INTRODUCTION

Psoriasis is one of the most prevalent chronic inflammatory skin diseases, affecting 1–3% of the Caucasian population and causes significant impairment of quality of life, at least to the same extent as other major medical diseases ***(Globe et al., 2009).*** Patients with psoriasis have a genetic predisposition for the illness, which most commonly manifests itself on the skin of the elbows, knees, scalp, lumbosacral areas, intergluteal clefts, and glans penis. The joints are also affected by psoriasis in up to 30% of patients with the disease ***(Gulliver, 2008).***

The most common form is chronic plaque psoriasis, which is characterized by sharply demarcated, erythematous, and scaly symmetrical plaques ***(Nickoloff and Nestle, 2004).*** The hallmark features of a psoriatic plaque include hyperproliferation of epidermal keratinocytes with resulting hyperkeratosis, infiltration of lymphocytes, and angiogenesis ***(Mercuri and Naldi, 2010).***

Although the precise pathomechanism of psoriasis remains unknown, various cytokines and growth factors are involved in this disease ***(Griffiths and Barker, 2007).*** TNF-α is a pleiotropic inflammatory cytokine, and studies indicate that TNF-α plays a critical role in the development of psoriasis ***(Boehncke et al., 2007).***

Psoriasis is associated with increased risks of cardiovascular disease, metabolic syndrome, diabetes and obesity compared with non-psoriatic skin disease ***(Mrowietz et al., 2006).***

Adiponectin is an adipocyte-specific secretory protein abundantly present in the circulation. Plasma levels of adiponectin are decreased in obesity, insulin resistance and type 2 diabetes ***(Matsuzaka, 2006),*** and hypoadiponectinaemia is assumed to be closely associated with the metabolic syndrome ***(Hulthe et al., 2003).*** Considering the fact that adiponectin is related to metabolic syndrome ***(Shibata et al., 2009)***, which can coexist with psoriasis, it cannot be excluded that this protein plays a role in pathophysiological processes in psoriasis ***(Gerkowicz et al., 2012)***.

AIM OF THE WORK

The aim of this study is to assess the level of circulating TNFα and adiponectin in the serum of chronic plaque psoriatic patients with different severities and normal healthy controls with and without metabolic syndrome in order to determine their possible role in pathophysiological processes in psoriasis and metabolic syndrome.

PSORIASIS

Introduction:

Psoriasis is a common chronic inflammatory skin disease that affects 1% to 3% of the general population. Both genetic and environmental factors have a role in its pathophysiology ***(Sales and Torres, 2014)***.

Psoriasis histological characteristics are epidermal hyperplasia, dilatation, and proliferation of dermal blood vessels and accumulation of inflammatory cells, particularly neutrophils and T lymphocytes in the dermis ***(Griffiths and Barker, 2007)***.

Psoriasis has a negative impact on quality of life, similar to that of patients living with diabetes, cancer, or heart disease ***(Krueger et al., 2001)***.

Epidemiology:

Psoriasis is a disorder with a relatively high prevalence in the general population. The estimated worldwide prevalence ranges from 0.6% and 4.8% of the population ***(Ruceviae et al., 2003 and Naldi, 2004)***. With an incidence of 2.5% in Caucasians and 1.3% in African-americans ***(Brzewski et al., 2013).***

Psoriasis can begin at any age & seems to be genetically determined. Men and women are equally affected. 25% of patients develop the disease before the third decade. Another peak incidence is recorded in the fifth and sixth decades ***(Burd, 2006)***.

The risk of developing psoriasis is greater when one of the parents is affected. Among the patients with childhood psoriasis, 49% have affected first degree relatives. Studies have shown affection of monozygotic twins up to 75% ***(Benoit and Hamm, 2007)***.

Predisposing factors:

1-Trauma:

Isomorphic phenomenon of Köbner manifests the onset of the lesion in healthy skin areas after the local trauma which may be physical, chemical, electrical, surgical, infective and inflammatory insults in patients genetically predisposed or affected by the disease ***(Romiti et al., 2009)***.

Köbner phenomenon occurs in 1/3 of the psoriasis patients. The lesions appear after few days or even years. The pathogenesis of this phenomenon remains controversial, focusing mainly on immune and vascular affections. The phenomenon may be evidenced in 50% of the children with psoriasis ***(Romiti et al., 2009)***.

2- Infection:

Acute guttate psoriasis is strongly associated with preceding or concurrent β-haemolytic streptococcal infection, particularly of throat infection. It has been postulated that cross-reaction between M protein (a virulence factor usually expressed by β-haemolytic streptococci) and human epidermal keratin (keratins 16 and 17 are not present in normal epidermis,

but both are markedly upregulated within psoriatic lesions) may play a role in the pathogenesis of psoriasis, most likely at the T-cell level, macrophages and Langerhans cells ***(Gudjonsson et al., 2003 and Thorleifsdottir et al., 2012).***

The association between human immunodeficiency virus (HIV) infection and psoriasis has been recognized in the form of induction or exacerbation of psoriasis. One study reported improvement of psoriasis associated with HIV by using zidovudine, not only through improving the HIV infection, but also through its direct effect on keratinocytes proliferation ***(De Socio et al., 2006)***. One study found that Candida may be one of the psoriasis causes confirmed by cytopathology ***(Picciani et al., 2013)***.

3- Sunlight:

Although sunlight is generally beneficial, in a small minority of patients, psoriasis may be aggravated by strong sunlight. Photosensitivity in psoriatic patients was associated with skin type I, advanced age and females. Photochemotherapy (PUVA) can be helpful in these patients ***(Griffiths et al., 2004).*** The beneficial effect of systemic treatment, PUVA, broad band UVB (290-320 nm) and narrow band UVB (311 nm) phototherapy is through anti-proliferative, anti-inflammatory and immunosuppressant activity ***(Romiti et al., 2009)***.

4-Drugs:

There are many drugs reported to be responsible for the onset or exacerbation of psoriasis. Chief amongst these are lithium salts, antimalarials, β-blocking agents, non-steroidal anti- inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors and the withdrawal of corticosteroids ***(Ridley, 2004).***

5-Obesity:

Obesity was speculated to provide a chronic level of low-grade inflammation via overproduction of inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin (IL)-1, IL-6, and IL-8 in adipose tissue and this may contribute to the pathogenesis of psoriasis and account for its severity ***(Hamminga et al., 2006)***.

6- Metabolic factors:

The provocation of psoriasis by high-dose estrogen therapy potentially indicates a role for hormonal factors in the disease ***(Griffiths et al., 2004)***.

Hypocalcaemia is a trigger factor of psoriasis particularly generalized pustular psoriasis, we can consider vitamin D analogues (e.g. calcipotriol) as a safe therapy for psoriasis and daily consumption of calcium supplements is suggested ***(Herizchi, 2007).***

7- Psychogenic factors:

Psoriatic patients exposed to psychological stress express increased number of monocytes and activated T-cells leading to a shift towards a Th-1 derived cytokine profile with subsequent psoriatic lesions, a condition that might be related to the release of substance P (SP) and nerve growth factor (NGF) ***(Paus et al., 2006 and Buske kirschbaum et al., 2007).***

8- Alcohol and smoking:

A number of studies support the role of ethanol and its metabolites as triggering factor for psoriasis ***(Kazakevich et al., 2011).***

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

9- Climate:

Climate appears to affect psoriasis prevalence, with higher rates recorded in countries at greater latitudes from the equator ***(Griffiths et al., 2004)***. Psoriasis symptoms improve in summer and worsen in winter for many patients ***(Schon and Boehncke, 2005)***.

10- Diet:

The psoriasis prevalence and severity decrease during fasting. Low-calorie diet leads to relief of symptoms and might be an important adjuvant factor in prevention and treatment of moderate non-pustular psoriasis ***(Ruceviae et al., 2003).***

The most important explanation is probably reduced intake of arachidonic acid (AA), resulting in lower production of inflammatory eicosanoids. Moreover, during fasting, there is calorie restriction that leads to reduced oxidative stress ***(Ghoreschi et al., 2003)***.

Etiopathogenesis:

Despite the fact that the initial factor or event inducing psoriasis is still unknown, many environmental factors have been shown to play a role in the development or exacerbation of psoriatic lesions. Trauma, infections, stress and some drugs (e.g. beta-blockers, angiotensin-converting enzyme [ACE] inhibitors, lithium salts, interferon-alpha [INF-α], chloroquine or hydroxychloroquine) have all been linked with the first psoriasis episode or worsening of its course ***(Diluvio et al., 2006; Fry and Baker, 2007).***

Pathogenesis of psoriasis can be explained by:

1. Genetic background
2. Immunological background:
    a) Inflammatory cells
    b) Cytokines & chemokines
    c) Innate immunity
    d) Role of keratinocytes
3. Vascular background
4. Neurological background

(1) Genetic background:

Psoriasis has a large hereditary component, and many genes are associated with it, but it is not clear how those genes work together. Most of them involve the immune system, particularly the major histocompatibility complex (MHC) and T cells**.** The main value of genetic studies is to identify molecular mechanisms and pathways for further study and potential drug targets ***(Barker et al., 2009)***.

Two major genes under investigation are IL12B on chromosome 5q, which expresses interleukin-12B; and IL23R on chromosome 1p, which expresses the interleukin-23 receptor, are involved in T cell differentiation. T cells are involved in the inflammatory process that leads to psoriasis. These genes are on the pathway that ends with upregulating tumor necrosis factor-α and nuclear factor κB, two genes that are involved in inflammation ***(Barker et al., 2009)***.

(2) Immunological background:

a) Role of inflammatory cells

1. T lymphocytes
2. Regulatory T cells
3. Mast cells
4. Dendritic cells

1. T lymphocytes:

Special dendritic cells (DCs) in the epidermis and dermis are activated with the onset of the disease; among other effects, these cells produce the messenger substances, tumor necrosis factor (TNF)-α and interleukin (IL)-23, which, in turn, advance the development of T helper (Th) 1, and Th17 cells. These T cells secrete mediators that contribute to the vascular and epidermal changes of psoriasis ***(Mrowietz and Reich, 2009).***

T-lymphocyte activation occurs in a series of steps, the first of which is incorporation of unidentified antigens by antigen-presenting cells (APCs) in the epidermis and dermis. This process involves binding of the antigens to the MHC on the APC surface, and the APC migrates to the lymph nodes. There, the APC binds reversibly and briefly with naïve or resting T cells through interactions between surface molecules located on both cells. Next, the MHC presents the antigen to a T cell receptor (TCR) on the surface of T-lymphocyte to begin its activation ***(Lebowohl, 2003)***.

The second signal for T lymphocyte activation is a non-antigen / cell-cell interaction known as costimulation. If costimulation does not occur, the T lymphocyte will either undergo apoptosis or become unresponsive. Costimulation involves pairing of receptor with ligand on the T cell; these pairs include lymphocyte functional antigen (LFA)-3 interacting with cluster of differentiation 2 (CD2), B7 interacting with CD28, and intercellular adhesion molecule -1 (ICAM-1) interacting with LFA-1 ***(Lebowohl, 2003)*** **as shown in figure (1)**.

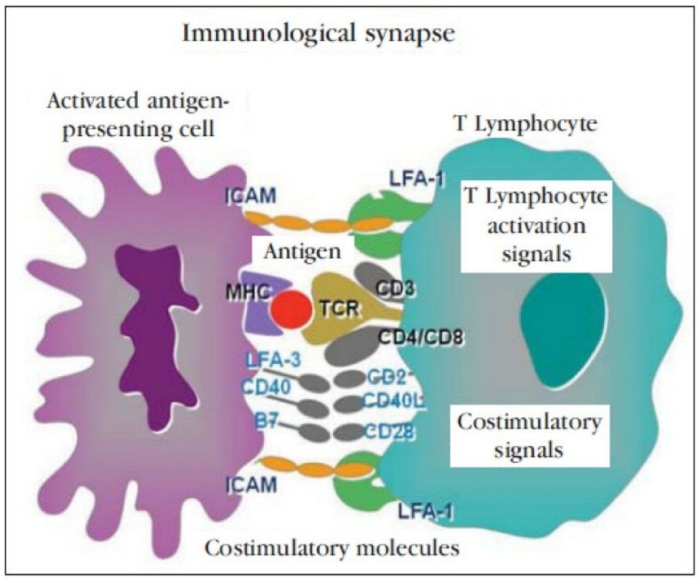

Figure (1): T cell activation by APCs ***(Lima and Lima, 2011).***

The activated T lymphocytes expand, which results in proliferation of antigen-recognizing T lymphocytes, memory-effector cells. The T lymphocytes enter the circulatory system and, via cell-cell interactions with endothelial cells of the blood vessel, migrate to the inflammed skin ***(Lebowohl, 2003)*** **as shown in figure (2).**

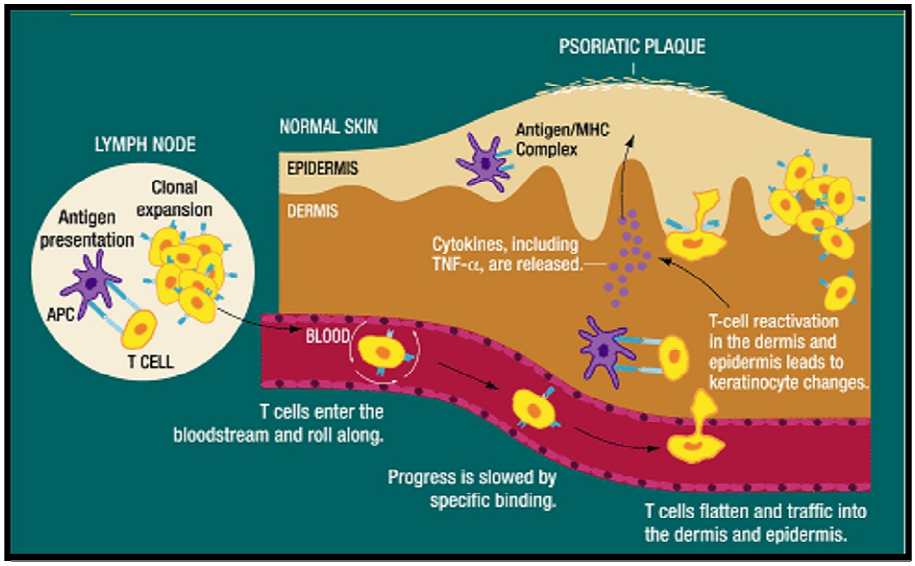

Figure (2): Migration of T lymphocyte from lymph node to skin ***(Papp, 2004).***

2. Regulatory T cells:

T regulatory (Treg) cell is a CD4+ T lymphocyte that constitutively expresses CD25 (the IL-2 receptor α-chain). Treg can suppress immune responses and prevent the development of autoimmune diseases. These cells proliferate in response to exogenous IL-2, which is an important growth factor for this cell type ***(El-Darouti and Abdel-Hay, 2010).*** These Treg cells can suppress the activities of CD4+ and CD8+ T lymphocytes in a non-antigen-specific manner, both in vitro and in vivo. This suppression of T lymphocyte responses is mediated by two nonexclusive mechanisms: cell contact and suppressive cytokines such as IL-10 and transforming growth factor (TGF)-β ***(Bruder et al., 2004).***

Sugiyama et al., (2005) had demonstrated deficient Treg cell activity in the peripheral blood and in skin lesions of patients with psoriasis. Although the absolute number of circulating Treg cells in patients with psoriasis was normal compared with healthy controls, they were relatively deficient in their ability to suppress effector CD4+T lymphocyte proliferative responses. This explains the defective immunoregulatory activity in psoriasis that permits unrestrained T lymphocyte activation and cytokine production in skin lesions of psoriasis.

3. Mast cells:

Mast cells are prominent in initial and developing psoriasis lesions ***(Lin et al., 2011).*** They are main source of TNF- α, and can produce IL-6, IL-12, IL-23, and reactive oxygen species. They are important for inducing and sustaining the inflammatory process leading to psoriasis ***(Ghoreschi et al., 2007)***.

4. Dendritic cells:

There is a significant role for DCs in the pathogenesis of psoriasis. It has been suggested that DCs act by direct contact with T cells, expression of co-stimulatory molecules and secretion of IL-12, IL-23, TNF-α and INF-γ ***(Nickoloff et al., 2007).*** Several DC subsets have been identified as being present in psoriatic lesions, including Langerhans cells, dermal DCs, myeloid DCs, (inducible NO synthase) iNOS-producing DCs and plasmacytoid DCs ***(Wang et al., 2006).***

It must also be noted that one of the earliest events in the development of psoriatic lesions is the secretion of INF-γ by plasmacytoid DCs. Plasmacytoid DCs induce activation of myeloid DCs, dermal DCs, and possibly autoreactive T cells to produce cytokines, further promoting the inflammatory cascade ***(Nestle et al., 2005).***

b) Cytokines & Chemokines:

Once at the inflamed skin site, the activated T lymphocytes encounter the initiating antigen, and release Th1 cytokines, which play a central role in the phenotypic expression of psoriasis ***(Guenther and Ortonne, 2002).*** Both CD4+ and CD8+ T lymphocytes produce Th1 cytokines. Key Th1-type cytokines involved in the pathogenesis of psoriasis are IFN-γ, IL-2, and TNF-α. IL-2 promotes clonal proliferation of Th1 cells and activates macrophages and T cytotoxic-1 (Tc-1) cells ***(Mehlis and Gordon, 2003)***. IFN-γ may inhibit apoptosis of keratinocytes by stimulating expression of the anti-apoptotic protein Bcl-x in these cells. This probably contributes to the hyperproliferation of keratinocytes observed in psoriatic lesions ***(Krueger and Ellis, 2005).***

TNF-α may promote psoriasis development in several ways, including increasing proliferation of keratinocytes and augmenting the production of proinflammatory cytokines from T lymphocytes and macrophages, chemokines from macrophages and adhesion molecules from vascular endothelial cells. In addition, Th1 cytokines cause the release of cytokines