INTRODUCTION

Psoriasis is a common inflammatory disease of the skin. It affects about 2% of the world's population. Males and females are equally affected. It has a bimodal distribution of age. The most characteristic lesions consist of red, scaly, sharply demarcated indurated plaques, present commonly over the extensor surfaces of the limbs and scalp, also it may affect the nails and joints. The disease is enormously variable in duration, periodicity of flares and extent. Many clinical variants have been described e.g. plaque psoriasis or psoriasis vulgaris (most common form), guttate psoriasis, pustular, erythrodermic…etc ***(Griffiths et al., 2004)***.

Histopathology of psoriasis shows three cardinal features: a) Epidermal hyperproliferation with loss of differentiation, b) Dilatation and proliferation of dermal blood vessels, c) Accumulation of inflammatory cells particularly neutrophils and T- lymphocytes ***(Bowcock et al., 2001).***

Inspite of being a common disease, the exact etiology of psoriasis is still unknown but many factors have been incriminated in the pathogenesis of

psoriasis as genetic, immunologic and environmental factors, all these factors may disrupt the normal events of cell maturation and proliferation. It has been known for quite a long time that psoriasis is seen more frequently in some families; positive family history was recorded by 36% of patients. Also a large German survey found that the risk of a child to develop psoriasis if both parents were affected was 41% and 14% if only one of the parents was affected ***(Van de Kerkhof, 2003).***

In addition to the genetic susceptibility for psoriasis, many triggering factors both external (e.g., trauma) and systemic (e.g., infections, stress, drugs, HIV, alcohol consumption, smoking … etc) can elicit psoriasis in genetically predisposed individuals ***(Chamian and Kreuger, 2004).***

Several observations have suggested that psoriasis is a T- lymphocyte mediated autoimmune disease. This was confirmed by the presence of T-lymphocyte subsets in an early phase of the disease and the response to T-lymphocyte targeting therapies. Activated T-lymphocytes produce two different patterns of cytokines. Th1 cells produce IL-2 and interferon (IFN)γ Whereas Th2 produce IL-4, IL-5 and

IL-10. Psoriasis can be considered as a Th1 dominant disease ***(Van de Kerkhof, 2003).***

Vitamin D, which is an ancient vitamin that is well known for its effect on regulation of calcium level in blood. It exerts its effects through the vitamin D receptor (VDR). The observation that keratinocytes, T-lymphocytes, Langerhans cells, endothelial cells and monocytes express VDR led to the recognition of vitamin D non-calcemic actions. It influence both the innate and adaptive immune systems , helps in cancer prevention through regulation of cell proliferation and differentiation , inhibition of apoptosis and the control of tumor invasion and metastasis (***Uliasz and Lebwohi, 2008).***

In the skin, $1,25(OH)_2$ D3 is a potent stimulator of keratinocyte differentiation provided a reasonable basis for the clinical use of VDR ligands for the treatment of psoriasis. The antipsoriatic activity of vitamin D analogs could be attributed to their differentiation, anti-proliferative and immunomodulatory properties. VDR ligands increase differentiation of keratinocytes resulting in the formation of a cornified envelope that provides the barrier function of the skin. It induce the expression of involucrin, transglutaminase, keratin 1, loricrin and

filaggrin. On the other hand, VDR ligands decrease the expression of proinflammatory cytokines (IL-2, IL-6, IL-8 and IFNγ) in T-cells, all of which play a role in cutaneous inflammation and proliferation of T- lymphocytes and keratinocytes ***(Chamian and Kreuger, 2004)***.

Antigen presenting cells (APCs) or dendritic cells (DCs) also play an important role in psoriasis and autoimmune diseases because they are involved in antigen presentation. Antigen presenting cells are one of the major targets for 1,25-$(OH)_2D_3$ mediated immunosuppressive action, as they prevent the differentiation, maturation, activation and survival of DCs (***Nagpal et al., 2005).***

Psoriasis is characterized by prominent epidermal hyperplasia and disturbed function of the immune system. So, polymorphisms of VDR gene may be associated with the risk of developing psoriasis. The VDR gene is localized to 12q12-14, consists of 11exons. Several polymorphism sites in the VDR gene have been reported as FokI, which is a protein synthesis start codon polymorphism, BsmI, ApaI and TaqI polymorphism, these four sites are the least to be associated with linkage disequilibrium (***Erden et al., 2007)***.

AIM OF THE WORK

The aim of this work is to identify whether VDR gene is to be considered as a candidate gene for the development of psoriasis. This work will be done to study the polymorphism of this gene in a group of patients with psoriasis vulgaris and comparing them with a control group to identify whether polymorphism of VDR is associated with psoriasis vulgaris.

PSORIASIS

Psoriasis is an autoimmune, common, chronic and recurrent inflammatory disease of the skin ***(Woodley, 2008)***.

Epidemiology:

A) Incidence:

Psoriasis is one of the most common chronic inflammatory skin disorders, affecting about 2% of the general population. Prevalence rates in Europe are quoted to be about 1.5%, where as in the United States of America., the prevalence is estimated to be about 4.6%. In contrast, lower prevalence rates have been observed in east Africans, American blacks, Indians (0.7%) and among the Chinese population (0.4%). This immune mediated disease, which is incurable and chronic, is characterized by periods of remission and relapse ***(Christophers, 2001)***.

B) Climate:

Climate appears to affect psoriasis prevalence, with higher rates recorded in single countries at greater latitudes from the equator. The symptoms of psoriasis improve in the summer and worsen in the

winter for many patients. The Dead Sea, with its unique optical, chemical and atmospheric properties provides an effective alternative treatment for psoriasis. Dead Sea climatotherapy leads to reversal of the immunopathologic abnormalities of psoriasis in involved epidermis and dermis ***(David et al., 2005)***.

C) Age:

The first manifestation of the disorder usually occurs around the age of 20 or between 50 and 60. However, it must be emphasized that psoriasis can manifest itself at any age. Psoriasis can be differentiated into two subgroups: type I which begins before age 40, and type II, which begins after age 40 ***(Henseler and Christophers, 1985)***. Type I psoriasis, which accounts for approximately 75% of all psoriasis patients, is associated with a more severe course of disease, limited success of treatment, increased prevalence of certain human leucocyte antigen (HLA) types and stronger hereditary ties **(*Sabat et al., 2007).***

D) Sex:

Psoriasis is not phenotypically different between both sexes inspite of significant female preponderance in the palmoplantar pustular type ***(Griffiths et al., 2004)***.

Aetiology:

Although that the aetiology of psoriasis is still not clearly understood but there is clearly a genetic component in the development of psoriasis. Twin studies show a 67% concordance for monozygotic twins versus 18% for dizygotic twins. This lack of complete concordance in monozygotic twins suggests multi-factorial inheritance and also suggests that psoriasis is a polygenic disease. It is the result of interaction between the genetic predisposition and various external or systemic triggering factors ***(Krueger and Ellis, 2005)***.

A) Genetic predisposition:

Although the inheritance pattern is currently still unclear, genetic disposition appears to play an important role in the susceptibility to develop psoriasis. This view is based on three observations.

First, the likelihood of developing psoriasis is raised when first-grade relatives suffer from the disease. Positive family history has been reported by 35% to 90% of patients. The risk is about 20% if one parent has psoriasis, and is about 75% if both parents are affected. If one monozygotic twin suffers from psoriasis, the probability is more than 55% that the other will be affected too ***(Schon and Boehncke, 2005)***.

Second, psoriasis is associated with certain histocompatibility antigens (HLA), they are surface antigens of human cells and the corresponding chromosomal region is called the major histocompitability complex (MHC). It is situated in the short arm of chromosome 6. Psoriasis is associated with multiple HLA: HLA-B13, HLA-B17, HLA -B37, HLA -Bw16. HLA-Bw57, HLA-DR4 and HLA-Cw6. People with HLA-Cw6 association are ten times more susceptible for psoriasis. HLA-CW6 also influences the age of onset of psoriasis. It is expressed in 90% of the patients with early onset psoriasis, 50% of those with late onset psoriasis, and only 7.4% of a control population. Some clinicians have designated patients with early onset psoriasis, a positive family history of psoriasis and expression of HLA-CW6 as having Type I psoriasis and those with late onset disease, no family history, and a lack of expression of HLA-CW6 as Type II psoriasis ***(Bowcock. and Krueger, 2005).***

In pustular psoriasis and acrodermatitis continua of hallopeau, an increase in the prevalence of HLA-B27 was observed which was not seen in pustulosis of the palm and soles. A significant association between guttate psoriasis in children, erythrodermic psoriasis and HLA-B13 and HLA-B17 expression was reported ***(Schon and Boehncke, 2005)***.

Thirdly, several psoriasis susceptibility loci have been described. The PSORS1 in the MHC region on chromosome 6 (6p21) appears to be associated with most cases of psoriasis. It is considered to be the major gene locus involving psoriasis. It is of significant importance as it contains the corneo-desmosin gene with its important biological function in keratinocyte adhesion ***(Zippin, 2009).***

Other gene loci linked to psoriasis are PSORS2 on chromosome 17q, PSORS3 on chromosome 4q, it contains the gene that regulates the production of type 1 IFN ***(Valdimarsson, 2007).***

PSORS4 on chromosome 1q, within the epidermal differentiation complex which also contains the S- 100 proteins, which are involved in leukocyte chemotaxis. PSORS5 on chromosome 3p, PSORS6 on chromosome 19p, it is of interest because it harbors the transcription factor JUNB gene, which is an important component of the activator protein-1 (AP-1) transcription factor, which controls the keratinocyte differentiation and affects cytokines expression as IL-23 ***(Zippin, 2009).***

PSORS7 is on chromosome 1p while the locus on chromosome 16q12-13is known as PSORS8 has been shown to have linkage with both psoriasis and Chron's

disease. Interestingly, some genes from this region are associated also with other immune diseases (rheumatoid arthritis, colitis and diabetes) ***(Bowcock and Krueger, 2005).***

PSORS 9 is located very close to the PSORS3 locus on chromosome 4q31; it contains numerous immunologically relevant proteins, such as IL-15. And lastly PSORS10 which is located on chromosome 16q ***(Zippin, 2009).***

Accumulating evidence indicates that psoriasis is a multifactorial disorder caused by the concerted action of multiple disease genes in a single individual, triggered by environmental factors. Some of these genes control the severity of multiple diseases by regulating inflammation and immunity (severity genes), whereas others are unique to psoriasis ***(Elder et al., 2001).***

Various combinations of these genes can occur even within a single family, accounting in large measure for the many clinical manifestations of psoriasis. The disease-causing variants (alleles) of these genes probably arose early in the history of modern humans. As a result, psoriasis disease alleles are common in the general population, have a worldwide distribution, and often

share the same ancestral chromosome with neutral alleles at adjacent loci. This phenomenon is called "linkage disequilibrium". Linkage disequilibrium explains why psoriasis is strongly associated with HLA-Cw6 worldwide, although HLA-Cw6 is unlikely to be the disease allele ***(Nair et al., 2000).***

Many unaffected individuals carry one or more disease alleles, but lack other genetic and/or environmental factors necessary to produce disease. This explains why psoriasis develops in only about 10% of HLA-Cw6-positive individuals, and why genome-wide linkage scans for psoriasis and other multifactorial genetic disorders have not been uniformly successful ***(Schon and Boehncke, 2005)***.

B) Triggering factors:

Many triggering factors were described to induce psoriasis in a genetically predisposed individuals, these triggering factors may be external (e.g: trauma) or systemic ***(Traub and Marshall, 2007).***

a) External triggering factors:

Trauma:

Psoriasis at the site of injury is well known (Koebner phenomenon or the isomorphic response). Many forms of cutaneous injury, e.g., physical (sun

burn), chemical, electrical, surgical, infective (viral exanthems) and inflammatory insults have been recognized to elicit psoriatic lesions. The lag time between the trauma and the appearance of skin lesions is usually 2-6 weeks ***(Griffiths et al., 2004).***

The cause of koebner phenomenon was refered to be caused by the signal transducer and activator of trans-cription (STAT3), it is a protein involved in wound healing if the skin is injured. The STAT 3 protein returns to an inactive state when its job in the healing process is completed. Sometimes, however, the protein stays active, and skin cells continue to multiply. This activated STAT3 protein has been found both in lesions and in unaffected skin of psoriasis patients ***(Mrowietz and Reich, 2009)***.

b) Systemic triggering factors:

1) Infections:

a) Streptococcal infection:

Infections in particular bacterial infections may induce or aggravate psoriasis. Provoking infections have been observed in up to 44% of psoriatic patients. Streptococcal infections, in particular pharyngitis, are the most common offenders. Sequence similarities between streptococcal M peptides and human keratins lead to the hypothesis that keratinocytes' proteins

function as autoantigens in psoriasis and that bacterial superantigens have a permissive role in the pathogenesis of psoriasis. Streptococci can also be isolated from other sites, e.g., dental abscesses, perianal cellulitis and impetigo. These streptococcal infections often lead to a flare of guttate psoriasis especially in children and adolescents, but also may precipitate pustular psoriasis or exacerbate plaque disease ***(Skov and Baadgaard, 2000)***.

Past and more recent evidence suggests that continuing, subclinical streptococcal infection might also be responsible for refractory chronic plaque psoriasis ***(Traub and Marshall, 2007)***.

b) Helicobacter pylori:

It has been suggested that Helicobacter pylori may be one of the organisms capable of triggering psoriasis ***(Qayoom and Ahmad, 2003).***

c) Human immune deficiency virus (HIV):

Human immune deficiency virus infection has also been shown to aggravate psoriasis. The frequency is not increased in HIV +ve patients, but the severity of the disease is greater in this population ***(Van de Kerkhof, 2003)***.

2) Endocrine factors:

Hypocalcemia has been reported to be a triggering factor for generalized pustular psoriasis. Psoriasis can be provoked by certain hormonal factors such as puberty, pregnancy and high dose oestrogen therapy. Pregnancy may alter disease activity: 50% of the patients in one series reported improvement. However, pregnant women may develop pustular psoriasis, also referred to as impetigo herpetiformis, sometimes in association with hypocalcemia ***(Van de Kerkhof, 2003)***.

3) Psychogenic stress:

Psychogenic stress is a well established systemic triggering factor for psoriasis. Stress induces the release of substance B and nerve growth factor which may lead to activation of T-cells and shift towards a Th-1 derived cytokine profile with subsequent triggering of psoriatic eruption ***(Gupta et al., 1989)***.

4) Drugs:

Several drugs have been incriminated as inducers of psoriasis, in particular lithium (it elevates pro-inflammatory cytokines, thereby stimulating cutaneous leucocyte recruitment), B-blockers (induce epidermal hyperproliferation associated with a