INTRODUCTION

Psoriasis is a common chronic, inflammatory immune mediated skin disease affecting about 2% of the population ***(Elnady et al., 2019).***

Plaque-type psoriasis, the most common disease variant, which is seen in _85% of cases, commonly manifests as dull-red, erythematous, scaly plaques particularly on the extensor surfaces of elbows, knees, and on the scalp. Less common psoriasis subtypes include pustular, guttate, inverse, erythrodermic, and palmoplantar psoriasis ***(Hawkes et al., 2017).***

Psoriatic arthritis occurs in up to one-third of patients with psoriasis and is categorized under seronegative spondyloarthropathies (SPA) ***(Moshrif et al., 2017).***

Enthesitis is the term used to describe inflammation at tendon, ligament, or joint capsule insertions to bone. The term ‘enthesopathy’, however, has a wider meaning and designates all pathological abnormalities of insertions including inflammatory metabolic, and degenerative changes ***(Mata et al., 2014).***

The assessment of enthesitis has been performed for a long time through clinical examination and conventional radiography. Recently, new imaging modalities such as magnetic resonance imaging (MRI), Positron emission

tomography (PET) and ultrasound (US) have been developed, offering a direct visualization of the enthesis and enthesal-related structures ***(Balint et al., 2012).***

Positron emission tomography (PET) is sensitive, noninvasive imaging of inflammatory arthritis (IA) of the whole body, but because of costs and radiation burden, it`s difficult to be done for all patients ***(Bruijnen et al., 2014).***

SO, ultrasonography (US) has become an important objective, inexpensive, available, easy to perform imaging tool which used in the evaluation of synovitis, tenosynovitis, enthesitis, and nail fold abnormalities in patients with psoriasis ***(Zabotti et al., 2017).***

US has emerged as the preferred modality to assess enthesitis because of its higher sensitivity and specificity in evaluating a number of entheseal locations in a short period of time compared with clinical examination and other imaging modalities ***(Zabotti et al., 2017).***

AIM OF THE WORK

This study is designed to compare Sonographic Madrid score index (MASEI) versus spondyloarthritis research consortium of Canada (SPARCC) for early detection and assessment of enthesopathy among psoriatic skin patients to prevent joint damage.

Chapter 1

PSORIASIS

Definition:

Psoriasis is a phenotypically heterogenous immune mediated skin disease that often follows a relapsing and remitting course. It is characterized by well-demarcated, scaly, erythematous lesions that often detected at sites of trauma (extensor surfaces of elbows and knees), however it may involve any part of the body ***(Mahil et al., 2016).***

Psoriasis causes great physical, emotional and social burden. Quality of life (QOL), in general, is often significantly impaired. Disfiguration, disability and marked loss of productivity are common challenges for people with psoriasis ***(Moradi et al., 2015).***

Epidemiology:

Psoriasis is documented to affect 1-3 % of the world's population. This estimate, built up on population based studies that based on geographic/ethnic groups. The prevalence of psoriasis is actually variable and has been documented to range from 0.05 to 3.7 % depending on ethnicity and geographic location with most research suggesting a higher rate of psoriasis in white compared to other ethnic groups ***(Kaufman and Alexis, 2018).***

Psoriatic arthritis (PsA) develops in at least 5% of patients with psoriasis, and it occurs in up to 1% of the general population ***(Henes et al., 2014).***

Risk Factors:

Environmental factors induce inflammatory activity in people having genetic susceptibility. Many alterations could be triggered by environmental risk factors such as diet, microbial infections (from bacteria, fungus and virus), chemical irritants or ultraviolet (UV) radiation exposure and bad habits (such as smoking and drinking alcohol) ***(Zeng et al., 2017).***

Pathogenesis of psoriasis and psoriatic arthritis:

Psoriasis is currently viewed as a systemic chronic inflammatory disease with an immunogenetic basis that can be triggered extrinsically or intrinsically ***(Schäkel et al., 2016).***

Early observations that characteristic skin lesions contained increased numbers of inflammatory cellular infiltrates largely composed of cluster of differentiation 41 (CD41) and cluster of differentiation 81(CD81) T cells ***(Hawkes et al., 2017)***.

The mounting evidence for the pathogenic role of T lymphocytes in patients with psoriasis in familial clusters led many to conclude that psoriasis was an autoimmune condition with a strong genetic basis ***(Hawkes et al., 2017)***.

The cytokine profile of auto-reactive T cells CD41 or CD81 T cells against LL-37/ cathelicidin, a cationic antimicrobial peptide (AMP) produced by keratinocytes and other immune cells (eg, neutrophils) in response to bacterial/viral infections or skin trauma) revealed increased levels of skin-homing receptors (eg, cutaneous lymphocyte antigen, Chemokine receptor 6(CCR6) and Chemokine receptor 10 (CCR10) and a strong interferon gamma (IFN-g) and interleukin IL-17 (IL17) phenotype consistent with examining the T-cell found in psoriatic skin (***Hawkes et al., 2017)***.

The LL-37 expression is up regulated in psoriatic plaques results in direct activation of plasmacytoid dendritic cells (pDCs) and myeloid dendritic cells (mDCs) by forming a complex with nucleic acids (DNA and RNA) released after skin trauma ***(Hawkes et al., 2017).***

Phospholipase A2 group IVD (PLA2G4D) is a novel protein found to be up-regulated in psoriatic plaques ***(Quaranta et al., 2014).***

Its expression is increased in psoriatic keratinocytes and mast cells and results in the generation of non peptide neolipid antigens presented on CD1a-expressing DCs for recognition (***Cheung et al., 2016).***

The murine T heper 17 (TH17) subset was characterized by its production of IL-17 and interlukin 22 (IL-22) by CD41 T cells. most IL-22 is synthesized by a distinct TH22 T-cell subset in human subjects.

A number of cell types found in the skin produce IL-17, including CD41 T cells (TH17), CD81 T cells (TC17), innate lymphoid cells, Gamma and delta (γδ) T cells ***(Kim et al., 2015).***

The cytokine signals create a ‘‘feed forward’’ inflammatory response in keratinocytes by activating CCAAT enhancer–binding protein (C/EBP) b or d, signal transducer and activator of transcription (STAT) 1, and nuclear factor kB, which lead to the up regulation of a number of keratinocyte-derived inflammatory products This inducing epidermal hyperplasia, regulating epidermal cell proliferation, and recruiting leukocyte subsets into the skin ***(Wang CQ et al., 2013)*** as shown in (Figure 1)**.**

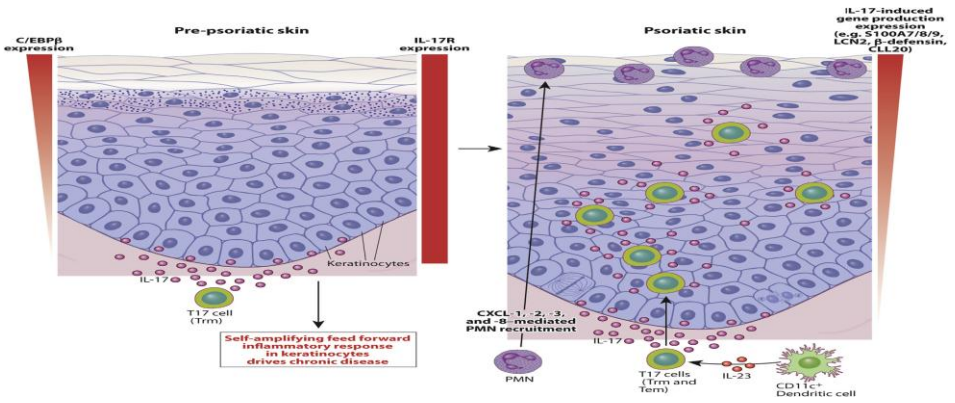

Fig. (1): IL-17–driven initiation of feed forward inflammation in keratinocytes and induction of psoriatic plaques ***(Hawkes et al., 2017)***

Recently, the idea of a shared pathogenesis between PsA and psoriasis has led to the concept of psoriatic disease. PsA and psoriasis share common genetic factors and environmental triggers and show striking similarities in immunopathology ***(Cafaro and Mclnnes, 2018).***

T lymphocytes expressing Cluster of differentiation4 (CD4) are the most abundant inflammatory cells in the tissues, with a 2: 1 ratio of CD4 to Cluster of differentiation 8 (CD8) T cells. B lymphocytes were also found in the skin and joints, occasionally forming primitive germinal centers. It has been suggested that CD8+T cells populate the developing skin lesion first, while also being the predominant T cell in the synovial fluid of PsA patients, suggesting these cells may be primary drivers of this immune response ***(El Miedany et al., 2012).***

The most striking feature in PsA is the abundant over expression of pro-inflammatory cytokines, especially tumor necrotic factor alpha (TNF α), interlukin 1β (IL−1β), interlukin (IL−6), and interlukin 13 (IL−13) ***(Cafaro and Mclnnes, 2018).***

Th17 derived cytokines, in particular the IL−23/IL−17 axis, can be hypothesized to play a role in the pathogenesis of PsA, drawing evidence from studies in mice ***(Dennis et al., 2015)*** as show in Figure (2).

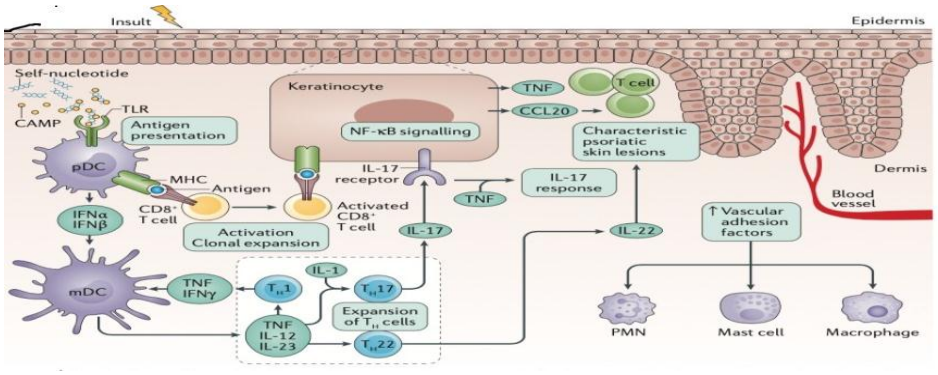

Fig. (2): Pathogenesis of psoriasis and psoriatic arthritis ***(Greb et al., 2016).***

Interfering with IL-17A or interleukin 23 (IL-23) are the most efficient treatment modalities against psoriasis ***(Girolomoni et al., 2017).***

Indeed, the IL-23/IL-17 axis seems to be particularly well-suited to exemplify the intricate cross talk between adaptive and innate immunity in psoriasis. Healthy human skin contains only a few IL-17-producing T cells, a population of CD4+ T cells distinct from the "classical" Th1 and Th2 cells ***(Poot et al., 2013)*** as show in Figure (3).

IL-17A is not only secreted by CD4+ Th17 cells, but also by CD8+ T cells and certain cells of the innate immune system including neutrophilic granulocytes ***(Dyring-Andersen et al., 2017).***

The presentation of IL-17 by neutrophil extracellular traps (NETs), which are generated upon activation of neutrophils in a clearly defined manner ***(Neubert et al., 2018).***

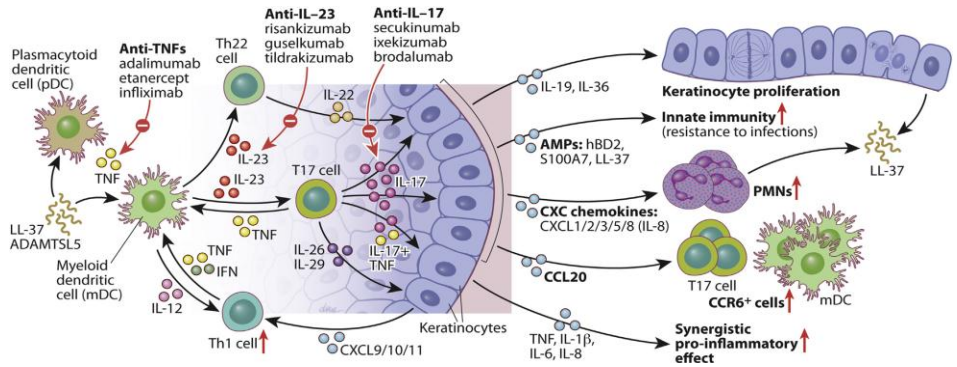

Fig. (3): IL-23/T17–mediated effects on epidermal keratinocytes (KCs) in psoriatic skin ***(Hawkes et al., 2017).***

Classifications and Clinical Types of Psoriasis:

Psoriasis is diverse skin disease, In psoriasis people have only one type of Psoriasis at a time, but sometimes two or more different types of Psoriasis can occur simultaneously.

There are five types of Psoriasis: *(Jadhav, 2017).*

1) Plaque: most common type of the disease. Plaque psoriasis is characterized by erythematous skin covered with silvery scales and inflammation.
2) Guttate: appears as small red dots on the skin.
3) Inverse: Occurs in armpits, groin, under the breasts, and in other skin folds around the genitals and the buttocks.
4) Pustular: White blisters surrounded by erythematous skin often found in adult patients. Pustular psoriasis is characterized by white pustules.
5) Erythrodermic Psoriasis: affects high percent of the body surface. It is characterized by periodic, widespread, redness of the skin. The erythema and exfoliation of the skin are often associated with severe itching and pain as show in Figure (4).

Fig. (4): Clinical types of psoriasis ***(Rendon and Schakel, 2019).***

Nail affection:

Nail involvement in psoriasis is one of clinical features of psoriasis.it is a typical, disfiguring picture of local changes and is accompanied by pain and functional disorders. Moreover, affection of nails is one of the known risk factors for the development of PsA ***(Krajewska-Włodarczyk et al., 2019).***

Nail pathology involve nail bed, nail matrix, or folds and may be classified according to their origin: pitting, leukonychia, nail plate thickening, crumbling, and red spots in the lunula occur in the matrix, whereas oil drop discoloration (salmon spots), nail bed hyperkeratosis, onycholysis, and splinter hemorrhages result from the nail bed ***(Galluzzo et al., 2019)*** as in Figure (5).

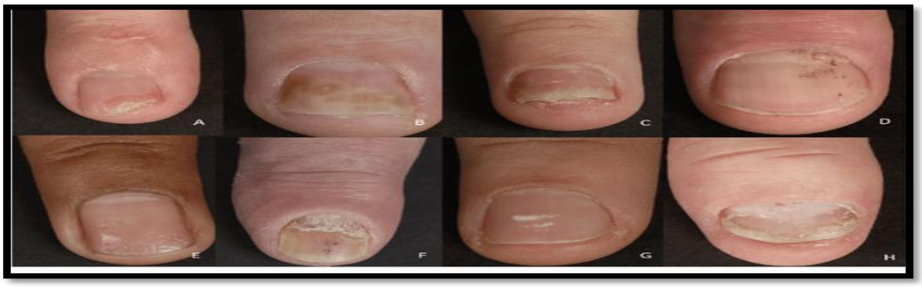

Fig. (5): Nail manifestations seen in nail psoriasis. *Nail bed features* ***(a)***oil-drop discoloration, ***(b***)onycholysis, ***(c***) subungual hyperkeratosis, ***(d)*** splinter hemorrhages. *Nail matrix features* ***(e)*** pitting of the nail plate, (***f***)crumbling in proximal quadrants of the nail plate,(***g***)leukonychia,***(h)*** *red spot* in the lunula ***(Pasch,2016).***

Co-morbidities Associated with Psoriasis:

Psoriatic Arthritis:

Psoriatic arthritis (PsA) is a heterogeneous, usually seronegative, chronic inflammatory spondyloarthritis associated with psoriasis. A combination of genetic predisposition and

environmental factors has been proposed as a possible pathogenesis for psoriatic arthritis ***(Yamamoto et al., 2016).***

The peak incidence of PsA occurs between ages 30 and 50 years. Clinically PsA is characterized by joint pain, swelling as well as stiffness, surrounding soft tissue pain mainly in the form of ligament and tendon inflammation (enthesitis and dactylitis), spinal pain and limited range of motion as well as nail changes. The association between synovitis and enthesitis of tendons and ligaments of a single finger/toe is called dactylitis or "sausage digit", and it is identified in 30% of PsA patients. In about 75% of the cases, skin affection precedes arthritis, whereas it occurs concomitantly in 10%. In the other 15%, arthritis may precede the skin lesion.

In 2006, the classification criteria of psoriatic arthritis (CASPAR) study group set up a highly sensitive (91–100%) and specific (97–99%) set of criteria that allow for the diagnosis of PsA even in cases of PsA sine psoriasis and in patients with positive rheumatoid factor ***(Hahn et al., 2019)***.

There are five distinct patterns in psoriatic arthritis as show in Figure (6).

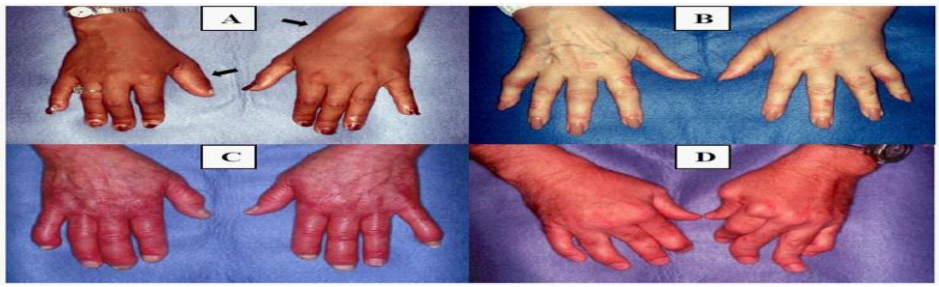

Fig. (6): Shows Clinical patterns of peripheral PsA, (A) Asymmetric oligoarthritis, (B) Symmetric polyarthritis, (C) Predominant DIP joint involvement, (D)Destructive(mutilans) arthritis ***(Poggenborg et al., 2015).***

Autoimmune diseases

There is a higher frequency of autoimmune diseases among psoriasis patients than recorded in the general population potentially evolving from cytokine pathways "dysregulation". Recently it is associated with rheumatoid arthritis, SLE, atopic dermatitis, sjogren syndrome and vitilligo ***(Ayala-Fontánez et al., 2016).***

Cardiovascular disease

Chronic inflammatory diseases, such as psoriasis, are considered as a risk factor for accelerated atherosclerosis and increased risk of cardiovascular events. Atherosclerosis is increasingly recognized as an inflammatory process, thus similarities between atherosclerosis and chronic systemic inflammatory diseases ***(Sajja et al., 2018)***.

Metabolic syndrome

Metabolic syndrome, also known as syndrome X or dysmetabolic syndrome, refers to a group of metabolic conditions that can lead to heart disease. The main characteristics of metabolic syndrome include insulin resistance, hypertension, dyslipidemia and an increased risk for clotting.

The higher prevalence of metabolic syndrome in patients with psoriasis reported by most studies justify the need for early detection of metabolic disorders and adequate early management of psoriasis ***(Milčić et al., 2017).***

Psychiatric and Psychologic Co-morbidities:

Patients with psoriasis may have a high prevalence of several mental disorders. Psoriasis has stronger relationship with psychiatric illnesses than other skin diseases ***(Ferreira et al., 2016)***.

Patients with more severe psoriasis were more likely prone to suicidal attempts. substantially impaired quality of life, and higher depression rates, all of which can contribute to greater suicidal attempts ***(Singh et al., 2017)***.

Hepatic disease:

The hormone resistin and the cytokines TNF-alpha, IL-6, and IL-1–beta are associated with insulin resistance, fatty liver, and psoriasis, but their pathophysiologic mechanism of action is unclear ***(Roberts et al., 2015).***

Other co-morbidities are also found in patients with psoriasis, including chronic obstructive pulmonary disease (COPD), renal disease, and obstructive sleep apnea (OSA). the prevalence of renal disease increases with psoriasis severity ***(Yeung et al., 2013).***

Lifestyle choices:

Such as tobacco and alcohol use can exacerbate psoriasis. The theory behind the smoking-psoriasis link is that nicotine and dioxin activate T cells that produce cytokines IL-12, IL-17, and IL-22 ***(Lee et al., 2017)*** as show in Figure (7).

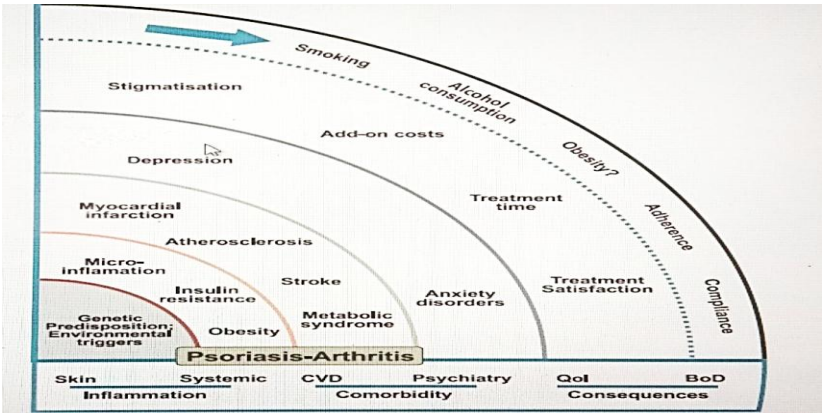

Fig. (7): Burden of disease; CVD, cardiovascular disease; QoL, quality of life ***(Mrowietz et al., 2014).***

Chapter 2

ENTHESIS

The term enthesis comes from an ancient Greek word and stands for insertion. In medical terminology, enthesis describes the insertion of tendons and ligaments into the bone surface. Entheses are essential structures for the transduction of mechanical forces from muscles to bones and hence are the basis for locomotion ***(Schett et al., 2017).***

Types of enthesis:

Histologically, enthesis can be classified in two types: fibrous and fibrocartilaginous. Most of entheses are fibrocartilaginous, characterized by the presence of a small plug of fibrocartilage at the attachment site itself. They are classified by the Achilles tendon and by the tendon of the supraspinatus muscle, and also include those of the digital collateral ligaments and many others ***(Watadet al., 2017).***

The fibrous enthesis are characterized by pure dense fibrous connective tissue that links the tendon or ligament to the bone and are typically anchored a long way from the joint with the most notable example being the deltoid tendon insertion. Virtually all of the inflammation in the SpA group of diseases affects the fibrocartilaginous structuresand not the fibrous ones ***(Watad et al., 2017).***

Enthesitis is characterised by pain and stiffness at tendon insertions, such as the Achilles tendon, the plantar fascia or the common extensor tendon insertion at the epicondyle of the elbow. Clinical assessment of enthesitis has been based