Introduction

Psoriatic arthritis is a chronic multisystem inflammatory disorder, part of the seronegative spondylarthropathies group that occurs in 10-30% of patients with psoriasis. The disease may involve variously joints, enthesis, tendons, nails and skin sometimes with a severe and deforming progression. The most common comorbidities described in the literature are the cardiovascular, metabolic, ophthalmologic and psychological, but the risk of malignancy, osteoporosis, renal impairment, neurological or pulmonary impairment is equally important, those being less studied and with contradictory data **(Ogdie et al., 2015).**

Although, a link between renal impairment and psoriasis has been proposed on the basis of case reports of kidney disease in patients with psoriasis, there is an increase incidence of nephropathy in the case of psoriasis, and this entity is called "Psoriatic Nephropathy". But the link between these two disorders is still controversial. Whether the nephropathy in psoriasis is coincidental or causative is still unknown **(Singh et al., 2005) (Ren et al., 2017).**

The reported prevalence in literature on renal abnormalities in the form of elevated serum creatinine is found in 0.53-23,3% of the psoriatic arthritis patients **(Alenius et al., 2001) (Casals et al., 2012) (Peluso et al., 2015).** Another study done on 2014 published a report which stated that 16% of seronegative arthritis patients including psoriatic arthritis suffer a decline in glomerular filtration rate **(Ogdie et al., 2014).**

Psoriasis may be able to directly induce inflammation and damage in the kidneys. T helper (Th) 1 and Th17 lymphocytes are the known major regulatory cells involved in the pathogenesis of psoriasis **(Ogawa et al., 2017).** Interestingly, studies have demonstrated that Th17 lymphocytes can induce inflammation in the kidneys especially tubular epithelial cells and mesangial cells, IL-17A stimulates tubular cells and mesangial cells to produce T cell, macrophage, and neutrophil chemoattractants **(Turner et al., 2010) (Kitching et al., 2011).**

Kidney activity and damage is likely to be reflected more accurately by biomarkers present in the urine rather than serum. Being easier to obtain in a non-invasive manner, urine is also an ideal biological sample for diseases requiring repetitive sampling **(Soliman et al., 2016).**

Retinol binding protein (RBP) is a 21-kDa protein that is hepatically synthesized. RBP had been initially studied as an adipokine, which binds to vitamin A and belongs to the lipocalin family (**Yang et al., 2005) (Ren et al., 2017).** Since it is low molecular weight protein it is freely filtered through the glomeruli and then almost completely reabsorbed in the proximal tubules, which makes this protein as useful biomarker of tubular renal impairment **(Rubinow et al., 2017).** Even a minor defect in tubular function can enhance excretion of RBP. It has been proposed as the most sensitive marker for loss of proximal renal tubule function in humans **(Norden et al., 2014) (Aggarwal et al., 2017).**

Tubular dysfunction is known to occur during flare of the lupus nephritis, which could explain the high urinary RBP levels. It can also explain high urinary RBP levels in patients of diabetic nephropathy, where tubular dysfunction is a well-known phenomenon **(Varghese et al., 2007)**. Another study observed that the pediatric lupus patients with active non renal disease, who had elevated urinary RBP levels, went on to develop active renal disease **(Marks et al., 2005) (Aggarwal et al., 2017).**

Domingos and his colleagues in 2016 suggested that urinary RBP is significantly associated to renal function in chronic kidney disease, a finding that expands the interest in this biomarker beyond the context of proximal tubulopathies, glomerulopathies or transplantation. They recommended that urinary RBP should be further explored as a predictive and independent marker of chronic kidney disease progression. One hypothesis is that by being related to proximal tubular function, urinary RBP might reflect tubule-interstitial fibrosis, which is a well-recognized and powerful histologic predictor of chronic kidney disease **(Pallet et al., 2014) (Domingos et al., 2016).**

A recent study in 2017 with ninety-seven prostatic patients (62 females, 35 males) and ninety-six age- and gender-matched control subjects without hypertension or diabetes reported that the prevalence of pathologic albuminuria was significantly increased in psoriatic patients in comparison to controls. Moreover, it found that abnormal urinary RBP was significantly higher in psoriatic patients than in controls (P=0.031) **(Ren et al., 2017).**

Aim of the Study

We aim at early detection of renal tubular damage by measuring the level of urinary retinol binding protein (RBP) as a novel biomarker in patients with psoriatic arthritis in relation to activity and severity.

Chapter (1)

Psoriatic Arthritis

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy, belonging to the spondyloarthritic group, usually associated with skin and/or nail psoriasis, **(Caso et al., 2014) (Scotti et al., 2018).**

PsA is characterised by inflammation of entheses and synovium, eventually leading to joint erosions and new bone formation. PsA affects approximately 10 % to 30 % of patients with psoriasis and has an estimated prevalence of approximately 1 % **(Dolcino et al., 2014).**

PsA has both peripheral articular manifestations (including synovitis, dactylitis, and enthesitis) and axial skeletal involvement. The patterns of PsA are asymmetrical oligoarthritis (most common type), symmetrical polyarthritis (rheumatoid like pattern), distal interphalangeal arthritis (5- 10%), arthritis mutilans (1-5%), and spondylitis with or without sacroiliitis A range of bone pathologies is observed in patients with PsA. Bone loss can occur, either locally in the form of bone erosion and osteolysis affecting the peripheral joints, or

systemically with loss of skeletal bone mineral density (BMD) **(Dalbeth et al., 2010) (Scotti et al., 2018).**

Incidence and Epidemiology:

A very recent systematic review and meta-analysis concluded that the prevalence rate for PsA is approximately 130 per 100,000 subjects **(Scotti et al., 2018).** PsA affect men and women equally. Although ankylosing spondylitis is a male predominant disease with a male to female ratio of 3–5:1. PsA gender distribution may change with relation to disease presentation as males tend to present with axial involvement, while females are more likely to suffer from peripheral arthritis. Variation in reported sex ratios may also be secondary to local differences in genetic and environmental factors and due to differences in diagnostic criteria **(Kemal et al., 2016).**

Etiology:

Environmental and genetic aspects have been suggested in the development of PsA **(Yamamoto et al., 2013).**

- **Environmental factors with PsA:**

There are several environmental risk factors for psoriatic arthritis. These include obesity; severe psoriasis;

scalp, genital, and inverse (or intertriginous) psoriasis; nail disease; and trauma or deep lesions at sites of trauma **(Thorarensen et al., 2016).**

Bacterial and viral infections have been implicated as trigger in PsA. Some studies on psoriatic plaque have suggested enhanced humoral and cellular immunity to gram-positive bacteria. Another environmental trigger has been proposed in relation to the Koebner phenomenon, whereby arthritis can develop at sites of traumatized skin higher levels of antibody to streptococcal exotoxin, which provides some evidence of a link between streptococcal infection and articular inflammation **(Kavanaugh and Cassell, 2005) (Olivieri et al., 2008) (Jayaraman et al., 2017).**

- **Genetic susceptibility of psoriatic arthritis**

Psoriatic arthritis is a highly heritable polygenic disease. The recurrence risk ratio (defined as the risk of disease manifestation in siblings vs. the risk in the general population) is greater than 27, which is substantially higher than the recurrence risk ratio for psoriasis or rheumatoid arthritis **(Chandran et al., 2009) (Ritchlin et al., 2017).**

Table 1 Loci Associated With Psoriasis (PSORS) and Psoriatic Arthritis (PSORSA).

Locus	Region	OMIM	Candidate Genes/Function
PSORS1	6p21.3	*612410*	*HLA-Cw6*
PSORS2	17q25.5-qter	*607211*	*CARD14*
PSORS3	4q34	*601454*	*IRF-2*
PSORS4	1q21	*603935*	Loricrin, filaggrin, Pglyrp3,4; S100 and late cornified envelope genes (in the epidermal differentiation complex)
PSORS5	3q21	*604316*	*SLC12A8*, cystatin A, zinc finger protein 148
PSORS6	19p13	*605364*	*JunB*
PSORS7	1p	*605606*	*PTPN22* (1p13), *IL23R* (1p32.1-31.2)
PSORS8/PSORSA1	16q	*610707*	*CX3CL1, CX3R1, NOD2/CARD15*
PSORS9	4q31	*607857*	*IL15*
PSORS10	18p11	*612410*	
PSORS11	5q31-q33	*612599*	*IL12B*
PSORS12	20q13	*612950*	*ZNF313/RNF114*, ubiquitin ligase
PSORS13	6q21	*614070*	*TRAF3IP2*

Table (1): Loci Associated with Psoriasis and Psoriatic Arthritis (Piug et al., 2014).

Despite the larger estimated heritability for PSA, the majority of genetic susceptibility loci identified to date are shared with psoriasis **as shown in table (1)**. This suggests a substantial difference in the genetic architecture of the two diseases with a heavier genetic burden for PsA. The majority of susceptibility loci identified to date are shared between the two phenotypes, which is expected, and is mediated by the presence of psoriasis in both traits. A well-established example to support genetic differentiation involves the associations to genes in the human leukocyte antigen (HLA) class I region of the major histocompatibility complex (MHC) on chromosome 6. Studies have demonstrated that certain alleles of HLA-B confer risk specifically for PsA (B08, B27, B38), while

HLA-C06 is specific for psoriasis. Evidence for a distinct PsA variant was found at the known psoriasis susceptibility locus, IL23R, and a PsA-specific association at chromosome 5q31 was identified. This highlights the important differences in susceptibility to PsA and psoriasis **(Bowes et al., 2015).**

Association studies have identified additional risk alleles in patients with psoriasis and in those with psoriatic arthritis, including interleukin-12A (*IL12A*), interleukin-12B (*IL12B*), *IL23R*, and genes that regulate NF-κB (**Harden et al., 2015) (Stuart et al., 2015) (Ritchlin et al., 2017).**

In PsA, the cytokine Macrophage migration Inhibitor Factor (MIF) is distinguished functionally by its ability to counter-regulate glucocorticoid immunosuppression and sustain pro-inflammatory activation by inhibiting activation-induced apoptosis. MIF further co-stimulates T and B lymphocytes and upregulates the production of interleukin-6, interferon y and Tumor Necrosis Factor alpha (TNF α). Two polymorphisms identified in the promoter region of MIF gene: a) the short tandem repeat (STR) -794 CATT58 MIF (rs5844572) which is a microsatellite repetition of Cytosine-Adenine-Thymine-Thymine (CATT) at position -794 bp, in which the repeat

length (5 to 8 repetitions) correlates with increased gene expression and with serum MIF circulation levels and b) the another polymorphism is a single nucleotide polymorphism (SNP) 173 G>C MIF (rs755622) at position -173 of the MIF gene in which there is a change from Guanine (G) by Cytosine (C). The -173*C allele is associated with susceptibility PsA **(Zambrano et al., 2014).**

Pathophysiology:

- **Immune Response:**

It has been shown consistently that T cells are important in psoriasis and psoriatic arthritis. A central role for CD8+ T cells in disease pathogenesis is supported by the association with HLA class I alleles, oligoclonal CD8+ T-cell expansion, and the association of psoriatic arthritis with human immunodeficiency virus disease **(Fitzgerald et al., 2014).**

Type 17 cells, which include CD4+ type 17 helper T (Th17) cells, and type 3 innate lymphocytes (cells that produce interleukin-17A and interleukin- 22), in addition to CD4+CD8+ lymphocytes, are increased in psoriatic synovial fluid as compared with rheumatoid synovial fluid **(Leijten et al., 2015).** Chemokines could be important in

the pathogenesis of PsA. Recruitment of T-cells into the synovium may be mediated by chemokines, such as CCL2, CXCL13, CCL21, and CCL22. CCL22 (macrophage-derived chemokine) and its ligand CCR4 play an important role in attracting skin- specific memory T-cells to the synovial tissues. T-cell- derived cytokines such as IL-1ß, IL-2, IL-10, interferon-y (IFN-Y), and TNF- α are dominantly detected in the synovium. Dendritic cells both myeloid DCs and plasmacytoid DCs were present in the synovial fluids of PsA. IFN- α enhances the activation of CD8+ T-cells by antigen-presenting cells. In addition, IFN-α amplifies cutaneous inflammation via the induction of chemokines such as CXCL9, CXCL10, and CXCL11, which recruit their receptor CXCR3 expressing lymphocytes, including CD8+ T-cells. Also, plasmacytoid DCs isolated fronm synovial fluids express CXCR3 and CXCR4, the receptors for CXCL10 and CXCL11, and for CXCL12, respectively **(Yamamoto et al., 2013), (Leijten et al., 2015).**

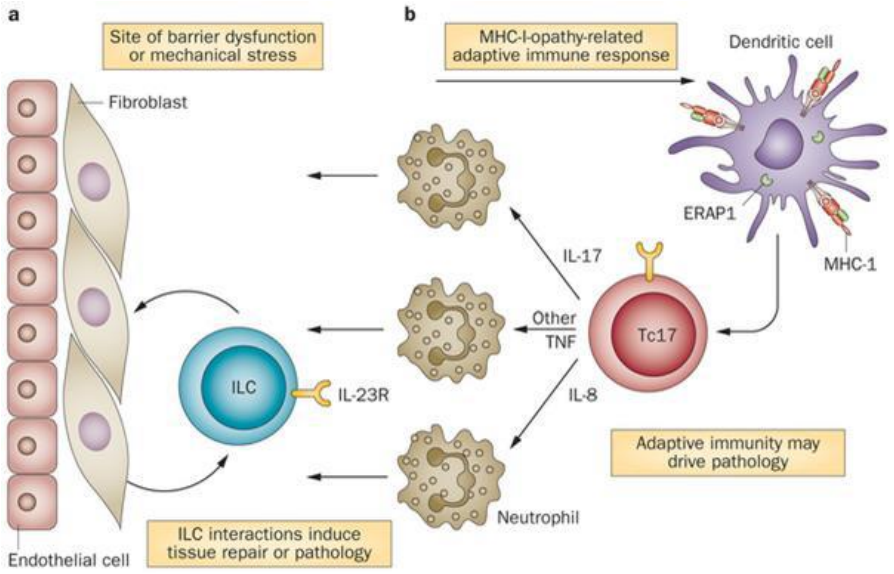

Figure (1): Neutrophil infiltration is a feature of the acute phases of all MHC-I-opathies, including in animal models of HLA-B27-related disease (Dennis et al., 2015)

Figure (1) shows **a** Physiological level of mechanical stress or barrier breakdown might induce tissue-specific dysfunction and interactions with various innate immune cells that result in tissue repair. **b** | These local interactions might also lead to MHC-1-related peptide presentation in the context of ERAP-1, culminating in the activation of CD8+ T-cell adaptive immune responses that drive neutrophil responses in the target tissues. Recruitment of Tc17 cells and their release of IL-17 and IL-8 rapidly lead to amplification of innate immunity by neutrophil recruitment and maturation. Thus, the adaptive immune response in MHC-I-opathies leads to prominent

neutrophil-mediated secondary amplification of innate immunity in the target tissues. **(Dennis et al., 2015)**

In PsA, expression of interferon-α by plasmacytoid dendritic cells activates dermal dendritic cells that trigger the differentiation of type 1 helper T (Th1) cells and Th17 cells in draining lymph nodes. These lymphocytes return to the dermis and orchestrate a complex immune mediated inflammatory response (as shown in fig 1) **(Lowes et al., 2014).** The importance of the interleukin-23–interleukin-17 and TNF pathways in the pathogenesis of psoriasis, psoriatic arthritis, and axial spondyloarthropathies has been proposed in several studies **(Leijten et al., 2014), (Ritchlin et al., 2017).**

TNF- α enhances endothelial cells to express adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin. Angiopoietin-1 receptor Tie-2 are involved in angiogenic processes. Angiopoietin-2 is an effector downstream molecule of vascular endothelial growth factor (VEGF) signaling pathway and promotes adhesion by sensitizing endothelial cells to TNF-a. IL-23-IL-17 stimulate endothelial cell migration and cord formation. Mast cell degranulation in human induces expression of E-selectin on vascular endothelial cells and

contribute to the synovial hyperplasia and angiogenesis **as shown in figure (2) (Yamamoto, 2013), (Jayaraman et al., 2017).**

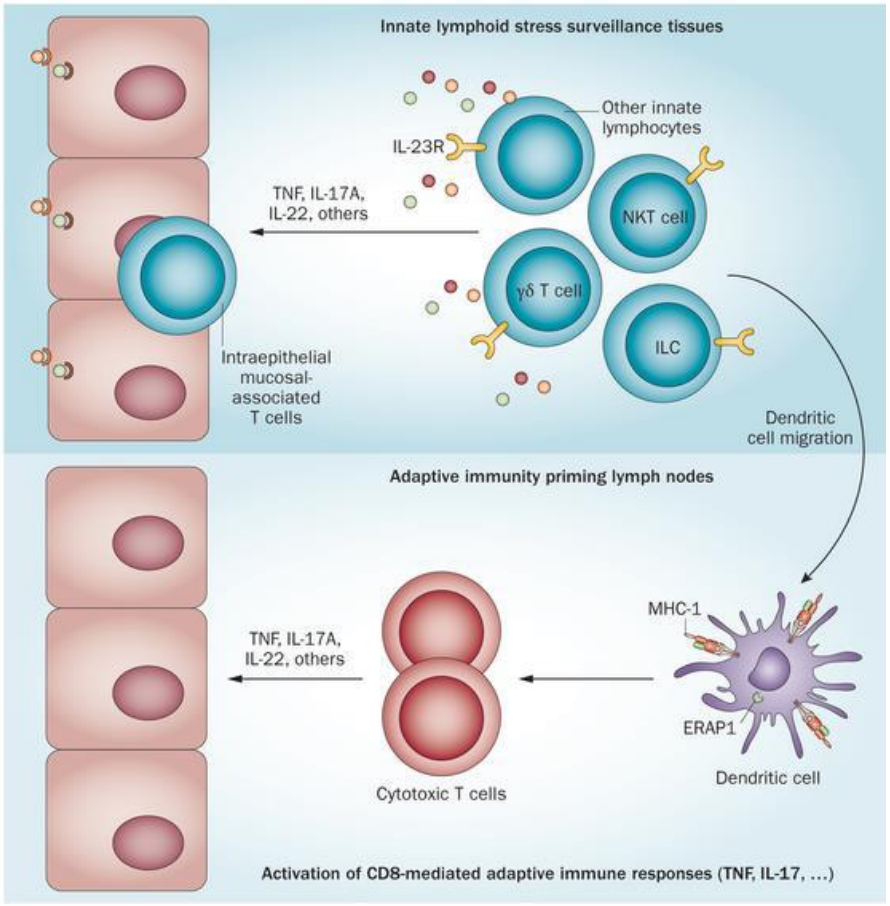

Figure (2): The IL-23–IL-17 axis is linked to the lymphoid stress surveillance response.

Figure (2) shows IL-23R-expressing unconventional lymphocytes—including ILCs, NKT cells, γδ T cells and mucosa-associated invariant T cells— participate in homeostatic tissue repair at mucosal surfaces. This