INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by intensely pruritic subacute and chronic eczematous plaques, the pathogenesis of which appears to involve a complex interplay of genetic, pharmacological, environmental and psychological factors. The development of skin lesions in AD patients results from sequential activation of T helper 2 (Th2) and Th1-type cells ***(Leung et al., 2003).***

There are at least 13 scoring systems and indices for assessment of disease severity in children with atopic dermatitis ***(Charman and Williams, 2000).***

Activin-A is a member of the TGF-β super family, participates in essential biological processes, such as development, hematopoiesis, wound repair, and fibrosis ***(Werner and Alzheimer, 2006).*** Activin-A was found to suppress Th1-driven responses, pointing to a broader immunoregulatory function ***(Xanthou, 2009).***

A strong immunoregulatory role for activin-A in allergic disease, with the suppression of T helper (Th) type 2 cell-driven allergic responses was demonstrated in some studies ***(Barbers, 2003).***

Activin-A as a pleiotropic cytokine, its effects on T helper (Th) cell-mediated immunity, critical for allergic and autoimmune diseases is still not fully understood ***(Robinson, 2009).***

It's suggested that activin-A orchestrates the regulation of key events involved in the pathogenesis of allergic asthma. The critical role of activin-A in allergic airway responses, places this cytokine as an exciting new therapeutic target for asthma ***(Kariyawasam, 2011).***

A strong immunoregulatory role for activin-A in allergic airway disease, with the suppression of T helper (Th) type 2 cell-driven allergic responses and protection against the development of cardinal features of the asthmatic phenotype was revealed by in vivo functional studies ***(Werner, 2006).***

Activin-A-mediated immunosuppression is associated with induction of functional allergen-specific regulatory T cells. In human asthma, although activin-A levels are increased in the airway epithelium and submucosal cells, the expression of its signalling components are markedly decreased, pointing to decreased regulation ***(Alzheimer, 2006).***

AIM OF THE STUDY

The aim of the study is to assess the role of activin-A in patients with atopic dermatitis (AD) through measuring its level in activity and in remission.

ATOPIC DERMATITIS

Definition:

Atopic dermatitis is an eczematous skin condition with a predilection for skin creases and flexures, most commonly developing in children, and often associated with other allergic phenomena such as asthma and allergic rhinitis ***(De-Benedetto et al., 2009).*** It is a chronically relapsing skin disorder with an immunologic basis. The clinical presentation varies from mild to severe. In the worst cases, atopic dermatitis may interfere with normal growth and development ***(Turner & Schwartz, 2006)***.

The term “atopy” was introduced by ***(Coca & Cooke 1923)*** as a broad term for a collection of diseases, particularly asthma and allergic conjunctivitis (hay fever). Its precise definition, in relationship to other immunologic terms such as “allergy” and “hypersensitivity" ***(Dubois et al., 1999)***.

Atopic dermatitis is considered by many to be the first step in the "atopic march" that can progress to include asthma and allergic rhinitis, as well as be a precursor to, rather than a consequence of, food allergies ***(Danby & Cork, 2010)***.

The theory of “Atopic March” favors the consideration of eczema as a systemic disease, and indicates that many children

with atopic eczema go on to develop asthma and allergic rhinitis as their eczema improves with time ***(Hon et al., 2012)*.**

The skin constitutes the largest bodily organ and is bombarded daily with environmental insults including infectious and toxic agents, allergens, ultraviolet light, and mechanical damage. Therefore, the skin is equipped with innate and adaptive properties to respond to the myriad of environmental factors encountered ***(Jessica et al., 2012)*.**

Atopic dermatitis is a chronic inflammatory skin condition that appears to involve a genetic defect in the proteins supporting the epidermal barrier. Atopic dermatitis (also termed atopic eczema and infantile eczema), a chronic, itchy, inflammatory skin disease that sets on at infancy or early childhood, is observed with increasing prevalence around the world, particularly in developed nations. *Atopy*, referring to "out of place", describes a group of disorders that include eczema, asthma, and allergic rhinitis. However such a link between atopic dermatitis and asthma and hay fever has been called into question and is now controversial ***(Chan, 2008).***

Allergic reactions are considered as multifactorial, heterogeneous disorders caused by an interaction of environmental and genetic factors and can express themselves in many different organs, and in any age group ***(Jenerowicz et l., 2012)***.

In most patients the condition is mild, but those with moderate to severe disease usually have intense itching and experience loss of sleep. The social stigma of a visible skin disease can be soul destroying for both patient and family ***(Williams, 2002)***.

Classifications:

Atopic dermatitis has traditionally been classified as acute versus chronic, intrinsic versus extrinsic, associated with ichthyosis vulgaris, based on morphology (nummular, atopic prurigo, lichen planus-like, pityriasis alba) or based on localization (hand, juvenile plantar and palmar, eyelid, cheilitis, nipple, periorificial). However, none of these classifications seem to be satisfying, because patients often experience dynamic changes between the suggested categories and with affection of different sites ***(Carson et al., 2012).***

Atopic dermatitis is subdivided into two distinct subtypes: an allergic subtype ("extrinsic" AD), and a non allergic subtype ("intrinsic" AD). This distinction has been elusive, at least in part, due to similar clinical presentations ***(Hanifin & Rajka, 1980)***. However, further investigation has revealed specific clinical and immunologic differences which have enabled the differentiation between these two subtypes ***(Turner & Schwartz, 2006)***.

Intrinsic subtype is associated with female predominance, and negative skin prick test ***(Schmid-Grendelmeier et al., 2001)***,

normal levels of total serum IgE (<150 kU/L), and the absence of allergen-specific IgE, other differences in cytokine levels, receptor expression, and frequencies of genetic polymorphisms have also been described, and help contribute to an overall understanding of the complex immunopathology involved in AD ***(Novak & Bieber, 2003; Turner & Schwartz, 2006)***.

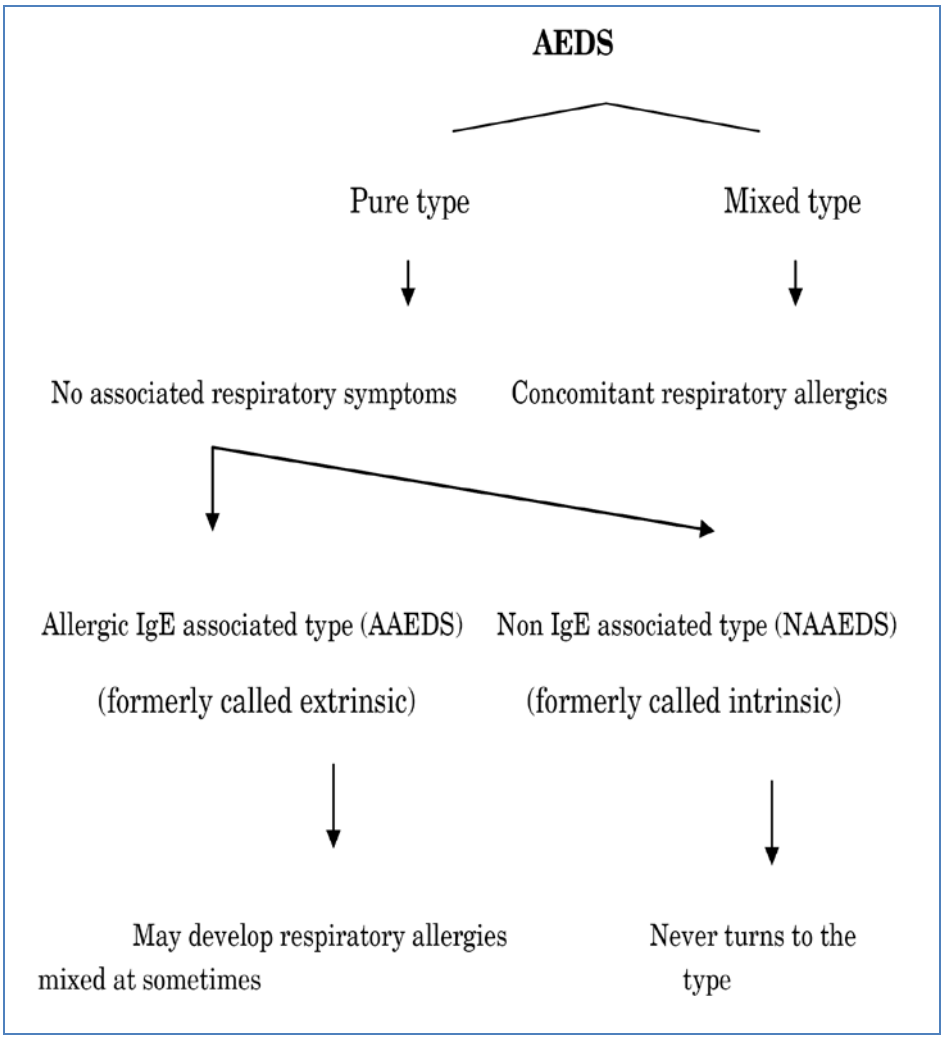

Figure (1): Classification of Atopic Eczema Dermatitis Syndrom (AEDS) ***(Schmid-Grendelmeier et al., 2002)***.

Epidemiology:

Since the beginning of the twentieth century, many mucosal inflammatory disorders have become dramatically more common; atopic eczema (AE) is a classic example of such a disease. It now affects 10–20% of children in industrialized countries ***(Leung and Bieber, 2003)***, but it remains much lower in countries with predominantly rural or agricultural areas ***(Saito & Hirohisa, 2005)***. The prevalence of AE has risen substantially in many countries in recent decades, and this increase has been attributed mainly to changes in lifestyle, nutrition, and environmental factors ***(Diepgen, 2000)***.

- Geographical distribution:

Little is known about the epidemiology of AE, however, geographical variations in prevalence among children have been described and findings closely match regional variations in hay fever ***(Levy et al., 2003)***.

- Prevalence:

Most of the studies on the epidemiology of AD are based on the Western population, mainly in UK and Northern Europe ***(Williams et al., 1996, Williams et al., 2008)***. The prevalence of AD appears to have increased over the past three decades in Western countries, affecting 2-3% of children before 1960 to 9-12% in those born after 1970 ***(Amri et al., 2003)***. However, only few studies have

addressed this issue in countries with a temperate climate, including those of the Mediterranean area ***(Kharfi et al., 2005)***.

Prevalence rates for atopic dermatitis in children over a 1-year period ranged from around 2% in Iran and China to about 20% in Australasia, England, and Scandinavia. Interestingly, populations that migrate from areas of low prevalence to areas of higher prevalence have shown an increased incidence of atopic dermatitis, bolstering the idea of strong environmental influences in the development of atopic dermatitis ***(Williams et al., 2008)***. The prevalence of AD is low (0.65%) in Tunisia by using the UK working party criteria in 6 to 7-year-old children ***(Amouri et al., 2011)***.The prevalence of AD is (19.37%) in Upper Egypt**(Abdel-Hafez et al.,2003).**

Gender distribution:

Atopic dermatitis (AD) is a common disease which tends to affect both males and females. In children aged less than 24 months, the prevalence of AD in males was higher than that of females, while the opposite results were found in children aged 2 yr or older. The difference in the prevalence by gender became more significant with age ***(Yu et al., 2012)*.**

- Age distribution:

It may occur in people of any age but often starts in infants aged 2-6 months. Ninety percent of patients with atopic

dermatitis experience the onset of disease prior to age 5 years ***(Ong & Boguniewicz, 2008)***. Atopic dermatitis (AD) often starts in early infancy; approximately 45% of all cases begin within the first 6 months of life, 60% during the first year, and 85% before 5 years of age. Up to 70% of these children outgrow the disorder before adolescence ***(Bieber, 2008)***.

Seventy-five percent of individuals experience marked improvement in the severity of their atopic dermatitis by age 14 years. However, the remaining 25% continue to have significant relapses during their adult life. A recent study concluded that the prevalence of atopic dermatitis in children younger than 2 years was 18.6% ***(Kvenshagen et al., 2009)***.

Pathophysiology

The pathogenesis of atopic dermatitis is unknown, but the disease seems to be the result of genetic susceptibility, immune dysfunction and epidermal barrier dysfunction ***(Jamal, 2007)***.

- **Epidermis:**
  - Epidermal barrier dysfunction:

It is well established that the first line of defense within the epidermal barrier is the stratum corneum, which serves several fundamental roles in maintaining protection from the environment as well as preventing water loss. This "outside-in" theory views a primary defect in the stratum corneum as a key condition that

drives the inflammatory cascade of AD, predisposing to increased trans-epidermal water loss (TEWL), penetration of irritants, allergens, secondary infection, and increased inflammation ***(Sugarman, 2008)***.

The first level of the barrier is the mechanical skin barrier represented by the stratum corneum and the upper part of the skin. The second level of the skin barrier is represented by structures of the innate immune system such as pattern recognition receptors expressed by skin cells or antimicrobial peptides. The third level of the skin barrier is represented by the cellular defense of components of the adaptive immune system ***(Novak, 2009)***.

Several lines of evidence demonstrate the capacity of the cutaneous barrier to initiate and perpetuate AD including observations that (1) the defects in the barrier result in elevated pH that activates proteases capable of directly inducing a Th2 inflammatory response ***(Briot et al., 2009)***, (2) the severity of the barrier defect parallels AD severity ***(Sugarman et al., 2003)***, (3) the barrier defect persists longer than both the clinical lesions and the underlying inflammation ***(Seidenari & Giusti, 1995)***, (4) several genetic disorders with skin lesions similar to AD implicate abnormal gene coding that affect the epidermal barrier ***(Elias & Wakefield, 2011)***, and (5) therapeutic strategies aimed at repairing the epidermal barrier, as further discussed below, also ameliorates both the inflammation and the clinically involved skin ***(Elias et al., 1999)***.

Patients with atopic dermatitis appear to have significantly decreased levels of skin barrier molecules compared with normal controls. Ceramide lipids in the stratum corneum, which are responsible for water retention and permeability functions, and skin barrier proteins such as filaggrin are expressed at significantly lower levels in the skin of patients with atopic dermatitis compared with the skin of patients without atopic dermatitis ***(Oranje et al., 2006)***.

Expression of ceramide and filaggrin ***(Palmer et al., 2006)*** decreases in skin with atopic dermatitis, particularly in lesions, and is considered as a primary cause of barrier dysfunctions. It is also considered as a secondary phenomenon associated with inflammation and as a cause of atopic dermatitis. Atopic dermatitis is accompanied by an acute itch allegedly due to a lowered threshold of itch. Involvement of IL-31 has been reported as a cause of the above ***(Snkoly et al., 2006)***.

Skin barrier abnormalities appear to be associated with mutations within the filaggrin gene, which encodes a structural protein essential for skin barrier formation. The skin of individuals with AD has also been shown to be deficient in ceramides (lipid molecules) as well as antimicrobial peptides such as cathelicidins, which represent the first-line of defense against many infectious agents ***(Fonacier et al., 2010)***.

These skin barrier abnormalities lead to transepidermal water loss (passage of water from inside the body through the epidermal layer of the skin to the surrounding atmosphere) and increased penetration of allergens and microbes into the skin. The infectious agent most often involved in AD is Staphylococcus aureus (S. aureus), which colonizes in approximately 90% of AD patients ***(Fonacier et al., 2010)***.

In dermatology, the "brick-and-mortar hypothesis" states the stratum corneum (the outermost layer of the epidermis) normally consists of fully differentiated corneocytes surrounded by a lipid-rich matrix containing cholesterol, free fatty acids, and ceramide; the structure of this matrix closely resembles that of bricks and mortar in a wall. In eczema, lipid metabolism is abnormal, causing a deficiency of ceramide that leads to transepidermal water loss ***(Sehra et al., 2008)***.

- **Immune dysfunction (Inflammatory Mechanism):**

Clinically, AD progresses as two distinct phases: an early, acute phase with intensely pruritic, erythematous, papular lesions, followed by a chronic phase characterized by dry, fibrotic lichenified papular lesions. Immunologic abnormalities have been demonstrated as a core feature in both phases of AD and have been investigated extensively ***(Leung et al., 2004)***.

Innate as well as adaptive immune systems play a major role in the pathophysiological puzzle of AD. The former are

able to promptly react to almost all kinds of microbial colonisation and attacks, while they are also involved in the initiation of the more specific but slower mechanisms of the adaptive immune response ***(Schroder & Harder, 2006)***.

Epithelial cells of the skin are equipped with highly conserved recognition structures called pattern recognition receptors (PRRs) such as the Toll-like receptors (TLRs). These TLRs can bind a variety of microbial structures due to highly conserved microbial surface molecules called pathogen-associated molecular pattern (PAMP) ***(Schroder & Harder, 2006)***.

The binding of microbial products to the cell surface of epithelial cells leads to cell activation, ultimately resulting in the production of newly described molecules with antimicrobial activities: the antimicrobial peptides (AMPs). In human skin the major AMPs are cathelicidin (LL37) and human beta defensin (HBD) 1, 2 and 3. It has been shown that the strong colonisation of AD with *Staphylococcus aureus* (which can trigger/enhance inflammation in an allergen independent way by the secretion of superantigens/enterotoxins) and the higher risk of developing widespread viral infections (eczema herpeticum) are due to a down regulation of AMPs secondary to the particular inflammatory micro-milieu ***(Howell et al., 2006)***.

Atopic dermatitis is characterized by multiple alterations of the adaptive immune system. A predominant systemic T-helper type 2 (Th2) dysbalance with increased IgE levels and eosinophilia are the hallmarks in this condition, while only eosinophilia is seen in non-atopic eczema. Interestingly, a Th2 profile is only detected in early/acute lesions of AD while chronic lesions rather have a Th1/Th0 pattern. Thus, chronic AD is not a classical Th2 disease but rather a biphasic (Th2 followed by Th1) disease. Another unsolved question is the role of reported Th1-mediated apoptosis since apoptotic cells are more observed in acute lesions with Th2 profile and not in chronic lesions ***(Novak & Bieber, 2003)***.

Atopic dermatitis is a disease included in the eczema/dermatitis group. The dominant mechanisms of atopic dermatitis in lesional skin are governed by Th2 cell-related cytokines such as IL-4 and IL-13, and chemokines such as TARC and eotaxin ***(Bieber, 2008)***.

Clinically unaffected skin in patients with atopic dermatitis has increased numbers of T-helper type 2 (Th2) cells compared with skin in patients without atopic dermatitis. Increased levels of interleukin (IL)-4 and IL-13 (Th2 cytokines) are seen in acute atopic dermatitis skin lesions, whereas chronic atopic dermatitis lesions show increased expression of IL-5 (Th2 cytokine) and IL-12 and interferon (IFN)-γ (Th1 cytokines). Chronic atopic dermatitis lesions also exhibit

greater eosinophil infiltration compared with skin in patients without atopic dermatitis ***(Flohr & Yeo, 2011)***.

IL-4 enhances differentiation of T-helper cells along the Th2 pathway, and IL-13 acts as a chemoattractant for Th2 cells to infiltrate atopic dermatitis lesions. IL-13 may also directly induce IL-5 expression and eosinophil infiltration, thereby facilitating the transition from acute lesions into chronic lesions ***(Ong & Leung, 2006)***.

- IgE auto-reactivity:

Repetitive allergen challenge and activation of the immune system is a typical feature of AD. Reactivity against self antigens with structural homology to environmental allergens is partly a result of a molecular mimicry between different B-cell epitopes ***(Zeller et al., 2008)***.

In the past, it was observed that patients with chronic AD showed IgE autoreactivity to a variety of human antigens. This IgE autoreactivity has been shown to be more frequently present in AD patients with an early onset of AD and a wide spectrum of sensitizations ***(Mothes et al., 2005)***.

One example in this context is the stress-inducible enzyme manganese superoxide dismutase (MnSOD), which has been shown to play a role as an autoallergen in AD. Specific IgE antibodies against this antigen have been shown to correlate