2.1 BACKGROUND OF PSORIASIS

Psoriasis is one of the longest known misunderstood illnesses of humans in medical history. It was described by Greek Physician Hippocrates in Greece in 460-377 B.C. He used term “Psora” which means “to itch” (Brian et al., 2004 and Kaur et al., 2011). Initially the psoriasis was confused with the leprosy. It was described as a type or variety of the leprosy. The Greeks used the term “lepra” which means scaly skin conditions. In the Bible, 'lepra' has been used to describe various skin diseases including leprosy, psoriasis, vitiligo, eczema and alopecia areata (Farber et al., 1961). Some authors have pointed out the 'tzaraat' mentioned in the Bible may refer to psoriasis.

In 18th century, English dermatologists Robert William and Thomas Bateman differentiated psoriasis from other skin diseases by the regular, circular form of patches while psoriasis is always irregular. Robert William (1757-1812) an English dermatologist was the first person to recognize psoriasis as its own kind of disease. He had classified psoriasis into two categories: Leprosa Graecorum was the term used to describe the condition when the skin had scales and Psora Leprosa was used to describe the condition when it became eruptive (Gudjonsson et al., 2007). The name Psoriasis was given by the Viennese Dermatologist Ferdinand Von Hebra in 1841 which is derived from greek word psora. So, Psoriasis was first diagnosed as psoriasis in Greece (Bellvue, 2011).

2.2 PATHOGENESIS OF PSORIASIS

The pathogenesis of psoriasis is unknown but genetic and immunologic mechanisms have been proposed. Genetic factors play a critical role in the pathogenesis of psoriasis (Griffiths et al., 2005 and Martin et al., 2012).

2.2.1 Genetical Aspect

Psoriasis has a very sound genetical history and is inherited by an autosomal dominant gene (Farber, 1971). Many genetic factors contribute to psoriatic skin disease susceptibility. The linkage analysis has been used to identify multiple loci and alleles that confer risk of the psoriasis. One of the main candidate genes responsible for psoriasis is HLA class 1 allele, specifically HLA – CW6 (Tiilikainen et al., 1980). First major susceptibility loci PSORS7 resides on the chromosome 1p and PSORS9 on
the chromosome 4q 31 (Trembath, 1997). Second major susceptibility locus PSORS2 resides with in 17q24-q25 (Tomfohrde et al., 1994 and Speckman, 2003). Six different susceptibility loci were designated for psoriasis from PSORS1– PSORS6. The major genetic determinant for psoriasis was PSORS1 region of Major Histocompatibility Complex 6p21 (Capon et al., 2002).

2.2.2 Immunological Aspect

The immunity system consists of an innate immune system and an adaptive immune system. In the innate immunity, the immune cells have receptors that have evolved to target specific protein and other antigens which are present on the pathogens. In adaptive immunity, immune cells respond to proteins and other antigens that they may never have seen before, which are presented to them by other cells. The innate immune system passes antigens on to the adaptive systems. In case of psoriasis, immune cells move from dermis to epidermis, where they stimulate skin cells to proliferate (Nestle et al., 2009). Dermal T lymphocytes are a mixture of CD4+ and CD8+ cells with CD4+ predominance. Most T cells in skin lesions are memory cells that express cutaneous lymphocyte antigen (CLA) (Fuhlbrigge et al., 1997 and Bogaard vanden et al., 2014).

The pathogenesis of psoriasis can be summarized in following steps (Lee and Cooper, 2006):

a) T cell activation: It is proposed that patients develop an immune response to an unidentified skin antigen. The activation of T cells requires three steps. The first step requires binding i.e. the T cell attaches to the antigen presenting cell (APC) through surface adhesion molecules. The second step is the antigen specific activation in which the antigen is presented to the T cell by the APC leading to conversion of naïve T cell into an antigen specific cell. The third step is non antigen specific cell to cell interaction or co-stimulation.

b) T cell proliferation and differentiation: Under the influence of IL-12 and IFN-γ, CD4 T cells differentiate into a Th1 phenotype.

c) T cell trafficking: The activated T cells home to the skin where they can exert their effects. This is a multi step process that involves interaction between the activated T cells and endothelium.
**d) T cell reactivation:** After exiting post-capillary venules, Th lymphocytes encounter dendritic cells within the dermis and Langerhans cells within the epidermis and subsequently release proinflammatory cytokines such as TNFα and IFNγ. The net result is the increased proliferation of keratinocytes manifested by the elongation of rete ridges, loss of granular layer, parakeratosis and endothelial proliferation.

![Fig. 2.1: Inflammatory Cytokines Involved in the Pathogenesis of Psoriasis](Nickoloff et al., 2007)

### 2.3 CYTOKINES

Cytokines (greek *cyto-* meaning cell; and *kinos*-movement) are small cell-signaling protein molecules that are secreted by the glial cells of the nervous system and by numerous cells of the immune system and are a category of signaling molecules used extensively in intercellular communication. They are low molecular weight soluble polypeptides (proteins), peptides or glycoproteins, which are secreted by immunocytes, epithelial and endothelial cells. They play an important role in the
biological activities of the host’s defense system against pathogens, functioning as mediators in inflammation, hematopoiesis, phagocytosis and apoptosis (Borish and Steinke, 2003). In addition to this, they are involved in homeostasis, tissue repair, cell growth and development (Mantovani et al., 2004).

2.4 CYTOKINE MECHANISM IN PSORIASIS

Chemical signaling of cytokines usually occurs locally and for a short time. Most of them act on their target cells in a paracrine or autocrine manner. When they act on the cell they are secreted, they are said to act in an autocrine manner. When we talk about paracrine manner, we mean that the secreted cytokines acts on the cells close to the cell which secretes the cytokine. Rarely, some secreted cytokines systemically travel through bloodstream and act on the cells at a distant site.

In the human body, cells are never exposed to a single cytokine (Wood, 2006). Cytokines can affect multiple phenotypic traits by affecting the activity of different cell types differently, which indicates their pleiotropic property. Also, different cytokines may have the same function, which makes them functionally redundant. In addition to these properties, synergism and antagonism properties are also observed between cytokines. Transforming growth factor-β (TGF-β) increases the gene expression of type 1 collagen whereas tumor necrosis factor α (TNF-α) reduces the expression which is an example of antagonistic property of cytokines (Verrecchia and Mauviel, 2004). On the other hand, the production of interferon-γ (IFN-γ) by interleukin 12 (IL-12) and tumor necrosis factor-α (TNF-α) is an example of synergism (Ahlers et al., 2001).

CD4+ T cells differentiate into three subsets with respect to the cytokines they produce. Th1 cells secrete cytokines which activate cell-mediated immune response like IL-2 and TNF-γ whereas Th2 cells secrete antibody response affecting cytokines like IL-4 and IL-5 (Coico et al., 2003). Both Th1 and Th2 secreted cytokines interact with B cells and according to the subset of the TH; B cells are induced to different Ig synthesis. By this way, cytokines involve in proliferation, differentiation and activation of immune response cells (Sarra et al., 2011).

Psoriasis is a T cell-mediated inflammatory skin disease and T helper (Th) cells – Th1, Th17 and Th22 – play an important role in the pathogenesis (Kagami et al., 2010 and Mak et al., 2009). Human IL-20 and IL-22 cytokines are members of the IL-10 family of cytokines and IL-17 is member of the IL-17 family of cytokine that have
been shown to be up regulated in psoriatic skin (Girolomoni et al., 2012). A large body of recent data from other groups suggests that two members of the IL-10 family of cytokines, IL-20 and IL-22, are the key mediators of the keratinocyte alterations in psoriasis (Kunz et al., 2006, Otkjaer et al., 2005, Romer et al., 2003, Wei et al., 2005, Wolk et al., 2004). Interestingly, IL-22 is even present in the blood of psoriasis patients, and IL-22 blood levels strongly correlate with the disease severity (Wolk et al, 2006). IL-20 and IL-22 have been shown to be altered in psoriatic skin (Otkjaer et al., 2005; Blumberg et al., 2001; Romer et al., 2003; Wolk et al., 2004, 2009; Sa et al., 2007). In addition, IL-20 and IL-22 promoted hyperproliferation and abnormal differentiation of keratinocytes both in vitro and in vivo (Blumberg et al., 2001; Wolk et al., 2004, 2006; Boniface et al., 2005; Sa et al., 2007). IL-22 induced hyperplasia and inhibited differentiation in a cultured reconstituted human epidermis (RHE) (Boniface et al., 2005). In view of the biological effects, IL-22 seems to be a novel type of immune mediator, which although produced by immune cells does not affect these cells but regulates functions of certain tissue cells (Wolk et al., 2004). IL-22 increases the innate immunity of tissue cells, protects tissues from damage, and enhances their regeneration.

2.5 INTERLEUKINS

Interleukins are a group of cytokines that were first seen to be expressed by white blood cells (leukocytes). The majority of interleukins are synthesized by helper CD4+ T-lymphocytes, as well as through monocytes, macrophages, and endothelial cells. They promote the development and differentiation of T and B-lymphocytes, and hematopoietic cells (Khadka, 2014). There are various families of interleukin’s some interleukins are described below.

2.5.1 Interleukin 10 Family

Interleukin-10 is an anti-inflammatory cytokine. In human body, IL-10 is encoded by the *IL10* gene. It is primarily produced by monocytes and, to a lesser extent, lymphocytes, namely type 2 T helper cells (Th2), mastocytes, CD4^+^CD25^+^Foxp3^+^ regulatory T cells(Tregs), and in a certain subset of activated T cells and B cells. It is a protein that inhibits the synthesis of a number of cytokines, including IFN-gamma, IL-2, IL-3, TNF-β, and GM-CSF produced by activated macrophages and by helper T cells. So it is known as human cytokine synthesis
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inhibitory factor (CSIF). Human Interleukin-10 (IL-10) is a pleiotropic cytokine that inhibits cell-mediated immunity while enhancing humoral immunity (Moore et al., 2001). The IL-10 family include cytokines, such as IL-20 (Blumberg et al., 2001), IL-22 (Dumoutier et al., 2000). Although these IL-10-like cytokines share limited primary and structure homology, their biological activities are quite different. In structure, IL-10 is a protein of about 160 amino acids that contains four conserved cysteines involved in disulphide bonds. IL-10 is highly similar to the Human herpesvirus 4 (Epstein-Barr virus) BCRF1 protein, which inhibits the synthesis of IFN-gamma and to Equid herpesvirus 2 (Equine herpesvirus 2) protein E7. It is also similar, but to a lesser degree, with human protein mda-7(IL-24). Mda-7 is a protein that has antiproliferative properties in human melanoma cells. Mda-7 contains only two of the four cysteines of IL-10 (Oral et al., 2006).

Table 2.1: Showing the various types of interleukins

<table>
<thead>
<tr>
<th>Name</th>
<th>Source</th>
<th>Target receptors</th>
<th>Target cells</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-10</td>
<td>Monocytes, Th2 cells, CD8+ T cells, mast cells, macrophages, Activated T and B cells subset, CD4+CD25+Foxp3+ regulatory T cells(Tregs)</td>
<td>CD210/IL10RA, CDW210B/IL10RB</td>
<td>macrophages</td>
<td>cytokine production</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B cells</td>
<td>Activation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mast cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Th1 cells</td>
<td>inhibits Th1 cytokine production (IFN-γ, TNF-β, IL-2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Th2 cells</td>
<td>Stimulation</td>
</tr>
<tr>
<td>IL-17</td>
<td>T helper 17 cells (Th17); Fibroblasts</td>
<td>CDw217/IL17RA, IL17RB</td>
<td>epithelium, endothelium, other</td>
<td>osteoclastogenesis, angiogenesis, hematopoiesis, increase inflammatory cytokines, fibroblast cytokine release, increase MMP release, decrease Chondrocyte GAG synthesis, increase Leukocyte cytokine production</td>
</tr>
<tr>
<td>IL-20</td>
<td>Activated keratinocytes and monocytes</td>
<td>IL20R</td>
<td></td>
<td>regulates proliferation and differentiation of keratinocytes</td>
</tr>
<tr>
<td>IL-22</td>
<td>Activated Th1-type T cells and NK cells and CD8+ T cells</td>
<td>IL22R</td>
<td></td>
<td>Activates STAT1 and STAT3 and increases production of acute phase proteins such as serum amyloid A, Alpha 1-antichymotrypsin and haptoglobin in hepatoma cell lines</td>
</tr>
</tbody>
</table>
2.5.2 Interleukin 17

Interleukin 17 was discovered in 1993 by Rouvier et al. originally identified as a rodent T cell cDNA transcript, cytotoxic T lymphocyte-associated antigen 8 (CTLA8). It is also known as IL-17A and CTLA-8. IL-17 is a potent proinflammatory cytokine produced by activated memory T helper 17 cells (Th17) such as activated CD4+ and CD8+ T lymphocytes (Zhu et al., 2010). Mammalian cells known to produce IL-17 are the CD4+ Th17 T cells, Paneth cells, GR1+CD11b+ myeloid suppressor cells, CD27-γδ T cells, CD1+NK1.1-iNKT cells, and CD3-CD4+ LTi-like cells (Serre et al., 2013).

![Diagram showing IL-17-producing helper T-cell plasticity.](image)

Showing IL-17-producing helper T-cell plasticity. Naive CD4+ T cells differentiate into distinct functional subsets. IL-23 induces the differentiation into IL-17-producing helper T (Th17) cells. IFN-γ and IL-4 antagonize each other in the differentiation of Th1 and Th2 cells, and also suppress the differentiation of Th17 cells. Treg cells suppress the differentiation and effector function of Th1 and Th2 cells. Treg-derived TGF-β induces the differentiation of Th17 cells from naive CD4+ T cells in the presence of IL-6 in vitro. A mixed Treg–Th17 subgroup, induced by TGF-β, has been also identified. These cells express FoxP3 and RORγt and produce both IL-17 and IL-10. In the absence of TGF-β, Th17 cells express Th1-specific transcription factors together with their conventional transcription factor RORγt. These are IL-17–IFN-γ dual-producing cells, also releasing other pro-inflammatory cytokines. FoxP3, Forkhead box P3; IFN, interferon; IL, interleukin; RORγt, retinoic acid orphan receptor-γ thymus; T-bet, T-box expressed in T cell; TNF, tumour necrosis factor (Liuzzo et al., 2013).
Human Interleukin 17 has a molecular mass of 35 kDa, variably glycosylated polypeptide that belongs to the IL-17 family of cytokines. Human IL-17/17A is synthesized as a 155 amino acid precursor that contains a 23 amino acid signal sequence and a 133 amino acid mature region that possesses a cysteine-knot fold. IL-17 is unique in that it bears no resemblance to other known interleukins. Furthermore, IL-17 bears no resemblance to any other known proteins or structural domains (Ouyang et al., 2008).

IL-17 is best known for its participation in the recruitment and survival of neutrophils. Its induction was initially described to be the result of antigen stimulation of dendritic cells, resulting in IL-23 secretion. In a T cell receptor-independent event, IL-23 induces T cell production of IL-17 (Gaffen et al., 2014). Once secreted, IL-17 in the bone marrow would seem to induce stromal/fibroblast expression of both G-CSF and stem cell factor (membrane form), an effect that increases polymorphonuclear neutrophils (PMN) differentiation and production. IL-17 may complement this by directly blocking neutrophil apoptosis, promoting greater circulating PMN numbers (Panopoulos et al., 2008). In the tissues, IL-17 would also seem to promote neutrophil extravasation, principally through its effects on macrophages and endothelial cells (EC). On macrophages, IL-17 induces TNF-α, IL-1b and IL-6 production. TNF-α and IL-1b then act on local ECs to induce G-CSF secretion, an effect that is potentiated by IL-17. IL-17 further contributes to PMN influx by inducing EC CXC chemokine release and nitric oxide production, which may increase vascular permeability (Mai et al., 2013). IL-17 effects are not limited to inflammation. In synovial joints, IL-17 upregulates RANKL expression on osteoblasts. This provides a stimulus for osteoclast formation and subsequent bone resorption. In conjunction with IL-4 and CD40L, IL-17A also promotes the generation of IgE secreting cells. And in white fat, IL-17A inhibits adipocyte differentiation from preadipocytes, and impairs glucose uptake by mature adipocytes (Nakajima et al., 2011).

Human IL-17 belongs to a recently discovered family of cytokines that contribute to the crosstalk between adaptive and innate immunity (Stumhofer et al., 2006). IL-17 and its relative IL-17F have strong proinflammatory properties on a broad range of cellular targets, including epithelial and endothelial cells, fibroblasts, keratinocytes, osteoblasts, and monocytes/macrophages (Weaver et al., 2007). The IL-17 family is thought to represent a distinct signalling system that appears to have been highly conserved across vertebrate evolution.
In human tissue infiltering of IL-17 cell expressed a distinctive pattern of chemokines receptors which can be detected and explained by flow cytometry analysis. Alterations in serum levels of IL-17 in psoriatic patients show somewhat interesting results with increased and decreased values (Gascan et al., 2008). Acted synergistically to enhance IL-17 the production of IL-20 and IL-22 in the psoriatic skin, which later on induced certain severity conditions in the affected individuals (Tohyama et al., 2009 and Martin et al., 2013).

Serum levels of diverse cytokines and growth factors in Japanese patients with psoriasis, including some cases with psoriasis guttate, erythrodermic psoriasis, and psoriatic arthritis. IL-17 levels were higher than those in healthy controls and strongly correlated with PASI (Takahashi et al., 2010).

Currently, many autoimmune diseases are believed to be Th17-mediated diseases, because the biologic functions of IL-17 are consistent with the chronic and destructive nature of inflammation. This review introduces accumulating evidence on the roles of IL-17 and Th17 cells in human autoimmune diseases (Nakajima et al., 2011).

2.5.3 Interleukin 20

Human Interleukin 20 is a protein molecule that in humans is encoded by IL-20 gene and is a member of the IL-10 family of cytokines (Bech et al., 2016). It exhibits approximately 28% amino acid identity with IL-10 and 76% amino acid identity with mouse IL-20. It was identified by searching databases for translated sequences containing a signal sequence and amphipathic helices found in helical cytokines. Human IL-20 is synthesized as a 176 amino acid precursor with a 24 amino acid signal sequence and a 152 amino acid mature segment. IL-20 appears to function as a monomer. Expression of IL-20 can be upregulated by treatment with lipopolysaccharide (Pestka et al., 2004).

IL-20 is produced by activated keratinocytes and monocytes and transmits an intracellular signal through two distinct cell-surface receptor complexes on keratinocytes and other epithelial cells. There are two heterodimeric receptor complexes for IL-20. The first is composed of IL-20 Rα and IL-20 Rβ. The second is composed of IL-22 R and IL-20 Rβ. Whereas the IL-22 R/IL-20 Rβ complex is shared with IL-24, the IL-20 Rα/IL-20 Rβ complex is shared with both IL-19 and IL-24. IL-20 has been shown to initiate transduction cascades involving STAT3 in keratinocyte and
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stimulates the induction of pro-inflammatory genes including TNF-α and MCP-1 (Tohyama et al., 2009).

Initial functional studies using transgenic mice suggest that IL-20 has the ability to regulate skin development. The over-expression of both human and mouse forms of IL-20 results in keratinocyte hyperproliferation, abnormal epidermal differentiation, and neonatal lethality. IL-20 regulates proliferation and differentiation of keratinocytes during inflammation, particularly inflammation associated with the skin. In humans, IL-20 and its receptors are upregulated in psoriatic skin, and polymorphisms in the IL-20 gene have been associated with plaque-type psoriasis. IL-20 may also have a role in hematopoiesis. It enhances the proliferation of multipotential progenitors in vitro and increases their numbers and cell cycling status in IL-20 transgenic mice. IL-20 is also shown to suppress COX-2 and PGE2 and acts as an inhibitor of angiogenesis in model systems. A specific receptor for this cytokine is found to be expressed in skin and upregulated dramatically in psoriatic skin, suggesting a role for this protein in epidermal function and psoriasis (Zhang et al., 2011).

IL-20 was capable of inducing signal transduction in keratinocyte cell line in vitro studies. Furthermore, it was demonstrated that both the receptor chains IL-20R1 and IL-20R2 were upregulated in human psoriatic skin compared with normal skin. Based on these data it was suggested that IL-20 and its receptor complex play a pathogenic role in psoriasis (Blumberg et al., 2001).

2.5.4 Interleukin 22

Interleukin 22 is a polypeptide that in humans is encoded by IL-22 gene. This cytokine is known as IL-10-related T cell-derived inducible factor (IL-TIF) and is a member of the IL-10 cytokine family. Other members of this family include IL-10, IL-19, IL-20, IL-24, and IL-26 (Li et al., 2014). IL-22 was initially identified as a gene induced by IL-9 in mouse T cells and mast cells. Human IL-22 cDNA encodes a 179 amino acid. A protein with a putative 33 amino acid signal peptide, sharing approximately 79% and 22% amino acid sequence identity with mouse IL-22 and human IL-10, respectively (Dumoutier and Renaud, 2006). Although the related IL-10 is thought to act as a dimer, the crystal structure of IL-22 suggests it may interact with its receptor as a monomer (Michalak-Stoma et al., 2013).

IL-22 is produced by activated dendritic cells(DC), activated Th1-type T cells, a subset of natural killer cells and lymphoid tissue-inducer cells and initiates innate
immune responses against bacterial pathogens especially in epithelial cells such as respiratory and gut epithelial cells. IL-22 can be also produced by Th17 cells and likely plays a role in the coordinated response of both adaptive and innate immune systems. In humans, this is supported by the observation that IL-22 is produced by synovial fibroblasts and macrophages of rheumatoid arthritis (RA) patients and is capable of inducing pro-inflammatory responses in RA synovial tissues. In addition, it stimulates the production of pro-inflammatory cytokines and anti-microbial defensins in human keratinocytes. These activities result in epidermal hyperplasia in models of human skin (Boniface et al., 2005). Mouse IL-22 expression is induced in various organs upon lipopolysaccharide injection, suggesting that it may be involved in inflammatory responses (Tachiiri et al., 2003).

Structurally, IL-22 is an α-helical cytokine and consists of two receptor subunits, IL-22 R (previously an orphan receptor named CRF2-9) and IL-10 Rβ (previously known as CRF2-4). The IL-10 Rβ chain is shared by IL-10, IL-26, IL-28A, IL-28B, and IL-29. IL-22 R is expressed primarily in the pancreas, and to a lesser extent, tissues of the gastrointestinal tract, kidney, and skin. A soluble receptor, IL-22 binding protein (IL-22BP), has also been described and may act as an endogenous inhibitor of IL-22 activity (Spencer et al., 1998). IL-22 has been shown to activate Jak/STAT and MAPK signaling pathways and upregulate the production of acute phase proteins. IL-22 also promotes hepatocyte survival in the liver and epithelial cells in the lung and gut similar to IL-10 (Lavoie et al., 2016).

IL-22 targets cells of the digestive, skin and respiratory organ systems play a crucial role in mucosal immunity. The importance of IL-22 in host defense against Gram-negative bacterial organisms (in gut and lung), this shows that IL-22 also plays a role in autoimmune disease, such as psoriasis (Yang and Zheng, 2014).

IL-22 plays a significant role in inflammatory bowel disease (IBD) by enhancing barrier integrity and epithelial innate immunity of intestinal tract. In psoriasis, IL-22 can synergize with other proinflammatory cytokines to induce many of the pathogenic phenotypes from keratinocytes and exacerbate disease progression (Ouyang Win, 2008).

IL-22, one of the cytokines secreted by Th17 cells, demonstrates both a protective and inflammatory promotion effect in inflammatory bowel diseases (IBD) through STAT3 signalling activation. IL-22 is related to development of human colon
cancer by activation of STAT3. IL-22 related proteins are also over expressed in human colon cancer and ulcerative colitis (Yamamoto-furusho et al., 2016). In human, mast cells are major IL-22 producers in patients with psoriasis and atopic dermatitis (Mashiko et al., 2015).

![Diagram showing the differentiation and function of interleukin-22 (IL-22)-producing T cells in skin immunopathology.](image)

Showing differentiation and function of interleukin-22 (IL-22)-producing T cells in skin immunopathology. Multiple factors modulate the differentiation of IL-22-producing, CD4+CCR6+CCR4+CCR10+ lymphocytes from naive T cells. Differentiation of IL-22-producing T cells (‘Th22’) is induced or enhanced by aryl hydrocarbon receptor (AHR) ligands, such as β-naphthoflavone (β-NF), 8-tetrachlorodibenzo-p-dioxin (TCDD) or 6-formylindolo[3,2-b]carbazole (FICZ), which promote IL-22 production while inhibiting the production of IL-17. IL-22 production of IL-22 is inhibited by transforming growth factor-β (TGF-β). Plasmacytoid dendritic cells (pDCs), matured with CpG, produce high levels of IL-6 and TNF-alpha and are able to prime the differentiation of ‘Th22’ cells. The presence of 1,25(OH)2D3, the active form of vitamin D3, enhances the priming efficacy of pDC and, together with IL-12, induces expression of CCR10 on T cells. The presence of the CCR10 ligand, CCL27, in the skin favors the homing of IL-22-producing cells to this tissue (Yssel and Pene, 2009).

IL-22 can inhibit keratinocyte terminal differentiation and can induce psoriasis like epidermis alterations; serum IL-22 levels were correlated with the disease severity of psoriasis patients and IL-22 in RNA was positively expressed in the psoriatic skin lesions, but negatively expressed in the normal controls (Hao, 2014).
Psoriasis is associated with several co-morbidities, including decreased quality of life, depression, increased cardiovascular risk, type 2 diabetes mellitus, hypertension, metabolic syndrome and Crohn’s disease (Traub et al., 2007 and Puig Sanz, 2007).

2.6 CO-MORBIDITIES ASSOCIATED WITH PSORIASIS

Psoriasis is associated with several co-morbidities, including decreased quality of life, depression, increased cardiovascular risk, type 2 diabetes mellitus, hypertension, metabolic syndrome and Crohn’s disease (Traub et al., 2007 and Puig Sanz, 2007).

2.6.1 Cardiovascular Disease

Of particular concern is the observed link between psoriasis and cardiovascular disease. Evidence indicates psoriasis is an independent risk factor for cardiovascular disease. Dyslipidemia, obesity, diabetes, hypertension, coronary calcification, increased highly sensitive C-reactive protein (hs-CRP), decreased foliate and hyperhomocysteinemia are found with significantly higher frequency in psoriasis.
patients. Inflammation is the common theme underlying both conditions, characterized by the presence of proinflammatory cytokines and endothelial activation (Traub et al., 2007; Kimball et al., 2008; Menter et al., 2008 and Shahwan and Kimball, 2015).

The cardiovascular risk factors in psoriasis and found psoriasis to be associated with atherosclerosis and this association applies to coronary artery, cerebrovascular and peripheral vascular diseases (Prodanovich et al., 2009). A cross sectional prevalence-based study from 2 American healthcare databases showed an increase prevalence of cardiovascular diseases and risk factors in patients with psoriasis compared with general population (Kimball et al., 2008). A strong association between psoriasis, atherosclerosis, heart failure and diabetes were found in the population of Israel (Shapiro et al., 2007 and Shiba et al., 2016).

2.6.2 Autoimmune Diseases

Although psoriasis has been previously thought to be a disease affecting primarily the skin and incidence of Crohn’s disease and ulcerative colitis is 3.8 to 7.5 times greater in patients with psoriasis than in the general population. The three diseases have susceptibility localized to a similar region of chromosomes 16, multiple other genetic loci are found in each condition. Studies suggest a possible link between multiple sclerosis (MS) and psoriasis, as psoriasis occurs more commonly in families of patients with MS compared with control subjects (Kimball et al., 2008 and Griffiths et al., 2005).

2.6.3 Obesity

Obesity has serious health consequences including hypertension, vascular disease, and type 2 diabetes mellitus. Psoriasis was first associated with obesity in several large European epidemiologic studies. Studies from the United States also show an elevated BMI in patients with psoriasis. These analyses of BMI compared subjects with and without psoriasis while controlling for age, sex, and race. An association between psoriasis and elevated BMI appears to be yet another factor that predisposes individuals with psoriasis to cardiovascular disease (Kimball et al., 2008 and Gudjonsson et al., 2007).

Obesity is the result of an interaction between genetic and environmental factors. BMI variation can be attributed to environmental factors in 60 to 70% in psoriatic patients, whereas genetic factors are responsible for 30 to 40%. Weight gain
would be the result of a confluence of factors such as low calorie burn associated with sedentaryism, little physical activity, and high respiratory coefficient (carbohydrate-to-fat oxidation ratio). Lastly, obesity results from an imbalance between food intake and calorie burn (Yosipovitch et al., 2007 and Lara et al., 2012).

2.6.4 Metabolic Syndrome

The combination of obesity, impaired glucose regulation, hypertriglyceridemia, reduced high-density lipoprotein, and hypertension is known as the metabolic syndrome. Patients with metabolic syndrome are at a significantly increased risk of developing cardiovascular morbidity and mortality. A recent study demonstrates that the prevalence of metabolic syndrome in psoriasis is significantly elevated (Kimball et al., 2008; Richard and Charles, 2004 and Menter et al., 2008).

2.6.5 Quality of Life (QoL)

Psoriasis causes psychosocial morbidity and decrement in occupational function (Griffiths et al., 2005). In a large study of more than 300 university-based patients with psoriasis, the physical and mental disability experienced by patients with psoriasis was comparable or in excess of that found in patients with other chronic illnesses such as cancer, arthritis, hypertension, heart disease, diabetes, and depression as measured by the SF-36 Health Survey Form. QOL measures are an important adjunct to skin lesion assessments to properly assess the full effect of an illness such as psoriasis that is not life-threatening. Dermatology specific, but not psoriasis-specific, instruments such as the Dermatology Life Quality Index or SKINDEX are very useful to assess the QOL impact of psoriasis, but may have a limited correlation with the actual severity of a specific skin disease such as psoriasis (Kimball et al., 2008; Mattei et al., 2014 and Hawro et al., 2015).

2.6.7 Depression/Suicide

Psoriasis is associated with lack of self-esteem and increased prevalence of mood disorders including depression. The prevalence of depression in patients with psoriasis may be as high as 60%. Depression may be severe enough that some patients will contemplate suicide. In one study of 217 patients with psoriasis, almost 10% reported a wish to be dead and 5% reported active suicidal ideation. Treatments for psoriasis may affect depression. One study demonstrated that patients with psoriasis treated with etanercept had a significant decrease in their depression scores when
compared with control subjects. Increased rates of depression in patients with psoriasis may be another factor leading to increased risk of cardiovascular disease (Griffiths et al., 2005; Menter et al., 2008 and Mattei et al., 2014).

Patients with psoriasis have an increased prevalence of cardio-metabolic risk factors as hypertension, atherogen dyslipidemia and diabetes (Prodanovich et al., 2008; Targher et al., 2010; Abuabara et al., 2010). The higher cardiovascular risk in patients with psoriasis may be secondary to accelerated atherosclerosis fueled by psoriatic cytokines (Davidovici et al., 2010). The presence of numerous genes common to psoriasis and metabolic and cardiovascular risk factors has been reported in previous studies, for example osteopontin, fibrinogen, IL-6, TNF, TNF-\(\gamma\) converting enzyme, IL-18, IL-12B and IL-23R, IL-8, PPAR—4 (Chen et al., 2005; Danik et al., 2009; Bis et al., 2008; Hou et al., 2009; Mangino et al., 2008 and Enquobahrie et al., 2008).

The impact of pregnancy and oestrogen on psoriasis and potential therapeutic use of selective oestrogen might improve psoriasis by suppressing the T-cell immune response, reducing the keratinocyte (KC) cytokine and chemokine production, restoring the balance of redox and enhancing the skin barrier. Female patients show improvement of psoriasis during pregnancy but sometimes minority of female patients experience worsening during pregnancy (Lin and Huang, 2016).

Potential therapeutic use of antioxidants in psoriasis cause Oxidative stress. Oxidative stress is an imbalance between oxidants and antioxidants. In the study, they focused on the impacts of oxidative stress on dendritic cells, T- lymphocytes and keratinocytes, on angiogenesis and on inflammatory signaling. Oxidative stress is involved in the pathogenesis of psoriasis; the possibility of using this information is to develop new strategies for treatment of patients with psoriasis (Lin and Huang, 2016).