Introduction

Psoriasis is a common, chronic, disfiguring, inflammatory and proliferative condition of the skin, in which both genetic and environmental influences have a critical role. The most characteristic lesion consists of red, scaly, sharply demarcated, indurated plaques, present particularly over extensor surfaces and the scalp. The disease is enormously variable in duration, periodicity of flares and remissions. There are several morphological variants of the disease ***(Griffiths et al., 2004).***

Histologically, psoriasis characterized by hyperplasia of the epidermis, infiltration of leucocytes into the dermis and the epidermis together with dilation and growth of blood vessels .The earliest diagnostic lesion is small smooth surfaced papule shows mounds of parakeratosis containing neutrophils, the earliest manifestation of Munro microabcesses. the older scaly lesions show aggregations of neutrophils in the upper stratum spinosum, which form small spongiform pustules of kogoj while mononuclear cells remain confined to the lower epidermis, meanwhile, the epithelium becomes increasingly, hyperplastic and more mitotic figures are seen above the basal cell layer and the epidermis develops the characteristic psoraisiform appearance, which refers to regular elongation of rete ridges, fully developed lesion may show orthokeratosis admixed with parakeratosis ***(Weedon et al., 2002).***

Adipose tissue is considered an endocrine organ secreting different cytokines known as adipocytokines as IL6, IL8, TNFα, as obesity is a state of chronic inflammation ***(Engström et al., 2003)***.

Lipocalin-2 has been recently identified as an adipokine present in the circulation. It is expressed in liver, lung, kidney, adipocytes, macrophages and epithelial cells; it is related to insulin resistance, obesity, atherosclerotic diseases and type

2diabetes. Lipocalin-2 and psoriasis are assumed to be closely associated with the metabolic syndrome ***(Kamata et al., 2012).***

Th1 and Th17 lymphocytes activation in psoriasis is a shared pathway with adipokine activation. Serum lipocalin-2 is related to Th17 mediated inflammatory markers Il-6 and TNF which are involved in pathogenesis of psoriasis ***(Johnston et al., 2008).***

Serum lipocalin-2 is related to innate immunity macrophages, adiposity, atherogenesis and inflammation ***(Kamata et al., 2012).*** It has also been known as neutrophil gelatinase-associated lipocalin (NGAL) and it is important in the innate immune response to bacterial infection ***(*Seo *et al., 2006).***

Previous results suggested that tissue lipocalin-2 expression reflects the different status of inflammation, and may be related with the epidermal hyperplasia. As lipocalin-2 is confined to distinct subpopulations of keratinocytes underlying areas of parakeratosis this suggests that the onset of keratinocyte differentiation may be a trigger for high induction of Lipocalin-2 expression ***(Mallbris et al., 2002).***

Circulating levels of lipocalin-2 have been reported to be increased in psoriasis ***(Kamata et al., 2012 and Romani et al., 2013).*** Some previous human studies have reported the association of serum lipocalin-2 concentrations with various metabolic parameters and inflammatory markers ***(Moreno-Navarrete et al., 2010).***

Serum lipocalin-2 concentrations were increased in patients with metabolic syndrome, with a significant correlation between lipocalin-2 and measures of insulin resistance ***(Wang et al., 2007).***

Aim of the work

The aim of this work is to assess the level of serum lipocalin -2 in psoriatic patients before and after treatment with Narrow Band Ultra violet-B.

Psoriasis

Psoriasis is a common chronic inflammatory disease that affects the skin and joints. In a genetically predisposed individual, all the elements present in the epidermis and dermis that are involved in the maintenance of barrier integrity are dysregulated in response to either an environmental or self-antigenic insult. Continued dysregulation of the skin immune system exhibits all the hallmarks of chronic skin inflammation ***(Perera et al., 2012).***

Epidemiology :

Prevalence :

Studies have estimated the prevalence of psoriasis being generally more common in the colder north than in the tropics. In Europe, the prevalence of psoriasis varies anywhere from 0.6 to 6.5%. In the USA, the estimated prevalence of diagnosed psoriasis is 3.15%. The prevalence in Africa varies depending on geographic location, being lowest in West Africa. A study from Rochester, USA showed an increasing trend over the last 2 decades. Although, study methodology and case definition may explain some of the variations, genetic and environmental factors are important ***(Chandran and Raychaudhuri, 2010).***

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. A study of the age of onset of psoriasis on 2400 patients showed 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 of age in males and 16 years of age in females. However, it must be emphasized that psoriasis can manifest itself at any age ***(Liu et al., 2007).***

The age of onset of psoriasis has been used for decades as an appropriate descriptor to define two subpopulations of psoriatic patients (types I and II) according to human leucocytic antigen (HLA) class I antigens ***(Quiero et al., 2013).*** However recently, no significant association was found between HLA-C alleles and family history, clinical findings or severity of the disease ***(Bahcetepe et al., 2013).***

Sex :

There is no evidence for morphological differences in psoriasis between males and females **(*Gudjonsson and Elder, 2007*)**. However, significant female preponderance can be seen in the palmoplantar pustular type **(*Griffiths et al., 2000 and Griffiths et al., 2004*)**.

Precipitating factors :

Psoriasis is a multifactorial disease that includes: a genetic predisposition and many triggering factors as seen in **(Figure 1).** These triggering factors may be infections, medications, or mechanical stimuli to the skin. About 40 percent of these patients have relatives who are also suffering from psoriasis ***(Adminon, 2012).***

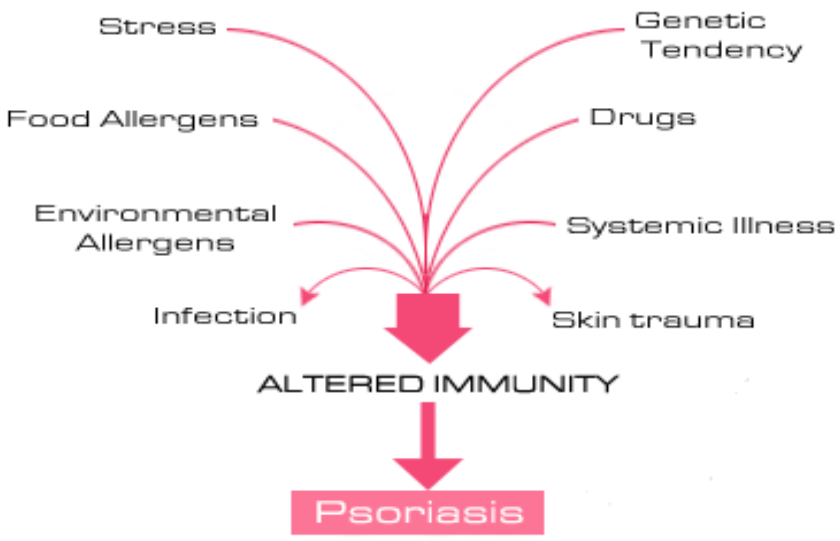

Figure (1): Precipitating factors for psoriasis *(Adminon, 2012).*

Genetic factors :

There are about ten different psoriasis susceptibility genes; PSORS1-PSORS9 and PSORASI, located on the Human Leukocyte Antigen (HLA) class I allele, specifically HLA-Cw6. PSORS1 and PSORS2 are the major genetic determinant for psoriasis ***(Tiilikainen et al., 1980, Tomfohrde et al., 1994, Capon et al., 2002 and Speckman et al., 2003).***

Seven non-MHC loci harbored genes with recognized immune functions were detected which are IL28RA, REL, IFIH1, ERAP1, TRAF3IP2, NFKB1A and TYK2 ***(Sawcer et al., 2010).***

Trauma :

A wide range of injurious local stimuli, including physical, chemical, electrical, surgical, infective and inflammatory insults has been recognized to elicit psoriatic lesions **(*Eyre and Krueger, 1982 and Griffiths et al., 2008*)**.

Mechanical injury causes keratinocytes to release a series of cytokines that are capable of direct stimulation of keratinocyte proliferation or induction of the production of other cytokines through recruiting immune cells **(*Kadunce and Krueger, 199*5)**.

Infection :

There is evidence that streptococcal infection may be important in chronic plaque psoriasis ***(Besgen et al., 2010)***.

Acute guttate psoriasis is strongly associated with preceding or concurrent streptococcal infection, particularly of the throat ***(Thorleifsdottir et al., 2012).***

McFadden et al. (2012), suggests that if streptococcal lytic enzymes are neutralized by host antibodies before irreversible and lasting damage to the basement membrane of the dermal papillae, then guttate psoriasis will resolve spontaneously. In contrast, if permanent damage is induced prior to effective neutralization of the relevant bacterial toxins, then keratinocytes will become chronically destabilized and continue to proliferate and elaborate plasminogen activation enzymes in response to various stimuli and thus sustain plaque psoriasis.

Human immunodeficiency virus (HIV) infection have also been associated with psoriasis **(*Griffiths et al., 2008*)**. However***, Chen et al. (2012)*** analyzed HLA I, II allels and found that psoriatic patients are more likely to have gene variants that are protective against HIV.

One study compared the presence of *Candida albicans* in the saliva of psoriatic patients to a control group, and found that *Candida* may be one of the psoriasis causes confirmed by cytopathology ***(Picciani et al., 2013).*** Helicobacter pylori infection plays a role in the severity of

psoriasis and eradicating such infections enhances the effectiveness of psoriasis treatment ***(Onsun et al., 2012).***

Drugs :

There are many drugs reported to be responsible for the onset or exacerbation of psoriasis. For example, beta adrenergic blockers may induce epidermal hyperproliferation associated with a decrease of intraepidermal cyclic AMP, lithium may elevate pro-inflammatory cytokines, so it stimulates cutaneous leucocyte recruitment and chloroquine blocks epidermal transglutaminase, an enzyme that is involved in the terminal differentiation of keratinocytes. Also rapid tapering of corticosteroids can induce pustular, extensive plaque or erythrodermic psoriasis ***(Tsankov et al., 2000, Schön and Boehncke, 2005).***

Worsening of psoriasis disease with non-steroidal anti-inflammatory drugs (NSAIDs) has been observed for both non-specific and cyclo-oxygenase-2 specific NSAIDs ***(Meyerhoff, 1983, Ben-Chetrit and Rubinow, 1986, Clark and Coulter 2003).***

Stress :

Psychogenic stress is a well-known triggering factor for psoriasis and is said to be as high as 40% in adults and higher in children. It has also been associated with flares of pre-existing psoriasis ***(Gupta et al., 1989 and Mak et al., 2009).***

Recently, it is believed that the main cause for exacerbation of psoriasis with stress is secondary hyperprolactinaemia **(Dilmé-*Carreras et al., 2011).***

Diet :

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 **(*Wilkinson et al., 1990 and Wolters et al., 2005*)**.

Alcohol and smoking :

Over past years, data have been accumulating regarding a possible association between psoriasis and alcohol. A number of studies support role of ethanol and its metabolities as triggering factor for psoriasis ***(Kazakevich et al., 2011).***

Alcohol consumption may adversely affect psoriasis through multiple mechanisms as increased susceptibility to infection, stimulation of lymphocyte and keratinocyte proliferation and production of proinflammatory cytokines ***(Cassano et al., 2011).***

Moreover, cutaneous distribution of psoriasis in heavy drinkers tends to be predominantly acral resembling that in immunocompromised patients ***(Kazakevich et al., 2011).***

Regarding smoking, recent studies suggest that cigarette smoking may trigger development of psoriasis through oxidative, inflammatory and genetic mechanism ***(Armstrong et al., 2011).***

Smoking initiates formation of free radicals that stimulate cell signaling pathways active in psoriasis including mitogen activated protein kinase (MAPK) and nuclear factor-KB ***(Emre et al., 2012)***

Sunlight :

Although sunlight is generally beneficial, in a small minority of patients, psoriasis may be provoked by sunlight and cause summer exacerbations in exposed skin ***(Rutter et al., 2009).***

Hormonal factors :

Many hormonal factors have been implicated in psoriasis. It has been reported that growth hormone (GH), thyroid hormones, estrogens and progesterone may have role in psoriasis **(*Weber et al., 1981, Dunna and Findlay, 1989, Arican et al., 2004 and Murase et al., 2005*)**.

Prolactin (PRL) may modulate the skin immune system and may be involved in the pathogenesis of psoriasis **(*Kanda and Watanabe, 2007 and EL-Kateeb et al., 2010)***.

It has become apparent that prolactin exerts a proliferative effect on human keratinocytes by binding PRL-binding sites on keratinocyte membranes and enhances the production of chemokine (CXC motif) ligand (CXCL)9, CXCL10 and CXCL11, which preferentially attract Th1 cell infiltration into psoriatic lesions ***(Dilmé-Carreras et al., 2011***).

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 ***(Behnam et al., 2005).*** Psoriasis improved in approximately 40% of pregnancies, and worsened in 14% ***(Dunna and Finlay, 1989).*** In contrast, in the 3-month postpartum period, 11% improved and 54% deteriorated. Thus, if psoriasis changes in pregnancy, it is more likely to improve than worsen, while in the postpartum period it is more likely to deteriorate ***(Boyd et al., 1996).*** Although rare, generalized pustular psoriasis precipitated by pregnancy has repeatedly been reported ***(Griffiths et al., 2004).***

Obesity:

Obesity leads to a higher risk in developing psoriasis and a poorer long term clinical outcome of psoriasis. This

fact is proved by the release of tumor necrosis factor α (TNF-α) which is presumed to be derived from inflammatory cells (macrophages) in the adipose tissue and high levels of leptin hormone which stimulates the release of pro-inflammatory cytokines as interleukin 1 β (IL-1β), interleukin 6 (IL-6) and (TNF-α) ***(Dandona et al., 2004).***

Metabolic factors :

Metabolic factors as hypocalcemia and dialysis precipitate psoriasis. Hypocalcemia has also been reported to be a triggering factor for generalized pustular psoriasis, and may be a predictor of poor outcome ***(Stewart et al., 1984 and Griffiths et al., 2004).***

Genetic Predisposition and Inheritance :

The susceptibility to psoriasis has been linked to class I and class II Major histocomptability complex (MHC) on chromosome 6. There are two distinct subtypes of psoriasis that differ in age of onset and human leukocytic antigen (HLA) association. **Type I** psoriasis is the early onset inherited form of the disease, generally developing well before the fourth decade of the life and **Type II** psoriasis present with a less strong familial background characterized by onset after the age of 40 years. In type I, HLA-Cw6, -B57 and DR-7 are strongly increased, whereas in type II, HLA-Cw2 is over presented compared to the general population ***(Lowes et al., 2007).***

Some studies link HLA-Cw*0602 positive patients with more extensive psoriasis of early onset, whereas nail involvement is more common in patients who are HLA-Cw* 0602 negative ***(Gudjonsson et al., 2006).***

With regards to the role of the epidermis in psoriasis development, 3 loci (PSORS1, PSORS2, and PSORS4) are

of particular interest. PSORS1 is also associated with acute-onset guttate psoriasis in adolescents **(*Asumalahti et al., 2003*)**, whereas such an association is missing for late onset psoriasis **(*Allen et al., 2005*)**. Some of these genetic loci have been also found to overlap with other chronic inflammatory diseases as asthma, eczema, chron's disease and rheumatoid arthritis **(*Nickoloff and Nestle, 2004*)**.

Pathogenesis of Psoriasis :

The cardinal features of lesional psoriatic skin are: epidermal hyperproliferation with loss of differentiation, dilatation and proliferation of dermal blood vessels and accumulation of inflammatory cells, particularly neutrophils and T lymphocytes **(*Griffiths et al., 2008*)**.

Epidermal Proliferation:

The increased keratinocyte proliferation observed in psoriasis is a consequence of an increase in the proliferating cell compartment in the basal and suprabasal levels of the epidermis, and not because of shortened cell cycle time. The number of cycling cells is increased approximately seven folds **(*Van De Kerkhof and Van Erp, 2007*)**.

Angiogenesis :

Angiogenesis occurs when activated endothelial cells migrate and form novel vessel networks. Keratinocytes are thought to be a major source of pro-angiogenic cytokines; vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8). However, the precise mechanism for angiogenesis in psoriasis is still unknown **(*Longo et al., 2002*)**.

Immunological factors :

Psoriasis represents a T-cell-mediated inflammatory skin disease, although the primary pathogenic mechanism is still unknown. Specific T-cell populations are stimulated by putative antigen presented by antigen presenting cell (APC) from the skin **(*Fearon and Veale, 2001& Ghoreschi et al., 2007*)**.

Although initial T-cell/APC (T-AP) interactions occur in lymph nodes, ongoing T-AP interactions appear to subsequently occur in psoriatic plaques in the skin. The activated T-cells induce secondary hyperproliferation of epidermal, vascular and occasionally synovial cells through the release of specific cytokine mediators. This multi-step process can be divided into 4 stages: T-cells activation, proliferation and differentiation, migration into the skin, and T-cell-mediated skin inflammation **(*Mehlis and Gordon, 2003 and Krueger and Ellis, 2005*) (Figure 2).**

(I) T-cell activation :

Normally, naïve T-cells are circulating between the lymph nodes and the blood stream. This is due to their high levels of expression of L-selectin that allows them to attach and then roll on surface of high endothelial venules within lymph nodes. Naive T-cells are kept in this circulatory pattern because they lack the specific combinations of adhesion molecules and chemokine receptors necessary to enter extranodal tissues **(*Butcher and Picker, 1996*)**.

T-cell activation takes place in the regional lymph nodes. The process starts with incorporation of unidentified antigens by APCs in the skin. This involves binding of the antigens to major histocompatibility complex (MHC) on the APC surface and then APC migrates to the lymph nodes **(*Trowsdale and Campbell, 1992 and Guenther and Ortonne, 2002*)**.

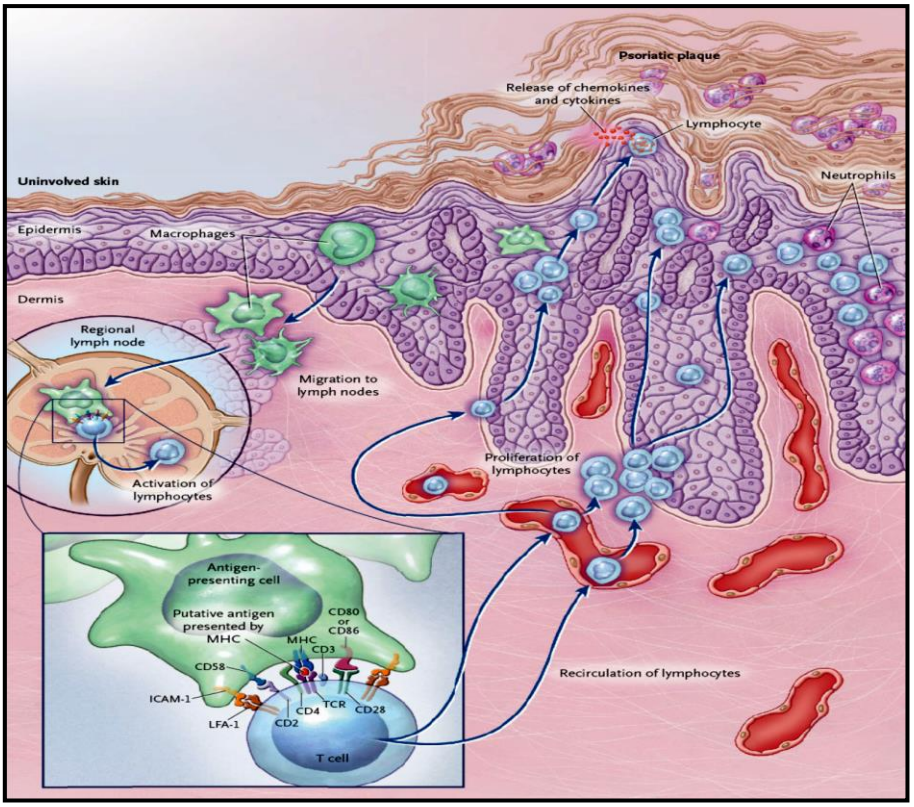

Figure 2: Pathogenesis of a psoriatic lesion (*Schön and Boehncke, 2005*).

In the lymph node, the APC binds reversibly with naïve T-cells through interactions between surface molecules located on both cells; intercellular adhesion molecule-1 (ICAM-1) on APC binds to lymphocyte functional associated antigen-1 (LFA-1) on naïve T-cell. Next, the MHC presents the antigen to a T-lymphocyte receptor to begin activation. The second signal for T-lymphocyte activation is a cell-cell interaction with pairing of receptor with ligand on T-cells; a process known as costimulation **(*Berridge, 1997*)**.

The pairs include LFA-3 interacting with CD-2, B7 (CD-80 and CD-86) interacting with CD-28 and ICAM-1 interacting with LFA-1. A defect in this process may lead to

unresponsivness or apoptosis of T-cells **(*Guenther and Ortonne, 2002, Lebwohl, 2003 and Mehlis and Gordon, 2004*)**.

The third set of signals delivered to the T-cell are from the cytokines; interleukin (IL-2) (made by activated T-cells) and IL-12 (made by mature Langerhans' cells). Binding of these cytokines to surface receptors expressed on activated T-cells regulates mitotic activation and differentiation of T-cells into type 1 effectors **(*Kruger, 2002*) (Figure 3).**

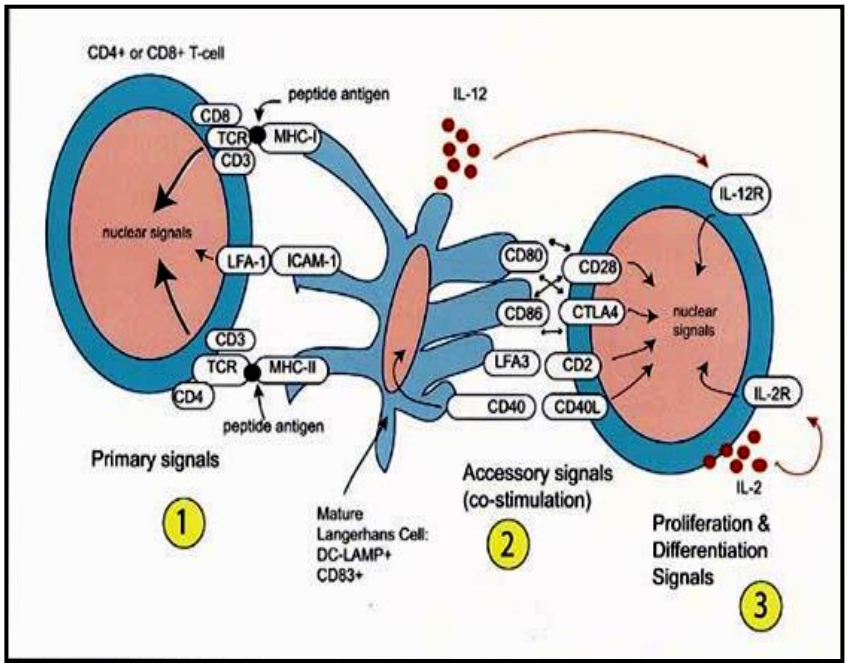

Figure (3): T cell activation signals (*Kruger, 2002*).

(II) T cell proliferation and differentiation :

After activation, naïve CD4+T-cells can be polarized into 4 different directions; T helper (Th) Th1, Th2, Th17 and T-regulatory cell (T-reg). Each pathway is enhanced when a certain inerleukin and/or transcription factor is produced during activation process **(*Weaver et al., 2006*) (Figure 4).**