Psoriasis

Psoriasis is chronic, relapsing / remitting, multifactorial, immune-mediated skin disease characterized by dry red papules, with white or silvery scales and plaques that are more active at the edge and usually itchy (Menter et al., 2008).

The skin lesions seen in psoriasis vary in severity from minor localized lesions to complete coverage of the body (Erythrodermic psoriasis) and most commonly on the skin of knees, elbow, scalp and intergluteal cleftes (Habashy and James, 2016).

❖ Epidemiology:

The prevalence varies among populations in the world, it affects 2-3% of population worldwide. In epidemiological studies, the factors that leads to the variability are genetic susceptibility, climate and environmental exposures (Enamandram and Kimball, 2013).

Psoriasis is divided into 2 types: Type1 psoriasis shows a family history for the disease and usually occurs before 40 years of age. Type 2 is not familial and usually occurs after 40 years of age. Psoriasis affects both sexes equally (Kupetsky and Keller, 2013).

❖ Etiology:

The etiology of psoriasis is still unknown; certain genetic and environmental factors are triggers (Ryan, 2010).
I-Genetic predisposition:

Around one-third of people with psoriasis have a family history of the disease, and researchers have identified 10 genetic loci associated with it referred to as psoriasis susceptibility loci (PSORS) with strong evidence for association with psoriasis (nomenclature, PSORS 1-10) (Kanazawa, 2012).

Most of the identified genes related to the immune system, particularly the major histocompatibility complex (MHC) and T cells (Nestle et al., 2009).

When two related individuals in a family have the same disease, they are called concordance. The concordance rate for monozygotic twins is around 70% as compared with that for dizygotic twins. These findings suggest both a genetic susceptibility and an environmental response in developing psoriasis (Krueger and Ellis, 2005).

II-Precipitating factors:

Trauma:

Psoriasis may be elicited by direct trauma to the skin, what is called Koebner's Phenomenon (Raychaudhuri et al., 2008).

Mechanical injury causes keratinocytes to release cytokines that can directly stimulate keratinocytes proliferation or induce the production of other cytokines by recruiting immune cells (Weiss et al., 2002).

Psoriatic lesions can also be induced by other forms of cutaneous injury, e.g. morbilliform drug eruption, sunburn, and viral exanthem. The
time between the trauma and the appearance of skin lesions is commonly 2 – 6 weeks (Van de kerkhof and Nestle, 2012).

Infection:

Various microorganisms are associated with the initiation and/or exacerbation of psoriasis. These include bacteria (Staphylococcus aureus and Streptococcus pyogenes), fungi (Candida albicans and Malassezia), and viruses (Retroviruses and Papilloma viruses) (Fry and Baker, 2007).

There is strong evidence that streptococcal infection, usually of the throat, is the primary cause of the initiation of guttate psoriasis. However, the pathological role of streptococci in chronic plaque psoriasis remains controversy (Mc Fadden et al., 2009).

Alcohol & Smoking:

Smoking damages the skin by increasing formation of reactive oxygen species and lowering the gene expression of antioxidants (Attwa and Swelam, 2011).

Ethanol can enhance lymphocyte and keratinocyte activation and proliferation and also increases the levels of mRNA of genes responsible for proliferating keratinocytes (Farkas and Kemény, 2013).

Drugs:

Exacerbation of psoriasis due to medications as: adrenergic antagonists, gemfibrozil, iodine, interferon, digoxin and chlonidine. Also, rapid withdrawal of systemic corticosteroids can cause pustular psoriasis and flares of plaque psoriasis (Milavec-Puretić et al., 2011). Also, drugs
as: lithium, Beta-blockers and antimalarials are inducers of psoriasis \cite{Peter2012}.

**Metabolic and Endocrinal factors:**

The severity noted to be changed with hormonal changes which peek at puberty and menopause. Pregnant woman's symptoms tend to improve, in contrast to the disease that is likely to flare in the postpartum period and provocation of psoriasis by high dose of estrogens therapy potentially indicates a role of hormonal factors in the disease \cite{Griffiths2004}.

**Stress:**

Stressful events have frequently been related with psoriasis onset or flare, it has been associated with increased number of monocytes and activated T cells and a shift towards a T helper 1 (Th1) which secrete cytokines with subsequent flare of preexisting psoriasis \cite{Buske-Kirschbaum2007}.

**Obesity:**

Obesity leads to a higher risk in causing psoriasis and a poorer clinical outcome of psoriasis. This fact is caused by the release of tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) which is derived from inflammatory cells as macrophages in the adipose tissue and high level of leptin hormone which stimulates the release of proinflammatory cytokines as interleukin (IL)-1, IL-6 and TNF-\(\alpha\) \cite{Hamminga2006}.
**Pathogenesis of psoriasis:**

Psoriasis is characterized by an abnormally increased and rapid growth of the epidermal layer of the skin (Ouyang, 2010).

In psoriasis, skin cells are replaced every 3-5 days rather than the usual 28-30 days (Parrish, 2012). These changes are due to the premature maturation of keratinocytes caused by an inflammatory cascade in the dermis involving macrophages, dendritic cells and T cells (Palfreeman et al., 2013).

The molecular pathogenesis of psoriasis is immune based and initiated and sustained primarily by T cells in the dermis and keratinocytes (Abdelnoor and Nayla, 2013).

At the onset of the disease, special dendritic cells in the epidermis and dermis are activated and produce TNF-α and IL-23 which in turn promote the development of Th1 and Th17 cells. These T cells secrete mediators that lead to the vascular and epidermal changes of psoriasis (Mrowietz and Reich, 2009).

The immune cells move from the dermis to the epidermis and secrete cytokines such as TNF-α, IL-1β, IL-6 and IL-22 (Nestle et al., 2009).

The aberrations in the stratum corneum leads to activation of innate immune mechanisms which leads to recruitment and activation of Th17 cells that provide cytokines, all leads to epidermal hyperplasia and a proinflammatory reactions (Lowes et al., 2007).
DNA released from dying cells acts as an inflammatory stimulus in psoriasis and stimulates the receptors on denderic cells, which produce cytokine which is interferon-α (IFN-α) (*Dombrowski and Schauber, 2012*).

Gene mutations of proteins that lead to the skin's ability to function as a barrier have recognized as markers of susceptibility for the development of psoriasis (*Ramos-e-Silva and Jacques, 2012*).

*Farkas and Kemeny, (2012)* reported that anyone of the mentioned triggering factors can induce cell death. The self DNA released from the dying cells, is generally tolerated and therefore, does not activate plasmacytoid dendritic cells (pDCs) because this DNA fails to enter the cells spontaneously. However, when Cathelicidin peptide (LL-37) forms a complex with self-DNA, this complex binds to toll-like receptor 9 (TLR9) on pDCs leading to internalization of self-DNA which then triggers pDCs to produce massive amounts of IFN-α which activates the local immune system mainly myeloid DCs "mDCs" and potentially auto reactive T cells which become capable of secreting cytokines that further promote the inflammatory cascade. (*Figure 1*)

In addition to stimulating pDCs, LL-37 has been shown to complex with self-RNA to trigger the activation of mDCs through TLR8. This stimulates mDC production of TNF-α and IL-6, and promotes their differentiation into mature dendritic cells (DCs) (Ganguly et al., 2009).

The activated DCs (Langerhans cells "LCs" or pDCs) migrate to skin-draining lymph nodes to present an unknown antigen (self or of microbial origin) to the naive CD4+ T cells. Mast cells also can play the role of antigen presenting cells to shape the inflammatory potential of human T- helper lymphocytes (Gaudenzio et al., 2013).
In the skin-draining lymph nodes, antigen-specific T cells are primed to differentiate into effector T cells bearing the skin addressing Cutaneous Lymphocyte Antigen (CLA+). Optimal T-cell activation requires at least two signals (Figure 2). One is provided by the interaction between antigen-specific T-cell receptor and antigen-major histocompatibility complexes. The other is provided by co-stimulatory signals. A well-characterized co-stimulation is mediated by CD28/B7 which is essential for T-cell proliferation following antigen stimulation; other important co-stimulatory pathways are interaction between CD2 and lymphocyte function-associated antigen-3 (LFA-3) and between Intercellular adhesion molecule (ICAM)-1 and LFA-1 (Khandpur and Bhari, 2013).

Figure (2): Co-stimulation signals


The differentiation of Th1 and Th2 cells is induced in naive T cells by DCs interaction in an IL-12- and IL-4-dependent way respectively.
In the human system, the combination of IL-23, transforming growth factor-β (TGF-β), IL-6, and IL-1β appears to be necessary for full development of Th17 cells. In fact, the removal of any of these four cytokines leads to decreased IL-17 production by at least 50%. In contrast, the differentiation of Th22 cells is most efficiently induced by pDCs in an IL-6, TNF-α, and IL-23 dependent way (Figure 3) (Sonnenberg et al., 2011).

**Figure (3): Differentiation, regulation and function of IL-22-producing T cell populations**

The activated T cells traffic to the skin where they induce together with pDCs, dermal DCs and other cells the formation of a primary psoriatic plaque. During this step some T cells and DCs start to infiltrate the epidermis and release pro-inflammatory cytokines, which in turn stimulate keratinocytes to produce the typical epidermal changes (Cai et al., 2012).

Once a patient has developed his first psoriatic lesion, his symptomless skin may be reactivated in a much faster manner due to the strategic positioning of pDCs, dermal DCs and T cells. The majority of skin-homing lymphocytes (CLA⁺) reside in normal skin and that there are twice as many T cells resident in the skin than are present in the circulation. The majority of these cells are memory T cells that are Th-1 polarized and involved in cutaneous immunosurveillance. Thus, an innocuous trigger could activate resident cells, eliciting the inflammatory cascade typical of psoriatic lesion, without recruitment of cells from the circulation (Tonel and Conrad, 2009).

The immune reactions responsible for psoriasis development can be simplified in three phases. Sensitization phase, resting phase and an effector phase. Different cell types are involved in each phase. The sensitization phase results in the generation of Th22, Th1 and Th17 cells. It seems that the effector phase of the pathogenesis of psoriasis comprises two different stages: a proximal or early stage in which immune cells infiltrating the skin and a distal or late stage in which the psoriasis typical epidermal alterations form. The patient and the treating physician usually notice only the late effector phase, when cutaneous lesions become visible. At this point of time, not only T cells (Th22 and Th17 cells), but
also monocytes/ macrophages, DCs and keratinocytes play an important pathogenetic role (Sabat and Wolk, 2011).

It has been proposed that various cytokines from infiltrating leukocytes orchestrate the development of psoriasis. In the proximal stage, TNF-α may initiate the infiltration process (Wolk et al., 2009). The T cell mediators IFN-γ and IL-17 may also be important in the proximal stage of psoriasis pathogenesis. In fact, IFN-γ causes Th1 cell infiltration and activation of antigen-presenting cells, and IL-17 is a strong inductor of neutrophilic granulocyte-attracting chemokines and may therefore play a major role in the development of the psoriasis typical Munro’s micro-abscesses (Wolk et al., 2010).

The late effector phase is controlled by different cytokines. Neither IFN-γ nor IL-17 play a role in this phase, but only IL-22 and, with lower potency, IL-20 can cause psoriasis-like morphological changes in a three-dimensional human epidermis model. In fact IL-22 and its downstream mediator IL-20, but not IFN-γ or IL-17, are the key mediators of the distal stage (Wolk et al., 2009). And also it regulates many of the important pathogenic features of epidermis in psoriatic skin (Ouyang, 2010).
**Histopathology of psoriasis**

![Histopathology of psoriasis](image)

Figure (4): Histopathology of psoriasis

1. Hyperkeratosis & parakeratosis
2. Neutrophils in the epidermis
3. Thinning of the epidermis overlying the dermal papillae
4. Vessels close to the epidermis
5. Elongated rete ridges (Weddon, 2010).

**Early lesions:**

The histologic picture of psoriasis vulgaris varies greatly with the stage of the lesion (Mobini et al., 2005).

At first there is capillary dilatation and edema in the dermis, with a lymphocytic infiltrate around the capillaries. This is followed by parakeratotic hyperkeratosis, disappearance of the granular layer and mild epidermal hyperplasia with the rete ridges are of variable lengths. In the lower part of the epidermis, mitosis occurs in the keratinocytes, as well as some spongiotic foci with leukocytic infiltration. In the malpighian layer, neutrophils accumulate to form the characteristic spongiform pustules of Kogoj. This stage is characterized clinically by early scaling, papules and a histologic diagnosis of psoriasis can be made (Kruger and Bowcock, 2005).
Fully developed lesions:

They are characterized by acanthosis with regular elongation of the rete ridges and thickening in their lower part (clubbing). Thinning of the suprapapillary portion of the stratum malpighii with presence of small spongiform pustules of Kogoj. Diminished to absent granular layer, with confluent parakeratosis and Munro's microabcesses (accumulation of neutrophils). Finally, elongation and edema of the dermal papillae along with dilated tortuous capillaries (Murphy et al., 2007).

Clinical features

Plaque psoriasis (Psoriasis vulgaris):

This is the commonest and well known form of psoriasis. It is characterized by raised, well defined erythematous papules and plaques with silvery coarse scales varying in size from 1 cm to several centimeters. There is wide variation in the intensity of erythema ranging from light pink to bright red to deep purplish red, thin diffuse white scales to thick hyperkeratotic scales and elevation of the lesion from flat to very thick. There is symmetric distribution, and the predilection sites include the extensor surfaces of the extremities, particularly the elbows and knees, scalp, sacrum, nape of the neck, and a lesser extent on the remainder of the face, trunk, genitalia, and ears (Johnson and Armstrong, 2013).
Pustular psoriasis:

It is classified into two main groups; localized and generalized forms. In this type, there is infiltration of neutrophils more than other leukocytes histologically, with erythema and the appearance of sterile pustules clinically. It is an uncommon manifestation of psoriasis, and triggering factors include rapid tapering of corticosteroids, pregnancy, hypocalcaemia and infections (Marrakchi et al., 2011).

Guttate psoriasis:

It appears commonly in children and young adults after acute streptococcal infection. Lesions vary from 2mm – 1cm in diameter, slightly oval or rounded in shape and scattered particularly on proximal parts of limbs and trunk (Mitra and Anupam, 2013).

Erythrodermic psoriasis:

It is characterized by generalized erythema and scaling involving more than 90% of the body. It may present suddenly or as a result of withdrawal of methotrexate, potent topical or oral corticosteroids moreover, it is precipitated by hypocalcaemia, infections and antimalarial drugs (Kimball and Boehncke, 2010).

Flexural (Inverse) psoriasis:

These lesions differs in morphology from that of typical plaque psoriasis lesions in that are characterized by shiny sharply demarcated erythema or thin plaques without significant scales. Inverse psoriasis is characterized mainly by its distribution as it involves the groin, vulva, axillae, body folds, submamary folds and gluteal cleft (Mitra and Anupam, 2013).
Mucous membrane lesions:

They have been associated with erythrodermic, generalized pustular psoriasis and plaque forms. The commonest site affected is the tongue with annular erythematous lesions (Kimball and Boehncke, 2010).

Psoriatic arthritis:

It is a form of chronic inflammatory arthritis with a highly variable clinical picture and frequently occurs in association with skin and nail psoriasis. It involves inflammation and pain of the joints and surrounding connective tissue and can occur in any joint; this can result in a sausage shaped swelling of the fingers and toes known as dactylitis (Chimenti et al., 2013). It occurs in 5-30% of patients with cutaneous psoriasis (Palfreeman et al., 2013).

Nail changes:

It is very common. It occurs in 10%-55% of psoriasis patients. Nail matrix involvement leads to irregular nail pitting (the most common finding of nail psoriasis), leukonychia and dystrophy, nail bed involvement leads to onycholysis, splinter hemorrhages, subungual hyperkeratosis, oil drop patches, and nail thickening, nail fold involvement may lead to paronychia (Mitra and Anupam, 2013).

Complications:

The co-morbidities commonly associated with psoriasis are chronic inflammatory intestinal disease, psoriatic arthritis, psychiatric and psychosocial disorders. An increased prevalence of cardiovascular co-morbidities secondary to the metabolic alterations associated with psoriasis; among them, obesity, diabetes, dyslipidemia, coronary disease
and hypertension. The risk of myocardial infarction is higher in younger patients with severe forms of psoriasis (Duarte et al., 2010).

Treatment of psoriasis

Generally, the goal of complete clearance of psoriasis is not realistic; few patients actually have prolonged clearance time (Feldman and Krueger, 2005).

Treatment of localized psoriasis:

Anthralin (Dithranol)

It acts by decreasing the rapid growth of skin cells associated with plaque psoriasis (Goodless, 2008).

Tar

The actual mechanism of action is not known; it has an antiproliferative effect (Feldman et al., 2011).

Topical Calcineurin inhibitors

The topical calcineurin inhibitors as pimecrolimus and tacrolimus have the advantage unlike topical corticosteroids, it is not absorbed systemically, they are selective and do not produce skin atrophy making them suitable for long-term application (Menter et al., 2009).

Topical corticosteroids

Steroids are effective by their anti-inflammatory, immunosuppressive, antiproliferative and vasoconstrictive properties (Gordon and Ruderman, 2006).
Topical Tazarotene

Topical retinoids can decrease the proliferation of keratinocyte and normalize their differentiation (Kumar et al., 2010).

Topical calcipotriene

Vitamin D analogues have the ability to stimulate cellular differentiation and inhibit their proliferation (Chaudhari et al., 2008).

Treatment of Generalized Psoriasis

Ultraviolet light:

Ultraviolet (UV) radiation may act via anti-inflammatory effects and antiproliferative effects slowing keratinization and inducing apoptosis of pathogenic T-cells in psoriatic plaques (Feldman et al., 2011).

Systemic therapy:

- Cyclosporine:

  It has potent immunosuppressive properties, reflecting its ability to inhibit the transcription of cytokine genes in activated T cells (Matsuda and Koyasu, 2000).

- Methotrexate:

  Methotrexate is a first-line systemic therapy for psoriasis because it is highly efficacious for severe disease and all clinical variants of psoriasis (Peter and Frank, 2012).
- **Retinoids:**

  Retinoids have immunomodulatory and antiproliferative properties. It is indicated in patients with severe psoriasis (*Nast et al., 2012*).

  Combination therapies such as immunosuppressive drug and biologic ones are used with good effect but the safety not studied well, all the systemic drugs except acitretin increase the risk of infections (*Lowes, 2014*).