INTRODUCTION

Soybeans are in the legume family, which also includes foods such as kidney beans, peas, lentils, and peanuts. Soybeans, are used in a lot of processed foods. Soy protein is an important component of soybeans and provides an abundant source of dietary protein ***(Asgar et al., 2010).***

Food allergy to soy has been described in young children. Soy bean-induced allergic symptoms can range from skin, gastrointestinal or respiratory tract reactions up to anaphylaxis ***(Kattan et al., 2011).***

Those symptoms could be due to an IgE-mediated reaction occurring immediately or within 1–2 hours of ingestion, or it could be due to non-IgE-mediated with delayed onset beyond two hours of ingestion, and finally it could be due to a mixed reaction which may present with acute or chronic symptoms. The diagnosis of soy allergy is based upon the clinical history, allergy testing and if needed, a diagnostic trial including elimination, challenge, and re-elimination ***(Kattan et al., 2011).***

The prevalence of soy protein allergy in general population is very common, affecting approximately 0.4% of all children ***(Savage et al., 2010),*** and 6% in allergic children ***(Sicherer and Sampson, 2010).***

Atopic diseases of infants and children are common, debilitating, chronic and sometimes even life-threatening ***(Lifschitz, 2015).*** Atopic dermatitis (AD) is recognized to be one of the first clinical signs of allergy ***(Strucinska et al., 2015).***

Food allergy has been demonstrated to play an important role in the pathogenesis of atopic dermatitis. The most common offending foods are cow's milk, hen's egg, wheat and soy. The diagnostic work-up of suspected immediate food hypersensitivity reaction includes skin prick tests (SPT) and the measurement of specific Immunoglobulin E, while that for delayed clinical symptoms is atopy patch test (APT) ***(Fiocchi et al., 2010).***

SPT is an essential test procedure to confirm sensitization in IgE-mediated allergic disease. It is minimally invasive, inexpensive, and results are immediately available. The recommended method of prick testing includes the appropriate use of specific allergen extracts, positive and negative controls, interpretation of the tests after 15 – 20 minutes of application, with a positive result defined as a wheal ≥3 mm diameter. SPT is highly specific and sensitive to diagnose inhalant allergens with 70-95% and 80-97%, respectively, while it has lower sensitivity and specificity for food allergens ranging from 30-90% and 20-60% ***(Heinzerling et al., 2013).***

Aim of the Work

This study aims at evaluating the incidence of Ig-E mediated soy-protein sensitization among children with clinical manifestation of atopic disorders by the use of SPT for soy protein and to correlate its results to clinical manifestations and laboratory parameters.

Chapter 1
ATOPIC DERMATITIS

Atopic dermatitis (AD) is a chronic relapsing pruritic inflammatory skin disease typically occurring in early childhood. It is also called eczema ***(Ricci et al., 2009)***. It is considered part of an atopic state whose manifestation includes asthma, allergic rhinitis, allergic conjunctivitis, and food allergies ***(Spergel, 2010)***. Atopic dermatitis includes two types; extrinsic and intrinsic, and each associated by eosinophilia ***(Yatagai et al., 2018)***.

The extrinsic form involves 70-80% of the patients and is associated with Ig-E mediated sensitization mostly to environmental allergens. Aeroallergens and food may affect the disease, with less contribution of hereditary factors. In contrast, the intrinsic form involves only 20-30 % of patients and does not seem to be associated with Ig-E mediated ***(Tokura, 2018).***

Evidence suggests that atopic dermatitis is a cutaneous manifestation of a systemic disorder that also gives rise to other atopic conditions. AD is often the initial step in the atopic march which is the phenomenon of switching from one expression of allergy to another ***(Hill et al., 2018).*** Children who are very allergic can develop different manifestations of allergy according to age ***(Dharmage et al., 2014).***

In the first year of life, infants usually start with food allergy manifesting as diarrhea, vomiting, failure to thrive, followed by eczema. Subsequently, they will switch to other expressions of allergy as allergic rhinitis and asthma. This phenomenon of switching from one expression of allergy to another is called the "Allergic March" ***(Hill et al., 2018).*** The exact mechanisms of switching from one expression of allergy to another are unknown. Probably, it has something to do with exposure to allergens and time for sensitization to allergic substances ***(Van Bever, 2009).***

Prevalence

Atopic dermatitis is considered the most frequent chronic skin disease of early childhood ***(Boguniewicz and Leung, 2010)***. Its prevalence has doubled or tripled in industrialized countries during the past three decades. Being significantly lower in rural areas, emphasizing the importance of lifestyle and environment in the mechanisms of atopic disease ***(Del Rosso, 2011).*** it affects up to 25% of children and 2 to 3% of adults ***(Eichenfield et al., 2014)***. In Egypt, A recent study included one hundred and forty children selected from the pediatric and dermatology clinics of Ahmed Maher Teaching Hospital and concluded that the prevalence of AD was 64.28% ***(Elhussieny and Eskander, 2015).***

In infants and children, males were found to be more affected with a ratio of (1.2:2) ***(Odhiambo et al., 2009).***

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 ***(Terui, 2009).*** When both parents are affected by AD, up to 81% of their children may manifest the disease. When one parent is affected, the prevalence drops to 56%. Twin studies of AD have shown concordance rate of 0.72-0.87 in monozygotic, and 0.21-0.23 in dizygotic twins ***(Figure 1) (Pyun, 2015).***

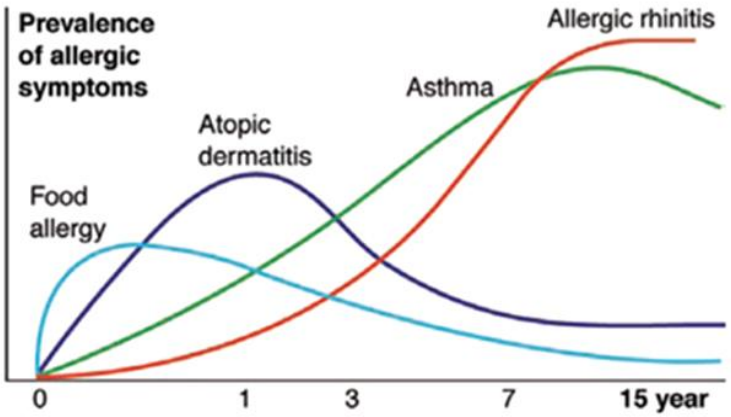

Figure (1): Prevalence of allergic symptoms in relation to age ***(Pyun, 2015).***

Pathogenesis of Atopic Dermatitis

The manifestations of AD result from a complex interaction between different environmental factors, skin barrier dysfunction, genetic susceptibility and immunological abnormalities ***(Boguniewicz and Leung, 2011)***. There are two primary disease models:

- First model; AD as a skin disease, which primarily develops from intrinsic defects of epithelial cells and the skin barrier, resulting in numerous abnormalities of the innate and adaptive immunity *(outside-inside hypothesis)* ***(Ando et al., 2013)***.
- Second model is primarily an immunologic disease with mechanisms related to over activation of the immune system and T-helper 2 (Th2)-dominated immune responses that impact on skin barrier function secondarily *(inside-outside hypothesis)* ***(Kuo et al., 2013)***.

It is likely that the combination of a continuous interplay between both hypotheses best explains the complexity of atopic dermatitis ***(Ando et al., 2013).***

Severely dry skin is a hallmark of AD which result from compromise of the physical and chemical structures of the epidermal barrier, which leads to excess trans-epidermal water loss ***(Elias and Wakefield, 2014).*** Filaggrin a component of the cytoskeleton, and its breakdown products are critical to skin barrier function. Genetic mutations in the Filaggrin gene family have been identified in up to 50% of severe patients with AD. Such patients have increased risk of bacterial, viral, and fungal infection related to impairment of innate immunity, including a loss of barrier function and impaired generation of antimicrobial peptides ***(Thyssen and Kezic, 2014).***

In extrinsic AD, memory T cells (expressing the skin homing receptor), and cutaneous lymphocyte-associated

antigen (CLA), produce increased levels of Th2 cytokines. These include interleukin-4 (IL-4) and interleukin-13 (IL-13), which are known to induce isotype switching to Ig-E synthesis, as well as interleukin-5 (IL-5), which plays an important role in eosinophil development and survival **(Figure 2)** ***(Czarnowicki et al., 2015)***.

These **CLA^+ T cells** also produce abnormally low levels of γ-interferon (IFN-γ), a T-helper 1(Th1) cytokine known to inhibit Th2 cell function. Intrinsic AD is associated with less IL-4 and IL-13 production than extrinsic AD ***(Tokura, 2018).***

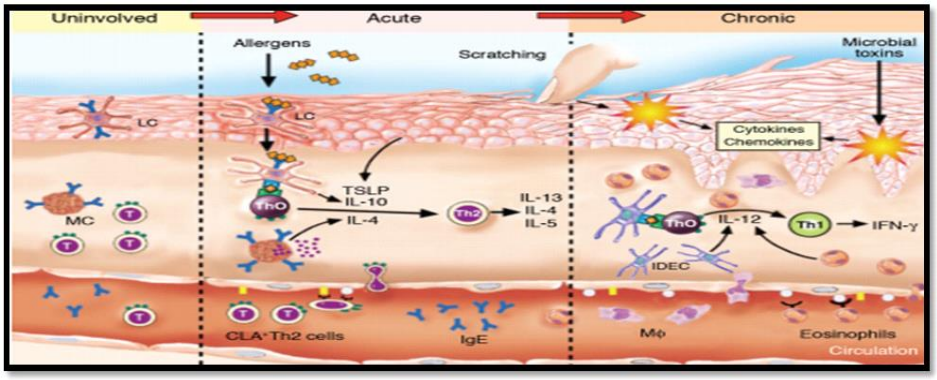

Figure (2): Immunologic pathway in atopic dermatitis. Th2 cells circulating in the peripheral blood of AD patient result in elevated serum Ig-E and eosinophils. These T-cells expressing the skin homing receptors. CLA, and mast cells (MA) that contributes to Th2 cell development. Skin injury by environmental allergens, scratching or microbial toxins activates keratocytes to release pro-inflammatory cytokines and chemokines that induces expression of adhesion molecules on vascular endothelium and facilitates the extravasation of inflammatory cells into the skin. Keratinocyte-derived thymic stromal lymphopoietin (TSLP) and DC-Derived IL-10 also enhance Th2 cell differentiation.AD inflammation is associated with increased Th2 cells in acute skin lesions. But chronic AD results in the infiltration of inflammatory IDECs, macrophages and esimophils.IL-12 production by these various cell types result in the switch of a Th1- type cytokine milieu associated with increased IFN- γ expression ***(Otsuka et al., 2017).***

Factors contributing to flares of AD

In many patients, atopic dermatitis takes a chronic, relapsing course when it is not possible to predict periods of activity or pinpoint aggravating factors. However, several exposures are well known for aggravating eczema and should be avoided e.g: a large number of patients are sensitive to woolen clothing, hot water, infections especially by staphylococci, foods and others ***(Thomsen, 2014)***.

Example to Foods causing exacerbations includes cow milk, egg, peanut, tree nuts, soy, wheat, fish and shellfish **(Figure 3)** ***(Murota, 2017*)**.

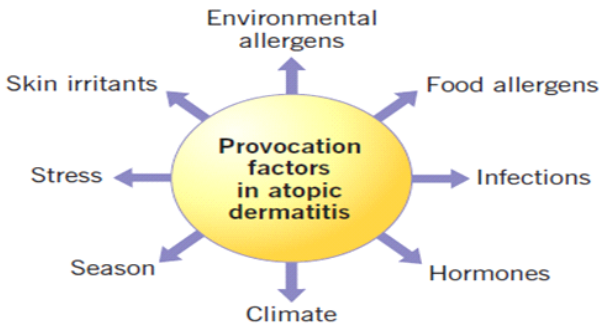

Figure (3): Common provocation factors in AD ***(Murota, 2017).***

Diagnosis of atopic dermatitis

Diagnostic Clinical criteria:

The clinical manifestations of AD vary with age, severity **(Table 1)** and disease course **(Figure 4).** In infants, in the first 2-6 months of life. Dermatitis usually begins with symmetric affection of both cheeks, may extend to involve the remainder of the face, neck, wrist, hands and extensor aspects of extremities, while the diaper area is usually spared. Pruritus is intense. There are marked dryness, erythema, vesiculation, oozing, crusting with bacterial or viral super-infection ***(Spergel, 2015).***

Children from 3 to 13 years typically have involvement of the flexural surfaces of the extremities with accentuation on the elbows and knees flexures, sides of the neck, wrists and ankles. Chronic inflammation with lichenification, xerosis often generalized, excoriation and crusting are prevalent. Pallor of the face with erythema and scaling around the eyes is frequently seen ***(Siegfried and Hebert, 2015).***

In adulthood, lesions become more diffuse with an underlying background of erythema; the face is generally involved with a dry scaly appearance. Xerosis is prominent and lichenification is present. A brown macular ring around the neck is typical but not always presents ***(Sehgal et al., 2016).***

Table (1): Categorization of physical severity of atopic eczema ***(Siegfried and Hebert, 2015).***

Clear	Normal skin, with no evidence of a topic eczema
Mild	Areas of dry skin, infrequent itching(with or without small areas of redness)
Moderate	Areas of dry skin, frequent itching, redness (with or without excoriation and localized skin thickening)
Severe	Widespread areas of dry skin, incessant itching, redness(with or without excoriation, extensive skin thickening, bleeding, oozing, cracking, and alteration of pigmentation)

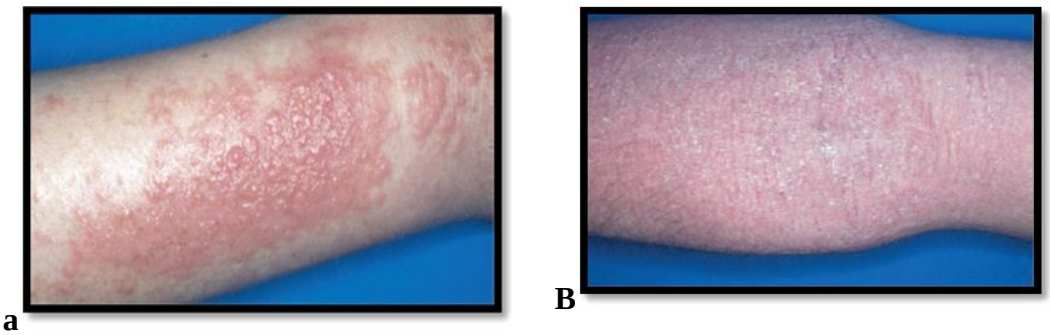

Figure (4): Morphology of acute versus chronic eczema (a) acute eczema characterized by marked erythema, superficial papules, and vesiclues. (b) Chronic eczema characterized by faint erythema, infiltration, and scaling ***(Breuer et al., 2004).***

Investigations:

Diagnosis of AD is usually based on clinical criteria and is rarely aided by investigation. Although there are investigations of exacerbating factors in AD involving a patient history, specific skin and blood tests, and challenge tests, which depend on the degree of the disease severity and on the suspected factors involved. Currently there is no diagnostic laboratory test for AD. Although the majority of AD patients have elevated total serum Ig-E, up to 30% of these patients have normal total serum Ig-E ***(Johansen et al., 2015)***.

Estimation of total serum Ig-E, Radio-allegro-immunosorbent tests (RASTs) and prick tests serve only to confirm the atopic nature of an individual. Patch test may also help to identify allergens responsible of deterioration of skin condition in AD ***(Kaminuma, 2018).***

Management of atopic dermatitis

Atopic dermatitis is, overall, quite difficult to treat. Many patients will experience a chronic course of the disease. Accordingly, the treatment of atopic dermatitis aims to: (1) Minimize the number of exacerbations of the disease (flares). (2) Reduce the duration and degree of the flare (if occurs) ***(Werfel et al., 2016).***

Whenever possible, the recognition and elimination of triggering and aggravating factors are the main priority in the

management of the disease; most patients also need pharmacologic intervention. Topical therapies comprise the foundation of AD treatment ***(Gerbens et al., 2017)***. The successful management of atopic dermatitis requires a multifaceted approach that involves patient and caregiver education, identification and elimination of flare factors, optimal skin care practices by trying to reduce the dryness of the skin, primarily via daily use of skin moisturizing creams or emollients along with avoidance of specific and unspecific irritants such as allergens and non-cotton clothing ***(Thomsen, 2014).*** When dryness is reduced, the desire to scratch will lessen and the risk of skin infection will decrease. Avoiding long, hot baths further prevents skin dryness, but when a bath is taken, an emollient should be applied directly after it to secure a moist epidermis and augment the skin barrier function. Reducing the flare is warranted when actual eczema occurs or when mild intermittent eczema worsens ***(Sidbury et al., 2014)***.

Management of an eczema exacerbation requires medical treatment often in the form of anti-inflammatory treatment with topical corticosteroids (first-line) and/or topical calcineurin inhibitors (TCIs), the use of first-generation antihistamines to help manage sleep disturbances, phototherapy (ultraviolet, UV light) and the treatment of skin infections. Systemic corticosteroids may also be considered in severe cases that cannot be controlled with appropriate skin care and topical therapy ***(Lewis-Jones and Mugglestone, 2007)***.

Table (2): Treatment of AD according to severity ***(Lewis-Jones and Mugglestone, 2007).***

Mild a topic eczema	Moderate a topic eczema	Severe a topic eczema
• Emollients • Mild potent topical CSTs	• Emollients • Moderate potent topical CSTs • Bandages • TCIs	• Emollients • Potent topical CSTs • Bandages • Phototherapy • Systemic therapy

CSTs; corticosteroids. TCIs: Topical calcineurin inhibitors

Topical corticosteroids are the first-line pharmacologic treatments for AD, as they can effectively control atopic flares through their anti-inflammatory, anti-proliferative and immunosuppressive actions ***(Wollenberg et al., 2018).***

Chapter 2
SOYA ALLERGY

Soybeans are in the legume family, which also includes foods such as kidney beans, peas, lentils, and peanuts. Soybeans, also called edamame, are used in a lot of processed foods. Soy protein is an important component of soybeans and provides an abundant source of dietary protein ***(Shurtleff and Aoyagi, 2009).***

Soy is introduced into the diet early in life, often in the form of infant formula in children with intolerance or allergy to cow's milk. Because they are very digestible, they are well-suited for children, pregnant and lactating women and elderly. Soybean exposure is widespread in Asia and the USA but its consumption has increased in Europe too during the past years, particularly in vegetarian cuisine and because of food technological benefits achieved by adding soy proteins to various processed food products ***(Nowak-Węgrzyn et al., 2015).***

In the last few years, interest in soybeans and soybean components has markedly increased, mainly because of the potential influence of soy on the development of heart disease, cancer, kidney disease, osteoporosis, and menopause symptoms. Unfortunately, soy protein formulas (SPFs) can cause allergies and other intolerance reactions. For many years after the first description by Duke in 1934, soy was considered