INTRODUCTION

Psoriasis is a chronic, debilitating, autoimmune disease that adversely affects an individual's quality of life; the disease progresses with periods of flare-ups and remission. Psoriasis affects approximately 2% of the global population. Psoriasis can begin at any age; however, the mean onset age is 15-20 years old, and the second peak period is 55-60years of age ***(Cakmur and Dervis, 2015).***

The most common form of the disease is chronic plaque psoriasis(psoriasis vulgaris), which manifests as plaques of red, scaly and well demarcated regions of inflamed skin ***(Baliwag et al., 2015).***

Psoriasis is due to a complex interplay between genetic and environmental factors. Over 40 genetic mutations have been associated with psoriasis, and among these mutations, psoriasis susceptibility locus 1 (PSORS1) and PSORS2 appear to play amajor role. In addition to genetic susceptibility, environmental factors as stress, infection,trauma, or medications. Exposure to triggers in a genetically predisposed individual creates a dysregulated immune response producing the characteristic lesions of psoriasis.

A dysregulated immune system involving T helper (Th)1 and Th17 cells drives the psoriatic inflammatory cascade ***(Mahmood et al., 2015).***

The cytokine pattern observed in the psoriatic plaque shows an increased expression of Interleukin (IL)-1,IL-6, IL-17, IL-22and tumor necrosis factor α (TNF-α) ***(Kouris et al., 2014).***

There has been a growing number of evidence that IL-17-producing Th17 cells play an important role in the pathogenesis of psoriasis. Th17 cells differentiate from naı¨ve Cluster of differentiation (CD)4+ T cells under the stimulation of IL-1b, IL-6, and IL-23 ***(Nakajima et al., 2011).***

Visfatin [also known as pre B-cell-colony-enhancing factor (PBEF)] is a 52-kDa protein mainly produced by macrophages in visceral adipose tissue ***(Gerdes et al., 2011).*** Various cells of innate immunity such as neutrophils, monocytes, macrophages as well as epithelial and endothelial cells can be a source of visfatin after induction with inflammatory stimuli ***(Luk et al., 2008).***

Visfatin is a pro-inflammatory cytokine that dose dependently up-regulates the production of IL-6, IL-1b and TNF-α in human monocytes. These cytokines play a substantial role in a wide range of infectious and inflammatory diseases***(Moschen et al., 2007).***It has several pro-inflammatory and immune-modulating properties, as it promotes T-cell activation by inducing costimulatory molecules such as CD80, CD40, and intercellular adhesion molecule 1 (ICAM-1) ***(Stofkova, 2010).***

Additionally, visfatin also may have a crucial role in autoimmune inflammatory diseases since enhanced visfatin levels have been reported in psoriasis, rheumatoid arthritis (RA), and inflammatory bowel disease (IBD) ***(Romacho et al., 2013).*** There are several reports demonstrating enhanced tissue expression of visfatin in inflammatory conditions including clinical sepsis, and severe generalized psoriasis ***(Sonoli et al., 2011).*** Increased visfatin levels in psoriatic patients correlated with psoriasis area and severity index (PASI) score have been previously reported ***(Okan et al., 2015).***

The role of visfatin in psoriasis might include modulation of inflammatory or immune response as it induces chemotaxis and increases the production of IL-1_, L-6, TNF-α and costimulatory molecules by CD14+ monocytes. This enhances their ability to induce proliferative responses ***(Gerdes et al., 2012).***

Another explanation is that visfatin level might be upregulated during inflammation and in response to inflammatory cytokines ***(Stofkova, 2010)***

Aim of the Work

The aim of this work is to investigate the role of visfatin in the pathogenesis of psoriasis and its relation to the duration, severity of the disease, and body mass index (BMI).

Chapter 1

PSORIASIS

Background:

Psoriasis is a common chronic immune-mediated inflammatory disorder affecting the skin, nails and joints in both children and adults ***(Bronckers et al., 2015)***. It is a common, persistent, and relapsing skin disorder, affecting approximately 2% of the population ***(Kouris et al., 2014)***.

Psoriasis is a chronic inflammatory disease caused by genetics; and affected by other factors. It is characterized by hyperproliferation and altered differentiation of keratinocytes, T-lymphocyte infiltration, and vascular changes ***(Sereflican et al., 2016)***.

Epidemiology:

Psoriasis can begin at any age, including birth and old age; however, the mean onset age is 15-20 years old(early onset psoriasis), and the second peak period is 55-60 years of age(late onset psoriasis) ***(Khoudri et al., 2013; Tang et al., 2013)***.

Patients with an early onset of the disease (type I psoriasis) have a more severe course and a positive family history, whereas patients with late onset (type II psoriasis) tend to have milder forms of the disease and often have a negative family history ***(Boehnche and Schön, 2015)***.

The skin disorder of psoriasis is estimated to affect 2.0-3.5 % of the global population Psoriasis begins in childhood in almost one-third of the cases ***(Bronckers et al., 2015)***.

Psoriasis is equally prevalent in both sexes, although results from a recent study have shown that on average men have more severe forms of the disease than do women ***(Hägg et al., 2013).***

Etiology:

The etiology of psoriasis remains unknown but the disease is believed to result from an interaction between genetic susceptibility and exogenous environmental factors, such as infection, in particular with β-hemolytic streptococci, stress and trauma ***(Dalamaga and Papadavid, 2013)***.

Psoriasis is due to a complex interplay between genetic and environmental factors. Over 40 genetic mutations have been associated with psoriasis, and among these mutations, PSORS1 and PSORS2 appear to play a major role. In addition to genetic susceptibility, environmental factors include, but are not limited to, stress, infection, trauma, or medications. Exposure to triggers in a genetically predisposed individual creates a dysregulated immune response producing the characteristic lesions of psoriasis ***(Mahmood et al., 2015)***.

Genetic factors:

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 these genes involve the immune system, particularly the major histocompatibility complex (MHC) and T cells ***(Barker et al., 2009)***.

The major determinant is PSORS1, which probably accounts for 35–50% of its heritability. It controls genes that affect the immune system or encode proteins that are found in the skin in greater amounts in psoriasis. PSORS1 is located on chromosome 6 in the MHC, which controls important immune functions. Three genes in the PSORS1 locus have a strong association with psoriasis vulgaris ***(Nestle et al., 2009).***

Trigger factors:

Psoriasis can be provoked by non-specific triggers such as mild trauma (scratching, piercings, and tattoos), sunburn, or chemical irritants. Systemic drugs such as β-blockers, lithium, antimalarials, and non-steroidal anti-inflammatory drugs (NSAIDs) can exacerbate the disease. Psoriasis can be triggered or substantially aggravated by occupational risk factors impairing the skin barrier function. In such cases, in particular with palmoplantar psoriasis, the patient's work environment should be assessed and adequate protective measures put in place. Human immunodeficiency virus (HIV) infection might

also be a trigger of psoriasis, because the prevalence of psoriasis in HIV-infected patients is the same or slightly higher than in the general population, and HIV-infected patients with pre-existing psoriasis often have a flare of lesions that are difficult to treat ***(Mahler et al., 2014)***.

Psoriasis at the site of injury is well known as Koëbner phenomenon. The injurious stimuli may be physical, chemical, electrical, surgical, infective and inflammatory (***Griffiths et al., 2004).*** It is observed in approximately 1/3 of the patients. The lag time between the trauma and the appearance of the skin lesions is usually between 10 and 14 days after trauma, however, the onset of lesions after few days or even years has also been reported. 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, and in 39% of the affected adults ***(Romiti et al., 2009; Sagi and Trau, 2011).***

Pathology of Psoriasis

In psoriasis, pathological findings are not confined only to the skin ***(Rajappa et al., 2015).*** The pro-inflammatory molecules released during chronic inflammation may lead to the presence of one or more disorders co-occurring with psoriasis, as atherosclerosis, atherogenesis, insulin resistance, hypertension, obesity, dyslipidemia, metabolic syndrome, and diabetes mellitus (DM) type 2 ***(Coban et al., 2016; Dikbas et al., 2016)***.

The cytokine pattern observed in the psoriatic plaque shows an increased expression of IL-1, L-6, IL17, IL-22 and TNF-α. IL-1 is also called a primary cytokine, since it can independently initiate a number of mechanisms capable of triggering inflammation ***(Dowlatshahi et al., 2013)***. IL-6 acts as an autocrine mitogen in psoriatic epidermis, and, in synergy with IL-1 and TNF-α, contributes to cellular hyperproliferation through its action on the epidermal growth factor receptor (EGF) ***(Nakajima et al., 2012; Stoma et al., 2013)***.

IL-17 is a proinflammatory cytokine, responsible for expanding and maintaining the Th17 pathway. This pathway has been the subject of many studies because of its relevance in the development and management of psoriasis ***(Martin et al., 2013)***. IL-22 is a member of the IL-10 cytokine family, produced by several different cellular sources including Th17 cells, natural killers cells (NKC), and Th22 cells. It works synergistically with IL-17 to enhance the expression of anti-microbial peptides (AMPs) that are increased in psoriasis. IL-22 mediates the epidermal acanthosis and abnormal differentiation of keratinocytes that are the main pathological findings in psoriasis ***(Pan et al., 2013; Baliwag et al., 2015)***.

Acting through transmembrane receptors, TNF-α is a pleiotropic cytokine produced by many different cell types, especially cells of monocytic lineage. Its central role in psoriasis has come to light through observations of the efficacy of anti-TNF-α biological therapies in psoriasis and psoriatic

arthritis ***(Cantini et al., 2012)***. TNF-α levels were found to be elevated in psoriatic skin lesions. There is increasing evidence that psoriasis also has an important systemic component. This is supported by the presence of inflammatory-mediated co-morbidities in psoriatic patients, and by the favorable impact of anti-TNF-α blocking agents on the course of the disease ***(Kouris et al., 2014)***.

Pathogenesis:

A dysregulated immune system involving Th1 and Th17 cells drives the psoriatic inflammatory cascade ***(Becher and Pantelyushin, 2012)***. A variety of triggers stimulate the innate immune system to produce cytokines that activate dendritic cells residing in the dermis. Activated dendritic cells produce inflammatory cytokines that induce proliferation and differentiation of effector T cells. The activated T cells migrate from the dermis to the epidermis and secrete cytokines, which induce proliferation of keratinocytes resulting in the classic inflammatory lesions of psoriasis. Although complex, the key cytokines in psoriasis act through a common signaling pathway known as JAK/Signal Transducers and Activators of Transcription (JAK/STAT) ***(Mahmood et al., 2015)***.

Research into the immunopathogenesis of psoriasis has resulted in several highly specific therapies that target components of the immune system ***(Balato et al., 2013)***.

Cross-talk between innate and adaptive immunity:

Psoriasis is mainly a dendritic cell and T-cell-mediated disease with complex feedback loops from antigen-presenting cells (APC), neutrophilic granulocytes, keratinocytes, vascular endothelial cells, and the cutaneous nervous system. Cross-talk between the innate and the adaptive immune system mediated by cytokines including TNF-α, interferon-γ, and IL-1 is a major research focus ***(Boehnche and Schön, 2015)***.

Complexes of host DNA and the epidermis-produced AMP LL-37 (cathelicidin) are thought to stimulate dermal plasmacytoid dendritic cells to produce interferon-α ***(Mahler et al., 2014)***. On exacerbation or onset of psoriasis, activated dendritic cells produce, among other mediators, TNF-α and IL-23. TNF-α is a pro-inflammatory cytokine that amplifies inflammation through several distinct pathways.It induces secondary mediators and adhesion molecules, all of which have been implicated in psoriatic disease. The clinical success of TNF-α blocking agents is therefore not surprising ***(Henes et al., 2014)***.

IL-23/Th17 axis:

Interest is rising in the IL-23/Th17 axis in psoriasis, which has resulted in several novel targeted therapies. Th17 cells are a subset of T-lymphocytes expressing IL 17, distinct from the classical Th17 cells that play a predominant part in the

pathogenesis of psoriasis and other inflammatory disorders ***(Fotiadou et al., 2014)***.

Expansion and survival of these T-cells depends on myeloid cell-produced IL-23, which drives the differentiation of Th17 cells. IL-23 acts mainly on memory T cells, because naive T cells do not express the IL-23 receptor. Other cytokines, such as IL-9, might support Th17-related inflammation ***(Singh et al., 2013)***.

Once activated, Th17 cells produce several mediators such as IL-17A, 17F, and 22, which induce keratinocyte proliferation and other hallmark features of psoriasis ***(Keijsers et al., 2014; Schön, 2014)***.

Effect of IL-23/Th17 axis on resident cells of the skin:

Complex dysregulation of almost every cutaneous cell type, which includes proliferation and cytokine production by epidermal keratinocytes, is affected by the TNF-α pathway and IL-23/Th17 axis pathway. Furthermore, AMPs, cytokines and chemokines secreted by keratinocytes act as chemoattractants for infiltrating immune cells. Thus, a positive feedback loop exists between cells of the immune system and resident epithelial cells in psoriasis. Vascular endothelial cells are also closely linked to psoriatic disease because the inflammatory milieu leads to induction and activation of a range of pro-angiogenic factors ***(Sugiura et al., 2014)***.

Regulatory T-cells (T reg) affect the vascular endothelial growth factor (VEGF)-related angiogenic microenvironment and contribute to hallmark features of psoriasis such as epidermal hyperplasia ***(Zibert et al., 2011)***.

Psoriasis is no longer thought of as a disorder that affects only the skin, but is instead seen as a systemic inflammatory disorder ***(Reich, 2012)***.

Clinical picture:

Chronic plaque psoriasis is the most common morphological variant of psoriasis. It presents with well-demarcated erythematous plaques covered with a thick, silvery/white adherent scale***(Ryan et al., 2014)***. It tends to be symmetrical, and it most often affects the occiput of the scalp, the postauricular space, the elbows, knees, shins, and gluteal cleft ***(Armstrong et al., 2013)***.

Scraping of the scale frequently causes pinpoint bleeding (Auspitz sign) and is pathognomonic for psoriasis. When the scaling is not evident, it can be induced by light tangential scratching with the edge of glass slide (Grattage test) ***(Ryan et al., 2014)***.

Inverse psoriasis presents as smooth, erythematous, well demarcated patches or plaques in skin folds that may have a slightly macerated surface. These areas include the axillae, the inframammary, abdominal, genital, and retro-auricular folds as

well as the perianal skin and gluteal cleft ***(Armstrong et al., 2013)***.

Guttate psoriasis appears as a sudden eruption of monomorphic, small, oval-shaped erythematous papules with a scaly crust distributed over the trunk and extremities. The eruption is usually preceded by streptococcal or viral infection, hence checking a throat culture or antistreptolysin-O (ASO) titer is recommended ***(Hugh et al., 2014)***.

Pustular psoriasis can be generalized or localized to the hands and feet. Localized pustular psoriasis is more common and tends to start on the middle of the palm or instep of the foot. The pustules are yellow initially, then turn brown and scaly as they come to the surface, with erythema and peeling of the surrounding skin. Pustular psoriasis can rarely be localized to a single digit and is very tender ***(Lee et al., 2013)***.

Erythrodermic psoriasis presents as wide-spread and generalized erythema with scale. It is usually precipitated by systemic corticosteroid therapy, phototherapy complications, abrupt stoppage of systemic therapies, and severe emotional distress or illness ***(Limayi, 2015)***.

It is estimated that approximately 40% to 50% of patients with psoriasis are affected by nail psoriasis, with a lifetime incidence of 80% to 90% ***(Merola et al., 2017).*** Nail psoriasis can accompany any form of psoriasis or occur of its own

accord. The most common presentation is of irregular pitting and "oil spots" with proximal nail onycholysis. Nail deformity can result when the nail matrix is involved, which results in fragmentation of the nail, causing it to crumble. Psoriatic arthritis (PsA) can occur in 5-42% of patients with cutaneous psoriasis. Disease can accompany, precede, or follow cutaneous psoriasis. The most conventional presentations are an asymmetric arthritis of single or multiple joints in the fingers or toes or swelling at the base of the Achilles tendon over the heel ***(Limayi, 2015)***.

Typically, the skin disease occurs before the onset of arthritis in more than 80% of patients. Nail dystrophy, Psoriasis of the scalp, and/or intergluteal/perianal Pso have been identified as clinical predictors for the development of arthritis ***(Canete and Mease, 2012)***.

The clinical presentation of PsA can manifest as peripheral arthritis, asymmetrical oligoarthritis, arthritis mutilans, or ankylosing spondylitis ***(Horreau et al., 2013)***.

Childhood psoriasis:

The onset of psoriasis in children often occurs as guttate (droplet) psoriasis, a disease that is often preceded by a streptococcal infection of the upper respiratory tract. Antigenic similarities between streptococcal proteins and keratinocyte antigens might explain the trigger by streptococcal infections.