Introduction

Psoriasis is an immune mediated disease that affects skin characterized by hyperproliferation and inflammation of the skin. It is the most common chronic inflammatory skin disease, affecting about 2-3% of the general population ***(Priya et al., 2013).***

It is clinically characterized by well-demarcated red papules and plaques covered with silvery laminated scales, mainly on the extensor surfaces with symmetrical distribution. Histopathologically, there is cutaneous inflammation, increased epidermal proliferation, hyper-keratosis, angiogenesis, abnormal keratinization, shortened maturation time and parakeratosis ***(Bowcock, 2003).***

Trace elements are essential to biochemical processes in the body and are involved in immunological and inflammatory reactions such as keratinization and melanin formation ***(Hinks et al., 1987).***

Zinc is one of the important trace elements constituting less than 0.005% of total body weight and is related to health and disease. In fact, congenital and acquired zinc deficiencies express as a variety of skin manifestations such as psoriasis like eruptions, blisters and loss of hair ***(Bergomi et al., 1998).***

Copper is also one of the important trace elements with a plasma level of about 90µg/dl. It is necessary for growth, development and maintenance of bone and connective tissue. Copper stimulates the immune system to fight infections. It also helps to neutralize 'free-radicals' which can cause severe damage to cells ***(Johnson et al., 1992; Failla and Hopkins, 1998).***

Some experts believe that elevated copper levels, especially when zinc levels are also low, may be a contributing factor in many medical conditions including hypertension, fatigue, muscle and joint pain, skin diseases and premenstrual syndrome ***(Turnlund et al., 2004).***

There are contradictory reports regarding serum level of trace elements in psoriasis ***(Dadres et al., 2012)***. Regarding zinc, some studies show decreased serum zinc level in psoriatic patient in relation to healthy volunteers ***(Lee et al., 1996; Al-Jebory, 2012),*** while others find no significant difference ***(Dadres et al., 2012; Ala et al., 2013)***. Regarding copper, some studies showed increased level of serum copper in psoriatic patients in relation to healthy volunteers ***(Hinks et al., 1987; Ala et al., 2013)***.

Aim of the Work

The aim of this study is to evaluate serum zinc and copper levels in psoriatic patients and their correlation with the severity of psoriasis.

Chapter 1

PSORIASIS

Psoriasis is a relatively common, chronic, inflammatory and hyperproliferative skin disease that may appear at any age and affects any part of the skin. It affects about 2.8% of the population and both sexes are equally affected ***(Ulrich and Kristian, 2009)***.

Psoriasis results from interaction between an individual's genetic susceptibility, specific environmental factors, and immune mechanism ***(Reich, 2012)***. The most characteristic lesions of psoriasis consist of red, scaly, sharply demarcated, indurated plaques, present particularly over extensor surfaces and scalp. The disease is enormously variable in duration, periodicity of flares and extent ***(Griffiths et al., 2004).*** It often causes functional impairment and psychological handicap leading to alterations in the quality of life ***(Augustin et al., 2010; Klaassen et al., 2014).***

I. Epidemiology of psoriasis:

-Incidence & Race:

Psoriasis is a worldwide occurring disease. Various studies showed that psoriasis affects approximately 2-3% of the population ***(Nickoloff and Nestle, 2004; Mak et al., 2009).***

The wide variation seen in prevalence worldwide is likely influenced, at least in part, by the environment, with higher frequencies seen in areas further from the equator ***(Parisi et al., 2013).*** Reasons for this are likely multifactorial and include differences in sun exposure and other climate differences ***(Namazi, 2004).***

One of the studies done in Saudi Arabia showed psoriasis prevalence to be equivalent to 5.3% ***(Fatani et al., 2002).*** Although psoriasis was described as rare in African Americans, its prevalence among them has been estimated at 1.3%. In the Caucasian population the prevalence is about 1.5% ***(Ferrandiz et al., 2001).*** In other ethnic groups such as the Japanese, the prevalence of psoriasis is much lower ***(Langley et al., 2005; Schon and Boehncke, 2005).***

-Age of Onset:

Psoriasis can begin at any age, although epidemiological studies showed that it mostly appears for the first time in between the age of 15 and 25 years. There are two peaks of onset, the first one from 16-22 years of age and the second from 57-60 years of age. Males and females are equally affected with peak incidence of 22 years in males and 16 years in females. However, it must be emphasized that psoriasis can manifest itself at any age ***(Liu et al., 2007).***

II. Genetic predisposition of psoriasis:

Several large genome-wide association studies, family-based studies, and other genetic studies for psoriasis have been performed, which revealed important risk genes for the disease ***(Ronni et al., 2012).***

The genetic basis of psoriasis is complex as multiple genes are involved. Based on twin studies, the heritability of psoriasis has been estimated to be 60%–90%, which is among the highest of all multi-factorial genetic diseases ***(Elder et al., 2001)***. Concordance rates as high as 70% have been reported among monozygotic twins, versus 12%–30% in dizygotic twins ***(Valdimarsson, 2007)***.

Family studies indicate that if both parents have psoriasis, the offspring have a 50% chance of developing the

disease. The risk decreases to 16% if only one parent has psoriasis. If neither parent is affected but a child develops psoriasis, then their grandchildren have an 8% risk of developing the disease. Men have a higher risk of transmitting psoriasis to offspring than women, which is likely due to genomic imprinting ***(Rahman, 2005).***

Genome-wide association studies have demonstrated at least 9 psoriatic susceptibility loci 1-9 (PSORS 1-9). The most strongly associated susceptibility genes are on chromosome 6p21 within the major histocompatibility complex (MHC) region called the (PSORS-1). These genes are mostly associated with molecules involved in the immune response, inflammation, cell proliferation, and apoptosis, and some are associated with skin differentiation and barrier formation ***(Bowcock, 2010).***

Psoriatic susceptibility locus 1 is believed to account for 35%–50% of psoriasis heritability. An association between psoriasis and other loci has also been reported on chromosomes 1p (PSORS-7), 1q (PSORS-4), 3q (PSORS-5), 4q (PSORS3), 17q (PSORS2), and 19p (PSORS6). The strength of associations between such genes and susceptibility to psoriasis, apart from PSORS-1, varies per study ***(Bowcock, 2010).***

Studies on human leukocyte antigen (HLA) have shown that psoriasis is associated with several HLA antigens, most frequently HLA-Cw6 ***(Trembath et al., 1997)***. In addition, HLA-Cw6 influences the age of onset of the disease. It is expressed in about 85%–90% of patients with early-onset psoriasis, but in only 15% of patients with late-onset disease ***(Richardson and Gelfand, 2008)***.

Human leukocyte antigen-B13, HLA-B17, HLA-B37, and HLA-Bw16 have also been associated with plaque psoriasis. HLA-B27 is expressed with an increased

frequency in pustular psoriasis and acrodermatitis continua of Hallopeau. A significant association between guttate psoriasis in children and HLA-B13 and HLA-B17 expression has been reported. These same HLA antigens are frequently expressed in erythrodermic psoriasis ***(Chen and Chang, 2012).***

Non MHC genes, such as protein tyrosine phosphatase non-receptor type 22 **(**PTPN22), may also play a role in the development of psoriasis as it affects the responsiveness of T and B cell receptors. Mutations of the immunity response are associated with increases or decreases in risks of autoimmune diseases ***(Chen and Chang, 2012).***

III. Precipitating factors of psoriasis:

1)Trauma (Koebner phenomenon):

A wide range of injurious stimuli including physical, chemical, electrical, surgical, infective and inflammatory insults have been recognized to elicit psoriatic lesions in previously uninvolved skin. Koebner reaction usually occurs 7-14 days after injury ***(Griffiths et al., 2004).***

2)Infections:

Acute guttate psoriasis is strongly associated with preceding or concurrent streptococcal infection, particularly of the throat ***(Therleifsdottir et al., 2012)***. Sequence similarities between streptococcal M peptides and human keratins lead to the hypothesis that keratinocytes' proteins function as auto-antigens in psoriasis, and that bacterial super-antigens have a permissive role in its pathogenesis ***(Schon and Boehncke, 2005).***

It has been suggested that Helicobacter pylori may be one of the organisms capable of triggering psoriasis ***(Qayoom and Ahmad, 2003).*** Psoriasis was found to flare severely or to appear de-novo in explosive form as features of human immunodeficiency virus (HIV) infection ***(Griffiths et al., 2004).***

3)Drugs:

There is a growing list of drugs that may aggravate existing psoriasis or induce it for the first time **(Table 1).** The frequency of this adverse event varies between drugs. The ones that are most strongly related to psoriasis are lithium, β-blockers, non-steroidal anti-inflammatory drugs, anti-malarial agents, and angiotensin-converting enzyme inhibitors ***(Fry and Baker, 2007).***

Table 1: List of drugs associated with psoriasis ***(Fry and Baker, 2007).***

Lithium [carbonate]
Propranolol: Inderal
Chloroquine: Aralen
Hydroxychloroquine: Plaquenil
Digoxin
Clonidine: Catapres
Amioderone: Cordarone
Quinidine
Fluoxetine: Prozac
Carbamazepine: Tegretol
Olanzapine: Zyprexia
Doxycycline: Vibramycin, Monodox
Penicillin
Amoxicillin: Amoxil
Ampicillin: Principin
α-Interferon: Pegasys
β-Interferon: Rebif, Avonex
Imiquimod: Aldara
Cimetadine: Tagemet
Gemfibrozil: Lopid

Mechanisms for certain medications are partially delineated. For example, β-adrenergic blockers may induce epidermal hyperproliferation associated with a decrease of intra-epidermal cyclic adenosine monophosphate (cAMP). Lithium may elevate pro-inflammatory cytokines, thereby stimulating cutaneous leucocyte recruitment, while, chloroquine blocks epidermal transglutaminase, an enzyme that is pivotally involved in the terminal differentiation of keratinocytes ***(Schon and Boehncke, 2005).***

Interferon gamma (IFN-γ) is thought to play an important role in the initiation of psoriatic lesions as demonstrated by the induction of pinpoint lesions of psoriasis at sites of IFN-γ injection in previously uninvolved skin. Furthermore, it modulates immune response, is required for activation of macrophages and is an inducer of endothelial adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in psoriatic lesions ***(Cohen et al., 2010).***

4)Sun light:

Although sunlight is generally beneficial, in a small minority of patients, psoriasis may be provoked by strong sunlight and cause summer exacerbations in exposed skin ***(Osmancevic et al., 2007).*** Approximately, 40% of these patients give a history of polymorphic light eruption with psoriasis appearing as a secondary phenomenon. Photosensitive psoriasis is associated with skin type I, advanced age and female sex. Photo-chemotherapy can be helpful in these patients ***(Griffiths et al., 2004)***.

5)Metabolic and endocrinal factors

Endocrinal factors as hypocalcemia have been reported to be a triggering factor for generalized pustular

psoriasis. Pregnancy may alter disease activity leading to psoriasis improvement. Pregnant women, however, may develop pustular psoriasis known as impetigo herpetiformis, sometimes in association with hypocalcemia ***(Van de Kerkhof and Schalkwijk, 2008).***

The early onset of psoriasis in women, with a peak around puberty, changes during pregnancy, and provocation of psoriasis by high-dose estrogen therapy, potentially indicates a role for hormonal factors in the disease ***(Benham et al., 2008).*** Although rare, generalized pustular psoriasis precipitated by pregnancy has repeatedly been reported ***(Griffiths et al., 2009).***

6)Psychogenic factors :

Psoriatic patients exposed to psychological stress express increased number of monocytes and activated T-cells leading to a shift towards T helper-1 (Th-1) derived cytokines profile with subsequent exacerbation of psoriatic lesions ***(Buske-Kirschbaum et al., 2007).***

7)Smoking :

There are many reports suggesting a greater risk of psoriasis among smokers compared to non-smokers ***(Raychaudhuri and Gross, 2000).*** Many of the adverse effects of smoking could result from oxidants in cigarette smoke and the activation of phagocytic cells that generate reactive oxygen species (ROS) ***(Naldi, 1998).***

8)Alcohol consumption:

Alcohol is associated with chronicity, severity and treatment failure of psoriasis, as heavy drinking may increase the risk of infection and mechanical trauma ***(Higgins, 2005).***

9)Diet

Diet plays a role in the etiology and pathogenesis of psoriasis. Polyunsaturated fatty acids such as arachidonic acid may enhance interleukin 1 (IL-1) production and tissue responsiveness to cytokines. Vegetarian diet may be beneficial for patients with psoriasis because it is associated with a reduced arachidonic acid intake with the resulting reduced formation of inflammatory eicosanoids (including leukotriene B4 and prostaglandin E2) ***(Rastmanesh, 2009).***

Vitamin B12 may influence psoriasis due to its role in nucleic acid synthesis. In-vitro studies demonstrated immuno-modulatory effects of vitamin B12 on T lymphocytes and cytokines. Calcitriol and its analogues exert anti-proliferative and pro-differentiative as well as immuno-regulatory activities. Vitamin D receptor (VDR) ligands directly influence T cell activation and modulate the phenotype and function of antigen-presenting cells (APCs) and dendritic cells (DCs) ***(Wolters, 2005).***

10) Obesity:

Obesity leads to a higher risk in developing psoriasis and a poorer long term clinical outcome of psoriasis ***(Menter et al., 2013)***. This fact is proved by the release of tumor necrosis factor (TNF) α which is presumed to be derived from macrophages in the adipose tissue ***(Hamminga et al., 2006).***

An association between psoriasis, obesity, and cardiovascular co-morbidity has been recognized among patients with plaque psoriasis. The association seems to be related to the metabolic syndrome, a state of chronic systemic inflammation characterized by at least 3 of the following: abdominal obesity, impaired glucose regulation

hypertriglyceridemia, reduced high-density lipoprotein levels or hypertension ***(Menter et al., 2008).***

11) Major and trace elements:

Major and trace elements and their compounds have been used since ancient times for their therapeutic as well as cosmetic effects on the skin ***(Afridi et al., 2006).***

It has been shown that essential elements like iron, copper, chromium and vanadium undergo redox cycling and have physiological significance. On the other hand, non-essential toxic elements like cadmium, mercury, nickel and lead, deplete glutathione and protein-bound sulfhydryl groups, resulting in production of ROS like superoxide-ion, hydrogen peroxide, and hydroxyl radical ***(Stohs and Bagchi, 1995).***

The unique process of keratinization and melanin formation is enzyme dependent and therefore could be influenced by their deficiency or excesses as these elements are involved in enzymatic activities and immunologic reactions ***(Bock et al., 2003***). In addition, altered levels of trace elements in the serum of psoriasis patients may serve as markers of the disease condition ***(Basavaraj et al., 2009).***

IV. Immunopathogenesis of psoriasis:

Psoriasis is a multi-factorial skin disease with a complex pathogenesis. Whether psoriasis represents a fundamental disease of skin, or the immune system, has been debated for several years. Various factors which have been suggested to play a key role in the pathogenesis are T cells, APCs, keratinocytes, Langerhans cells (LCs), macrophages, natural killer (NK) cells, an array of Th1 type cytokines, certain growth factors like vascular endothelial growth factor

(VEGF), keratinocyte growth factor (KGF), and others ***(Parisi et al., 2013).***

It has been hypothesized that the disease starts with the activation of T cell by an unknown antigen, which leads to secretion of an array of cytokines by activated T cells, inflammatory cells, and keratinocytes. The characteristic lesion of psoriasis is due to the hyper-proliferation of the keratinocyte ***(Krueger and Bowcock, 2005).***

Activated LCs migrate from skin to lymph nodes presenting the antigen to nodal naïve T cells (cells that have not been activated by antigen previously). The T cells activated by non-antigen-dependent mechanism may, however, become antigen-specific memory cells that react with a cross-reactive auto-antigen such as keratin (molecular mimicry) **(Fig. 1)** ***(Das et al., 2009)***.

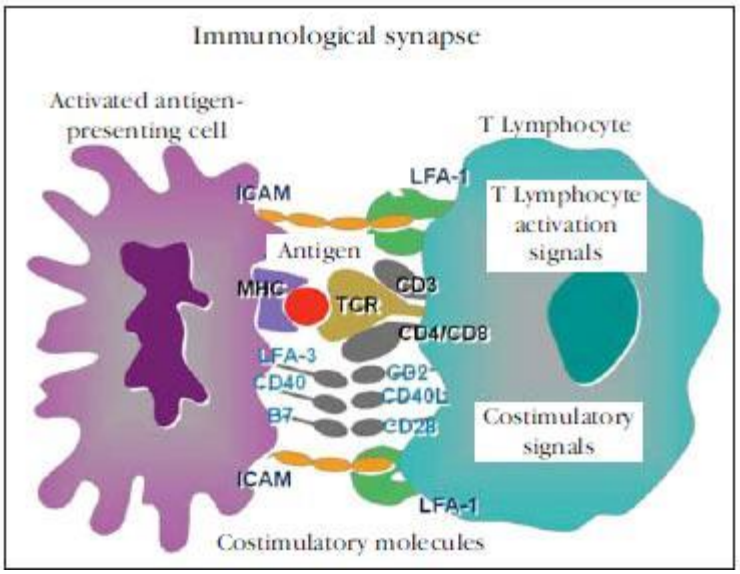

Fig. (1): Immunological synapse model between T-cell and APC at the onset of the psoriatic immune response ***(Das et al., 2009)***.

The pathologic collaboration between innate immunity (mediated by APCs and NK T-lymphocytes) and acquired immunity (mediated by T-lymphocytes);

results in the production of cytokines, chemokines and growth factors. These contribute to the inflammatory infiltrate seen in psoriatic lesions ***(Gaspari, 2006).***

Psoriasis is recognized as the most prevalent T-cell–mediated inflammatory disease in humans. In the dermis, cluster of differentiation (CD) 4+ cells are present in higher numbers than CD8+ cells, while CD8+ cells predominate in the epidermis. The involvement of T lymphocytes in the pathogenesis of psoriasis can be described in terms of 3 events; the initial activation of T-cells, the trafficking of T-cells and the various roles played by cytokines released from T-cell and other cells ***(Krueger and Ellis, 2005).***

1- T-cell activation:

T-cell activation takes place in the regional lymph nodes and it occurs in a series of steps, the first of which is incorporation of unidentified antigens by APCs in the epidermis and dermis. This process involves binding of the antigens to the MHC class II on the APC surface and the APC migrates to the regional lymph nodes ***(Michael et al., 2005).***

In the regional lymph node, the APC binds reversibly with naïve or resting T cells through interactions between surface molecules located on both cells. The MHC presents the antigen to a T lymphocyte receptor to begin activation of the T-lymphocyte. The second signal for T-lymphocyte activation is a cell - cell interaction known as co-stimulation ***(Feelter et al., 2009).***

Co-stimulation involves pairing of receptor with ligands on the T-cell and APC. These pairs include lymphocyte functional antigen (LFA)-3 interacting with CD2, B7 a co-stimulatory molecule interacting with

CD28, and ICAM-1 interacting with LFA-1. A defect in the process of co-stimulation will either lead to unresponsive T-lymphocyte or apoptosis of this T-cell **(Fig. 2)** ***(Sabat et al., 2007)***

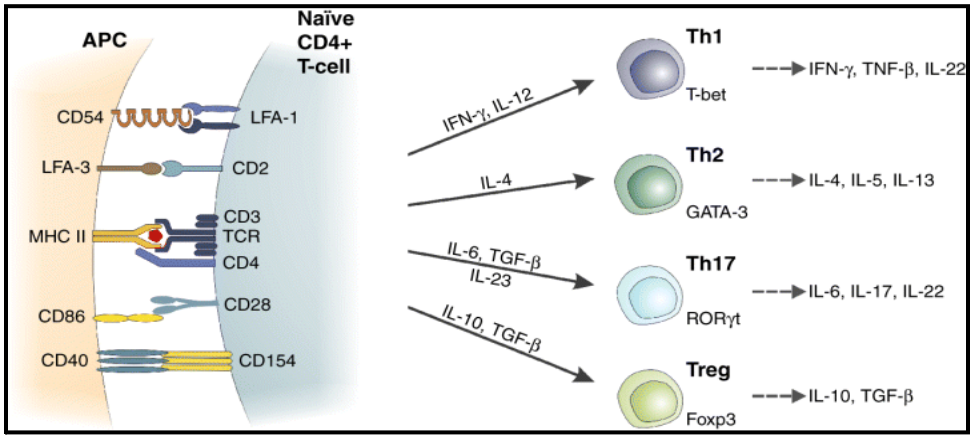

Fig.(2): Activation of naive CD4+ T cells by APCs ***(Sabat et al., 2007).***

This link counts on the participation of biochemical signaling and the co-participation of other agents, particularly the CD28 glycoprotein, located on the surface of the T lymphocytes, and CD80 and CD86, located on the surface of the DCs. This results in an increase in mRNA and the transcription of cytokines such as IL-2, IFN-γ, TNF-α and granulocyte macrophage colony-stimulating factor, which are crucial for T lymphocyte activation. If the co-stimulation promoted by CD28 fails to occur, T lymphocyte activation is partial ***(Mehlis and Gordon, 2004).***

2- T-cell migration to the skin (Trafficking):

During maturation, T-cells express new cell surface proteins. Perhaps the most important trafficking protein on the memory T cell in psoriasis is a glycoprotein termed cutaneous lymphocyte antigen (CLA), which is an