen, 2014 and Eyerich & Novak, 2013). If the allergic state of AD remains, the Th2 differentiation of CD4+ T cells prevails (Thomsen, 2014). The next one is called by Thomsen (2014) as the skin barrier hypothesis followed

by the encoding of a gene that affected the skin barrier and transepidermal water storage that may end up with eczema. Hence, The France Foundation (2022) mentioned the integrity of the skin barrier itself may assist in preventing the loss of moisture and act as the first line of defense against injury from microbes and other skin irritants. The itchiness and dryness of the skin cause them to have a mechanical reaction of scratching. Further, The France Foundation (2022) added that protein filaggrin is responsible for skin hydration and moisturising effect. The defectiveness of skin dehydration may result in the disruption of keratinocyte differentiation in interrupted integrity and cohesion of cells in the stratum corneum (The France Foundation, 2022). The permeability of the skin barrier and reduced water retention may occur as well (The France Foundation, 2022). The dryness of the skin and some environmental concerns raise microbial growth (The France Foundation, 2022).

As mentioned by The France Foundation (2022), the filaggrin defectiveness may also release epithelial cell-derived cytokines which reduce the level of flagrant and promote inflammation by causing an increase of IgE and eosinophils mechanical injury external irritants and microbes also trigger skin's immune cells increase the formation of inflammatory cytokines, especially IL- 25, IL- 33, and TSLP which activates the Th2 combining all factors working together to further compromise with the integrity of the skin creating a permeability for external irritants to penetrate the barrier in increased transepidermal water loss. In terms of atopic pruritus Th2, The France Foundation (2022) found that it is a significant source of itching-inducing cytokine, IL- 31. Kim et al. (2019) mentioned about type 2 cytokines so as interleukin 7 and interleukin 22 contribute to skin barrier dysfunction and the development of AD.

Thus, The France Foundation (2022) summarised the disrupted skin barrier and decreased levels of filaggrin create a cycle of inflammation, pruritus, and increased skin barrier disruption fueled by inflammatory cytokines.

Classification of Atopic Dermatitis

The heterogeneity of AD includes diagnosis, disease activity, selection of appropriate therapy, and monitoring treatment responses (Chovatiya & Silverberg, 2022). Tokura & Hayano (2021) beg to differ when they propose that the classification of AD should be based on skewing T-cell populations and their cytokines. Alternatively, AD subtypes were recognised by Tokura & Hayano (2021) to be ideally categorising AD in terms of its endotype. That is, Tokura & Hayano (2021) added the classification is done based on phenotype, endotype, or both. Further, they found that genotype may have an influential effect on endotype (Tokura & Hayano, 2021). However, those attempts as given by Tokura & Hayano (2021) have gone out the door since there is no clear clarification on the categorisation of the AD subtypes.

Therefore, Tokura & Hayano (2021) explained that the subtypes are connected with each other instead of having distinctive properties that go along with it. They further strategise to expand the intrinsic and extrinsic properties of AD subtypes (Takuro & Hayano, 2021). The two main interests of classifying the AD subtypes were narrowed down based on extrinsic/intrinsic, ethnic, pediatric/adult subtypes (Takuro & Hayano, 2021). The dominant types of AD subtypes can be broken down by Takuro & Hayano (2021) in terms of Th2- and Th1- dominant conditions respectively. Based on the most recent study researched by Takuro & Hayano (2021) and Koga et al. (2008), interleukin, IL- 17A is in the acute lesions. Otherwise, Takuro & Hayano (2021) and Czarnowicki et al. (2019) found IL-22 to portray that AD is at a chronic stage.

History, Takuro & Hayano (2021) mentioned that asthma in 1947 was classified according to intrinsic and extrinsic generic types. So as, AD which implies the same concept in the 1980s (Takuro & Hayano, 2021). Hence, Takuro & Hayano (2021) decided to use the derivation terms, mixed AD vs. pure AD, allergic AD and non-allergic AD, and classical AD and atopiform dermatitis. The term mixed implies the meaning of a combination of AD and respiratory allergies, such as asthma (Takuro & Hayano, 2021; Diepgen et al., 1992).

Among adults diagnosed with AD, 40% have active lesions in flexural areas (the movement of bending), and 5.4% estimated flexural distribution (the folded body parts, such as armpits) (Chovatiya & Silverberg, 2022 and Silverberg et al. 2019). Chovatiya & Silverberg (2022) reported skin conditions began to develop in the form of genital and buttock lesions (abnormal tissues) in older generations. Chovatiya & Silverberg (2022) mentioned that Hispanic citizens and African American ethnicity were associated with truncal lesions. Patients who are native to Africa have an increased risk of developing follicular eczema (Chovatiya & Silverberg, 2022; Yew et al., 2019).

Risk Factors of Atopic Dermatitis

Familial history is one of the major contributors to the manifestation of AD among patients (Thomsen, 2014). For instance, Thomsen (2014) discovered monozygotic twins reported 75% of the other half will develop AD in the future as compared to only 30% accounted for dizygotic twins. AD tends to have interaction effects between gene-to-gene and gene-to-environment interrelationships among each other (Thomsen, 2014). He also mentioned that the FLG gene becoming the strongest risk factor in developing AD (Thomsen, 2014). Accumulated by Thomsen (2014) that around 10% of people from Western regions of the world are FLG gene carriers while 50% of the patients with AD inherited such gene. The impairment of the skin's protective barrier seems due to the lack of filaggrin proteins resulting in dry skin conditions and a high risk of eczema (Thomsen, 2014).

In terms of environmental risk factors, there is a so-called hygiene hypothesis stating that there is a decrease in childhood prototypical infections, such as hepatitis A and tuberculosis has increased the risk of developing AD (Thomsen, 2014; Bach 2002).

Therapeutic Strategies and Treatments for Atopic Dermatitis

Thomsen (2014) studied the complications of AD and it turned out to be incurable if the skin condition is prolonged then, the patient will either experience other complication(s) or the chronic status of it. Thus, Thomsen (2014) strategising in prevention and treatment at the same time. First, for prevention, daily use of a skin moisturiser or emollients to avoid the dryness of the skin so as, allergens and type of clothing (Thomsen, 2014). Thomsen (2014) referred to emollients as hydration for the skin epidermis to avoid any crustiness and flakiness of the skin which is embroiled in a scratching and itchiness of it. Next is the topical corticosteroids as suggested by Thomsen (2014) for moderate to severe AD among children and adults. As mentioned by Avicenna, short baths were prescribed for those with dry skin whereas long baths may cause severe dryness to the skin (Jaworek and Wojas-Pelc, 2017). Henceforth, therapeutic bathing as prescribed by Avicenna is also suitable for those with skin lesions resembling hand eczema (Jaworek & Wojas-Pelc, 2017).

The newest kind of treatment given for AD is the pimecrolimus cream and tacrolimus ointment also known by Thomasen (2014) and El-Batawy et al. (2009) for healing flares and as a maintenance therapy for AD. It has been stated by Thomasen (2014) that the treatment for AD may take a longer time for recovery but with phototherapy, the process took for 1 to 2 months three to five times a week accompanied by topical corticosteroids. The side effect of using this method of skin treatment if prolonged, might turn into a nightmare with the exposure to skin cancer (Thomsen, 2014). Cortisone as mentioned by Taieb et al. (2006) and Debre et al. (1951) was prescribed by dermatologists in the early 1950s to treat atopic eczema among infants and children. However, serious side effects of cortisone might affect the child's growth and development (Taieb et al., 2006). If the skin condition gets serious, Thomsen (2014) recommended taking oral corticosteroids along with topical corticosteroids for the lasting effectiveness of the treatment itself. This does not stop there a second immunosuppressant drug as recommended by Thomsen (2014), such as azathioprine, methotrexate, or cyclosporine may reduce the severe itchiness and the patchiness of the localised site of AD. Oral and sedative antihistamines are also found by Thomsen (2014) to reduce itchiness for sleep comfort.

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