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Department of Clinical Laboratories

Study the serum levels of Interleukin 17 & 23 and Toll-Like Receptors 4, 7 in psoriasis patients

A thesis

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صدق اللَّهُ العلي العظيم

(سورة الزمر، آية : ٩)

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31 / 12 / 2023

DEDICATION

I dedicate this work to .....

-The reason of my presence in this life ... my father and mother who supported me though my journey……

-To my wife and children ... the best thing that happened in my life

Abdullah

2023

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We certify that the thesis entitled (Study the serum levels of Interleukin 17 & 23 and Toll-Like Receptors 4, 7 in psoriasis patients) partial fulfills requirement of the degree of Master in Clinical laboratories.

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Summary

Psoriasis is an autoimmune disease that affects the skin and has a complicated hereditary and immunological basis. Psoriasis treatment may be improved with a better understanding of the involvement of immunological markers and socio-demographic factors. The purpose of this study is to examine the relationship between immunological markers (IL-17, IL-23, TLR-4, and TLR-7) and several socio-demographic parameters, including age, sex, disease severity, and BMI classification in patients with psoriasis.

The current study was conducted on psoriasis patients at the Imam Al-Hussein City Hospital in Karbala Province, Iraq, from December 2022 to April 2023. The blood samples of participants were healthy individuals and newly diagnosed, untreated psoriasis patients. Pregnant women, those with chronic conditions, and those receiving psoriasis medication were excluded. A case-control observational study is conducted using convenience sampling to select participants. The PASI scoring method was used to evaluate four body areas, and the sandwich ELISA method is used for immunomarker analysis.

The study finds that psoriasis patients (50 (56%)) were more prevalence than the control (40 (44%)), with no significant difference in age or gender. Females (26 (56%) outnumbered male 14 (35%)) in both groups. There is a significant difference in body mass index (BMI) between healthy control and psoriasis patients, but the average BMI was statistically different. Most patients reported moderate symptoms, with the remainder experiencing severe symptoms. Age differences are not significant, but severe psoriasis patients are older in certain age groups. Immunological markers (IL-17, IL-23 TLR-4, TLR-7,) were found to be higher in psoriasis patients than healthy controls, suggesting a possible involvement in the disease's origin.

The study explored various aspects of psoriasis, revealing a higher prevalence among patients compared to controls, with no significant differences in age, gender, or BMI. Notably, no significant distinction was found in the severity of psoriasis symptoms between moderate and severe cases. Immunomarkers (IL-17, IL-23, TLR-4, TLR-7) emerged as potential disease indicators, suggesting a crucial role in modulating psoriasis impact on socio-demographic factors. Psoriasis patients exhibited elevated immunological marker levels in severe cases, followed by moderate cases, compared to healthy individuals.

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List of Abbreviations

Code	Words
ADAMTSL5	thrombospondin type-1 motif-like 5
BMI	Body Mass Index
CD4 + Tcell	Cluster Differentiation 4 + T Cell
CD8 + Tcell	Cluster Differentiation 4 + T Cell
CRP	C-Reactive Protein
DC	Dendritic Cells
ECs	Endothelial Cells
EDTA	Ethylenediamine Tetraacetic Acid
PLA2G4D	Phospholipase A2 Group IV D
HNRNPA	Heterogeneous Nuclear Ribonucleoproteins Proteins
ICAM-1	Intercellular Adhesion Molecule-1
ICU	Intensive Care Unit
IFN- α	Interferon - Alpha
IFN- β	Interferon – Beta
IFN- γ	Interferon - Gamma
IFNAR	Infection – Induced Type 1 Interferon Receptor
IL	Interleukin
ILCs	Innate lymphoid cells
KC	Keratinocytes
mDC	Myfeoid Dendrites
PAMPs	Pathogen Associated Molecular Pattern Molecules
PDC	plasmacytoid dendritic cells
PLA2G4D	phospholipase A2 group IV D

PLTs	Platelets
PsA	Psoriatic arthritis
RBD	Receptor – Binding Domain
RNA	Ribonucleic Acid
SARS-CoV-2	Severe Acute Respiratory Syndrome Corona Virus -2
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
TLR	Toll Like Receptor
TNF	Tumor Necrosis Factor
UV	Ultraviolet

Chapter One
Introduction

Chapter One

Introduction

1.1 Introduction

Psoriasis is a chronic inflammatory skin disorder that affects a relatively high proportion of the global population (estimates range from 2% to 3%) (Lowes *et al*., 2007). Psoriasis has been studied extensively, but its specific etiology is still unclear. However, It is thought that it is a complex autoimmune inflammatory illness with hereditary underpinnings. Psoriasis, like inflammatory bowel disease, rheumatoid arthritis, and multiple sclerosis, is an autoimmune inflammatory disease that has shared immunological and genetic features with these other disorders. Particularly, Th17 cells, a subset of CD4+ T-helper (Th) cells, have been shown to play a pivotal role in the onset and progression of various disorders (Kanda, 2021; Rendon & Schäkel, 2019).

In the past, the main focus was on interferon (IFN-γ) producing Th1 cells as the primary immunological drivers of psoriasis. But, new study has shown that Th17 cells play a crucial role in developing psoriasis and similar disorders. Psoriasis and related illnesses have been renamed "Th17 diseases" by certain specialists who have realized that Th17 cells, not Th1 cells, play a crucial role in developing the condition (Blauvelt, 2007).

Psoriasis is a skin condition characterized by erythematous plaques coated with white-silver scales, most often on the extensor surfaces of the body (e.g., elbow, knee, lumbosacral areas, scalp). Psoriasis comes in many different manifestations, the most common of which is plaque psoriasis (psoriasis vulgaris), but others include flexural or inverse psoriasis, guttate psoriasis, pustular psoriasis, erythrodermic psoriasis, and psoriatic arthritis. Nearly 90% of all instances of psoriasis are caused by plaque psoriasis. The condition affects both sexes equally, with an incidence of 1%-3% depending on the community. There is

an increased chance of psoriasis among first-degree relatives of those with the condition. Although its precise cause is unknown, genetic, environmental, and autoimmune variables are all thought to have a role in the development of psoriasis (Krueger *et al*., 2012; J. Li *et al*., 2007).

Psoriasis pathogenesis is widely believed to entail an unbalanced cytokine profile, with IL-17 playing a pivotal role. Biological treatments targeting the IL-17 pathway have demonstrated encouraging results in treating psoriasis (Hassoon *et al*., 2014).

Clinical investigations examining the therapeutic effectiveness of drugs targeting T cells have further reinforced the significance of T cells in psoriasis (Abrams *et al*., 2000). High mRNA and protein levels of interferon-gamma (IFN-γ), tumor necrosis factor (TNF-α), and interleukin-12 (IL-12) have been found in studies defining the cellular and cytokine components implicated in the onset and maintenance of psoriasis. Based on these findings, psoriasis was reclassified as a disease of the T helper (Th) 1 subset (Lew *et al*., 2004). Critical in initiating autoimmunity, IL-23 has been related to Th17 cell growth and survival (Kastelein *et al*., 2007). Psoriatic patients' cutaneous lesions and blood samples have been shown to include elevated amounts of IL-23 and Th17-associated cytokines. Evidence for the functional relevance of Th17 cells in autoimmunity and the correlation of IL23R gene polymorphisms with psoriasis has led to a rise in curiosity about the IL-23/Th17 axis in this autoimmune disease (Blauvelt, 2008)

The IL-23/IL-17 pathway is the primary focus of current psoriasis categorization because of its prominent role in the disease's immunobiology. Auto-inflammatory and pro-proliferative circuits are formed as a consequence of the interaction of several cell types, such as dendritic cells (DCs), T cells, keratinocytes (KCs), neutrophils (neutrophils), mast cells (mast cells), innate lymphoid cells (ILCs), fibroblasts, and endothelial cells (Anand *et al*., 2017; Gottlieb *et al*., 2000).

Upstream cytokines mediate these circuits, including IFN-α, IFN-β, and TNF-α, as well as synergistic cytokines like IL-22 and TNF-α. Feed-forward loops that maintain and amplify the inflammatory response are generated by downstream mediators such as IL-8, IL-1F9, and CCL20 (Gottlieb *et al*., 2000).

The production of crucial cytokines like IFN-α, IL-17, and IFN- βis linked to the early activation of plasmacytoid dendritic cells (pDCs) and autoreactive T cells in the autoimmune hypothesis for psoriatic disease. This activation is triggered by various auto-antigens, which cause a molecular mimicry of an inflammatory response. Auto-antigens include proteins such type-I Ks (K16 and K17), ezrin, maspin, peroxiredoxin 2, heat shock protein 27, LL-37, thrombospondin type-1 motif-like 5 (ADAMTSL5), phospholipase A2 group IV D (PLA2G4D) lipid neoantigens, and HNRNPA1 (Ben Abdallah *et al*., 2021).

Various chemicals activate the innate immune cells, namely plasmacytoid dendritic cells (pDCs) expressing Toll-like receptors (TLR) 7/9 and myeloid dendritic cells (mDCs) expressing TLR3/8. Complexes of self-nucleic acids (DNA and RNA from damaged cells) and antimicrobial peptides (AMPs) like LL-37, DEFB4, hBD3, lysozyme 9, and IL-26 are effective against a wide variety of bacteria and other microbes (a Th17-derived cytokine). Thymic stromal lymphopoietin (TSLP), generated by keratinocytes (KCs), and chemerin, produced by fibroblasts, mast cells, and endothelial cells, also contribute to the activation process (Arakawa *et al*., 2015; Ben Abdallah *et al*., 2021).

After being stimulated, these immune cells differentiate into the more inflammatory cutaneous dendritic cells and secrete inflammatory cytokines such interferon-gamma (IFN-γ; via pDCs), interleukin-23 (IL-23), tumor necrosis factor (TNF), nitric oxide (NO), and interleukin-20 (IL-20) (by mDCs). These cytokines indicate the beginning of psoriatic disease progression by setting off a chain reaction of pathogenic inflammation. The characteristic pathologic cell underpinning psoriatic pathophysiology is the IL-17+ T-cell phenotype (Th17, Tγ17), promoted by interactions between IL-23-producing dendritic cells and T

cells in the dermis. Dendritic cells that produce IL-23 also stimulate T cells, ILC3, mast cells, macrophages, dendritic cells, and neutrophils, all of which produce IL-17 (Morizane & Gallo, 2012).

1.2 Aim of the Study

The role of Toll like receptors TLR4 and TLR7 that induce IL17 & IL23 with severity of psoriasis disease.

1.3 Objective of the study

1. Collect blood from patients and control.
2. Determine the groups of the study.
3. Evaluation of cytokine of TLR concentration.

Chapter Two
Literature Review

Chapter Two
Literature Review

2.1 Introduction to psoriasis

Psoriasis is a skin condition characterized by persistent inflammation that affects up to 2.5% of the global population. Red, raised, scaly plaques are a hallmark of this condition caused by epidermal hyperproliferation and inflammation. A rising collection of clinical and experimental data suggests that T lymphocytes play a significant role in the development of psoriasis (Christophers, 2001; Rendon & Schäkel, 2019).

Conditions affecting the skin are distinguished from those affecting the internal organs because the skin is the organ with the most direct contact with the outside environment. Many skin illnesses are easily detectable by others, because of the historical stigma attached to these sorts of ailments, those who suffer from them have to deal with both their sickness and the unfavorable response of others. However, in contrast to other illnesses, skin is easily accessible for tissue biopsy, which allows for a more in-depth investigation of the cellular and molecular drivers of cutaneous diseases and the subsequent development of successful targeted therapeutics (Ahlehoff *et al*., 2011; Ainali *et al*., 2012).

The chronic inflammatory skin illness psoriasis is one ailment whose historical and more recent history parallels both situations described above. Since ancient times, several biblical allusions to “leprosy” more likely describe psoriasis; accordingly, people living with psoriasis have been thrown away from society in biblical and medieval periods due to fear, ignorance, and prejudice. Recognized as a unique entity by Robert Willan in the early 19th century and named by Ferdinand Hebra in 1841, psoriasis’ influence on quality of life is still far-reaching and profound in current times, especially in the absence of stigmatization. On the other hand, it is one of the most frequent skin ailments. Clinicians and fundamental

scientists alike have used psoriasis as a model to investigate chronic inflammation (Raharja *et al*., 2021).

For example, extensive and tiny plaque psoriasis represent opposite ends of the same illness's dynamic, anatomical, or qualitative spectrum. In other circumstances, the name psoriasis (from the Greek psora to itch) most likely relates to a very different entity (e.g., generalized pustular psoriasis [GPP]) (Kimmel & Lebwohl, 2018).

For example, extensive and tiny plaque psoriasis represent opposite ends of the same illness's dynamic, anatomical, or qualitative spectrum. In other circumstances, the name psoriasis (from the Greek psora to itch) most likely relates to a very different entity (e.g., generalized pustular psoriasis [GPP]) (Kimmel & Lebwohl, 2018).

2.2 Epidemiology of Psoriasis

The prevalence of psoriasis varies from 2% to 4% of the population in Western nations, depending on factors such as age, region, and genetics (Chandran & Raychaudhuri, 2010). Psoriasis is a prevalent condition, as shown by recent studies of psoriasis epidemiology, which included data from 46 studies reporting on psoriasis prevalence and seven studies relating to disease incidence in the general population (Parisi *et al*., 2013, 2020)

Adults have a more considerable prevalence (0.91–8.5%) than children (0–2.1%), and there are two peaks in incidence: ~30–39 years and ~60 years in comparison. In keeping with the favorable effects of UV radiation exposure and clinical amelioration of psoriasis, a geographical trend shows a higher incidence in nations closer to the equator than the more distant ones (Hart *et al*., 2011).

Europe has a prevalence of 0.73 to 2.9%, which is comparable to that of the United States (0.7% to 2.6%), but far greater than that of Latin America (0% to 0.5%), Africa (0% to 0.5%), or Asia (0% to 0.5%). Psoriasis was formerly thought to be a condition that affected both sexes equally, but new information on differences in

prevalence by age within each gender suggests otherwise. Recent evidence regarding age stratification within gender, however, reveals an increased occurrence in girls younger than 18 and a decreased occurrence in men less than 18 years old (Icen *et al*., 2009; Tollefson *et al*., 2010).

2.3 Disease Classification and Clinical and Histological Features

Traditionally, diseases have been categorized based on how they seem to a trained eye, with distinctions made mainly based on where in the body they manifest. This study uses the classification proposed by the International Psoriasis Council, which identifies four primary forms of psoriasis: plaque-type, guttate, GPP, and erythroderma, as well as several further subphenotypes according to distribution (localized vs. widespread), anatomical localization (flexural, scalp, palms/soles/nail), size (large vs. small) and thickness (thick vs. thin (active vs. stable) (C. E. M. Griffiths *et al*., 2007).

2.4 Types of Psoriasis

2.4.1 Plaque-Type Psoriasis

Plaque psoriasis, the most common kind, is characterized by red, raised plaques that are clearly defined and covered in silvery scales (Figure 2.1 A-C). Plaques may appear anywhere on the body and tend to do so symmetrically; however, they most often appear on the extensor surface of the elbows, knees, scalp, and lower back. Depending on whether the lesions are tiny and pinpoint-shaped or large and diffuse, there are two distinct clinical sub-phenotypes (Di Meglio *et al*., 2014; Kanda *et al*., 2020a).

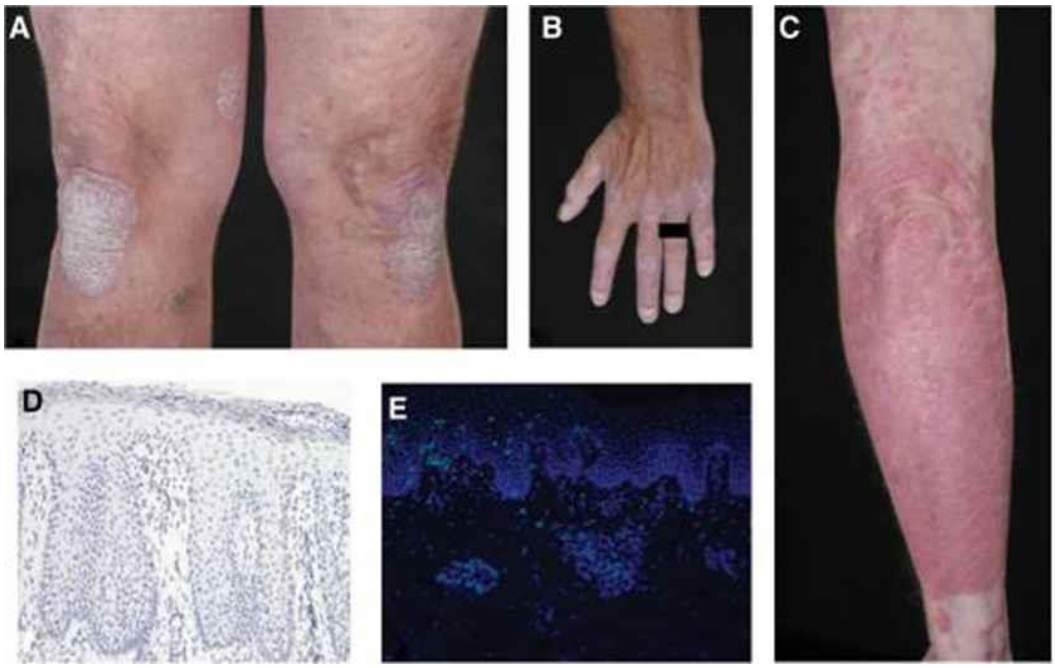

Figure (2.1): Psoriasis's distinctive appearance in the clinic and under the microscope. Chronic plaque psoriasis as seen in the clinic, A through C. Be aware of B's nail involvement—a section of a chronic psoriatic plaque stained with hematoxylin (D). Typical histological findings include acanthosis, papillomatosis, parakeratosis, and Munro abscess in the stratum corneum. (E) Skin-invading CD3+ T lymphocytes are stained green in this persistent psoriatic plaque immunofluorescence staining (Di Meglio *et al*., 2014).

Active lesions, which share most of the histological properties of freshly formed lesions, may steadily expand into an advanced plaque, whereas stable lesions, which preserve the morphology of the advanced stage, do not vary in size or appearance. The papillary dermis, the outermost layer of skin, undergoes the first alterations in developing a new plaque. The blood arteries expand and twist, releasing lymphocytes and neutrophils ("squirting" papilla) that reach the epidermis, which otherwise seems unaffected. However, shortly after this, aberrant keratinocyte (KC) proliferation and migration start, leading to epidermal thickening, incomplete terminal differentiation (with initial loss of the "stratum granulosum"), and the appearance of foci of parakeratosis, or the retention of the nucleus by corneocytes (Theodorakopoulou *et al*., 2012).

Acanthosis (a thickening of the "stratum spinosum") and papillomatosis (an extension of the rete ridges extending downward between dermal papillae) characterize the advanced stage of identified psoriasis hyperplasia. Confluent parakeratosis, the lack of stratum granulosum, the presence of lymphocytes (mostly CD8+ T cells) among the keratinocytes (KCs), and the accumulation of neutrophils inside the parakeratotic scales to create Munro microabscesses are all hallmarks of this condition (Figure 2.1D, E) (Di Meglio *et al*., 2014). When a scale is removed, the affected area bleeds pinpoint-sized amounts because the dilated blood vessels reach up into the papillae. Countless T cells and dendritic cells (DC) have invaded the dermis. Rarely, lesions may heal on their own. Histologically, healed lesions are characterized by orthokeratosis or thickening of the stratum corneum without parakeratosis and restoration of the stratum granulosum and by a unique rim of blanching (Woronoff's ring) (Hu *et al*., 2021; Prinz, 2003).

2.4.2 Guttate Psoriasis

The term "guttate" refers to the tear-shaped plaques that define this kind of psoriasis, which often appear on the torso, upper arms, and thighs. Type I psoriasis is characterized by a rash that appears suddenly, often within two to four weeks following an upper respiratory tract infection, most notably streptococcal pharyngitis in children and young adults. Guttate psoriasis has four possible outcomes: full resolution without treatment, improvement with topical therapy, persistence, and progression to plaque psoriasis (Backel & Cain, 2017; Levine, 2000).

2.4.3 Generalized Pustular Psoriasis

Global plaque psoriasis (GPP), also known as von Zumbush psoriasis, is an uncommon but potentially fatal skin and systemic inflammatory disorder. Prominent aggregation of neutrophils entering the stratum spinosum (spongiform pustules of Kogoj) and resulting in sterile cutaneous pustules is a hallmark of GPP on histological examination. There are also prominent systemic symptoms, such as high

temperature, tiredness, and a rise in neutrophils leukocytosis, that accompany the cutaneous signs (Marina *et al*., 2013; Rivera-Díaz *et al*., 2023).

Pregnancy is a high-risk time for acute episodes, which things like illness, drug exposure, or medication withdrawal may bring on. Plaque psoriasis and palmoplantar pustular psoriasis are two psoriasis types often seen along with GPP. However, GPP's distinctive clinical and histological characteristics have long indicated that it is a disease with a separate origin, even though it is currently categorized as a variety of psoriasis. The finding of autosomal recessive inheritance in certain instances of familial GPP due to mutations in the IL36RN gene producing the anti-inflammatory IL-36-receptor antagonist, IL-36Ra, provides more genetic evidence in favor of this concept (Marrakchi *et al*., 2011; Onoufriadis *et al*., 2011; Sugiura *et al*., 2013).

2.4.4 Erythrodermic Psoriasis

The most severe manifestation of psoriasis, erythrodermic psoriasis, affects only 1% to 2.2% of persons with psoriasis and is associated with significant morbidity and even mortality. The condition is characterized by widespread erythema that affects 75% of the skin's surface and may or may not be accompanied by scaling. In contrast to the deeply embedded scales seen in plaque psoriasis, the scales in guttate psoriasis are relatively superficial. The widespread vasodilation underlying the erythema may generate additional systemic signs such as myalgia, tiredness, fever, hypothermia, and limb edema. If pustule development in GPP ceases, the condition may return to erythrodermic psoriasis. Systemic corticosteroids, methotrexate, sunburn, and psychological stress have all been proposed as potential precipitating causes (Armstrong & Read, 2020; Ayala, 2007).

2.4.5 Psoriatic Arthritis

Psoriatic arthritis (PsA) is a condition characterised by the absence of certain antibodies in the blood, chronic inflammatory musculoskeletal condition that affects roughly 20%-30% of psoriasis patients about a decade after the onset of psoriasis (Gladman *et al*., 2005).

PsA's vast range of clinical manifestations and prognoses reflect its complicated etiology. Involvement of distal joints, asymmetric articular distribution, erythema over-affected joints, spinal involvement, and enthesitis are all characteristics of PsA, as are erosion and loss of function due to the disease (Anandarajah & Ritchlin, 2009).

Since about 80% of psoriasis patients also develop PsA, the two conditions are often treated as separate diseases. Psoriasis and some of the susceptibility genes for PsA have similarities. However, there are distinctions in the genetic background of the two disorders, and distinctive genetic factors have been found, although not on a genome-wide scale (Anonymous., 2012; Eder *et al*., 2011; Ellinghaus *et al*., 2012).

Lymphocyte infiltration of the inflamed skin or joint and important cytokines, including tumor necrosis factor (TNF), IL-23, and IL-17, are only a few examples of the same cellular and molecular mediators between PsA and psoriasis (Gullick *et al*., 2010). The presence of oligoclonal expanded CD8 T lymphocytes in the joint fluids of persons with active PsA is supported by genetic connection with class I HLA molecules and clinical data. Anti-TNF medication is effective in 70% of individuals with psoriasis, as measured by improvement in signs and symptoms and, in some instances, by radiographic advancement (Anandarajah & Ritchlin, 2009).

2.5 Etiopathogenesis

Like many other complicated illnesses, Psoriasis often begins when a person is exposed to environmental triggers that cause a dysregulated immune response in those genetically prone to developing the condition. Critical variables of this

pathogenic interaction have been found despite the lack of mechanistic linkages connecting different environmental stressors with particular genetic markers and dysregulated immunological mechanisms. The etiopathogenesis of psoriasis is shown in Figure (2.2). Psoriasis arises when a genetically predisposed person is exposed to environmental factors that cause a dysregulated immune response (including DC, T cells, and KCs) in a person who has one or more psoriasis susceptibility genes (either skin-specific or of immunological function) (McCormick *et al*., 2016; Schön, 2019a).

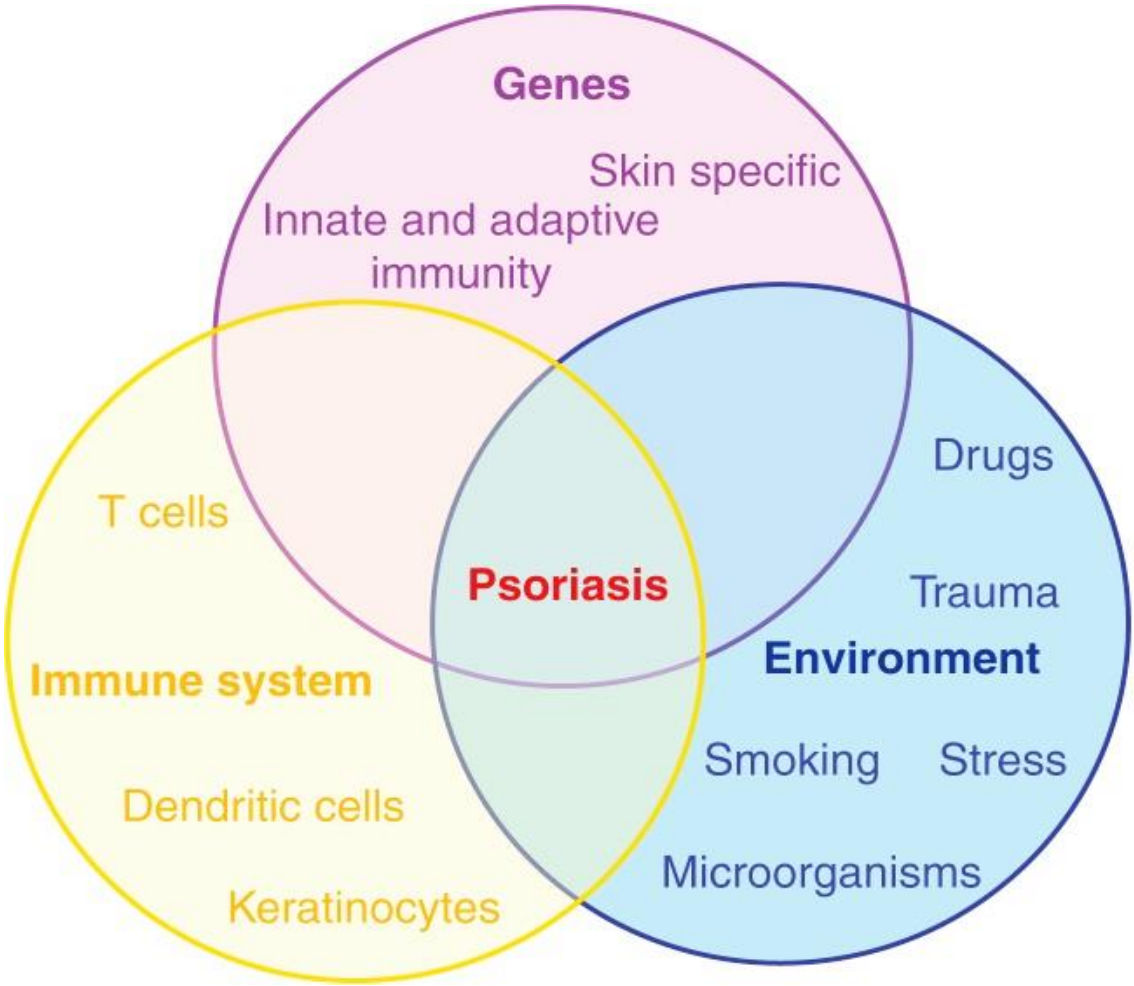

Figure (2.2): Psoriasis's complex pathogenesis (Di Meglio *et al*., 2014)**.**

2.6 Environmental Triggers of Psoriasis

The list of psoriasis susceptibility genes is expanding rapidly, but the environmental variables that contribute to the onset of the illness are still poorly

understood. Drugs, infections, trauma, cigarettes, alcohol, and stress have all been linked to flare-ups of psoriasis. Clinical evidence links the use of medications such as imiquimod, an antiviral and antiproliferative agent; lithium, an antidepressant; beta blockers, an antihypertensive; interferons; and anticytokine therapies used to treat psoriasis (anti-TNF antibodies) to the development, progression, and worsening of the disease (G. K. Kim & del Rosso, 2010).

2.7 Immunopathogenesis of Psoriasis.

The firs type of psoriasis which is the vulgaris is a widespread, persistent, and relapsing skin condition. It's characterized by both visible (clinical) and invisible (histological) changes to the skin, and it significantly lowers patients' quality of life. Extreme extracutaneous alterations may also occur with some types of psoriasis (such as the arthropathic variety). Researchers have focused on psoriasis not just because it is prevalent and may be disabling for sufferers, but also because its pathophysiology is thought to be similar to that of other chronic immune-mediated inflammatory illnesses. A better understanding of the pathogenesis of psoriasis is expected to aid in the understanding of other chronic inflammatory diseases and lead to novel treatment options, as similar reactions are hypothesized to contribute to the initiation and maintenance of diseases like rheumatoid arthritis and Crohn's disease. Psoriasis is a condition that affects people everywhere (Kimmel & Lebwohl, 2018; Langley *et al*., 2005)

Psoriasis is often understood in two stages, the first flare-up and the chronic psoriatic skin condition (Saraceno *et al*., 2008). Injured keratinocytes produce the antimicrobial peptide cathelicidin (LL-37), which stimulates plasmacytoid dendritic cells (pDC) and sets off the pro-inflammatory cytokine cascade (Rønholt & Iversen, 2017). Similarly, ADAMTS-like protein 5 (another potential autoantigen in psoriasis) may be produced by injured melanocytes (Prinz, 2017). IFN-γ, a critical cytokine of the initiation phase, is secreted by plasmacytoid dendritic cells (pDCs) in response to the stimulation (Georgescu *et al*., 2019). It does this by stimulating the

proliferation of local myeloid dendritic cells (mDCs) and enticing them to migrate to lymph nodes in the area. The immune response involves a complex interplay of various cells and signaling molecules. In dendritic cells, like myeloid dendritic cells (mDCs), several cytokines play a role in their activation. Interferon-alpha (IFN-α), tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) are among the key cytokines that are secreted by other innate immune cells and contribute to the activation of mDCs. The activation of mDCs is a critical step in the immune response, as these cells are potent antigen-presenting cells that help initiate and shape the adaptive immune response. (Conrad & Gilliet, 2018).

Activated mDCs release cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-12 (IL-12), and interleukin-23 (IL-23) that stimulate the differentiation and proliferation of naive T lymphocytes into effector cells like T helper type 1 (Th1), T helper type 17 (Th17), and T helper type 22 (Th22) that can then enter the bloodstream and populate the skin. The pro-inflammatory cytokine IL-17A is generated by a variety of cell types, including T lymphocytes, NK cells, mast cells, and innate lymphoid cells (ILCs), and is secreted by T17 lymphocytes in response to activation (H. O. Kim *et al*., 2021).

Psoriatic phenotypic development is associated with the cytokines IL-22 and IL-17A/F, which are part of the IL-23/Th17 axis, and result in keratinocyte proliferation and poor differentiation. Keratinocytes are not merely bystanders; in response to stimuli, they secrete antimicrobial peptides (AMPs), cytokines, and chemokines that further activate T lymphocytes and mobilize other inflammatory cells, primarily macrophages, dendritic cells, and neutrophils, thereby encouraging the development of chronic inflammation, i.e., the maintenance phase of the disease (Rønholt & Iversen, 2017).

Furthermore, angiogenesis is stimulated by the inflammatory cascade, which aids in the subsequent migration of immune cells into the psoriatic lesion. To produce their function, cytokines ultimately stimulate the transcription of critical messenger genes through intracellular signaling pathways. Phosphodiesterase-4

(PDE-4) blocks the anti-inflammatory effects of the cAMP (cyclic adenosine monophosphate) signaling molecule, whereas interleukin (IL)-1, IL-12, IL-22, and IL-23 activate the JAK-STAT (Janus kinases—signal transducer and activator of transcription proteins) pathway. (Psomadakis & Han, 2019; Solimani *et al*., 2019).

The major effector cells and signaling pathways involved in the immunopathogenesis of psoriasis are shown in Figure (2.3. Psoriase's immunopathogenesis is initiated by innate immune cells and includes a complicated inflammatory cascade (keratinocytes, dendritic cells, NKT cells, macrophages). Conversely, keratinocytes, dendritic cells, NKT cells, and macrophages interact with adaptive immune cells, which drives disease progression and keeps it going (T lymphocytes). Keratinocyte proliferation, synthesis of pro-inflammatory cytokines, chemokines, and AMP, and the establishment of a positive feedback loop that continues the inflammatory process are all results of the IL-23/Th17 axis. Increased expression of disease-related cytokines and the genes that code for them is caused by cytokines activating signaling and transcription pathways (cAMP, JAK-STAT) (Alwan & Nestle, 2015).

The diagram depicted in Figure (2.4) illustrates the sequence of pathophysiological events involved in the development of psoriasis. The occurrence of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) within the epidermis, prompted by environmental triggers, can activate pattern recognition receptors (PRRs) located in keratinocytes (KCs). This activation subsequently leads to an excessive expression of Toll-like receptors (TLRs), resulting in the production of pro-inflammatory cytokines. The involved entities in this process include Toll-like receptors (TLRs), plasmacytoid dendritic cells (pDC), myeloid dendritic cells (mDC), interleukin 12 (IL-12), interleukin 23 (IL-23), tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), T-helper cell type 17 (Th17), T-helper cell type 1 (Th1), and nitric oxide synthase (NOS) (Benhadou *et al*., 2019).

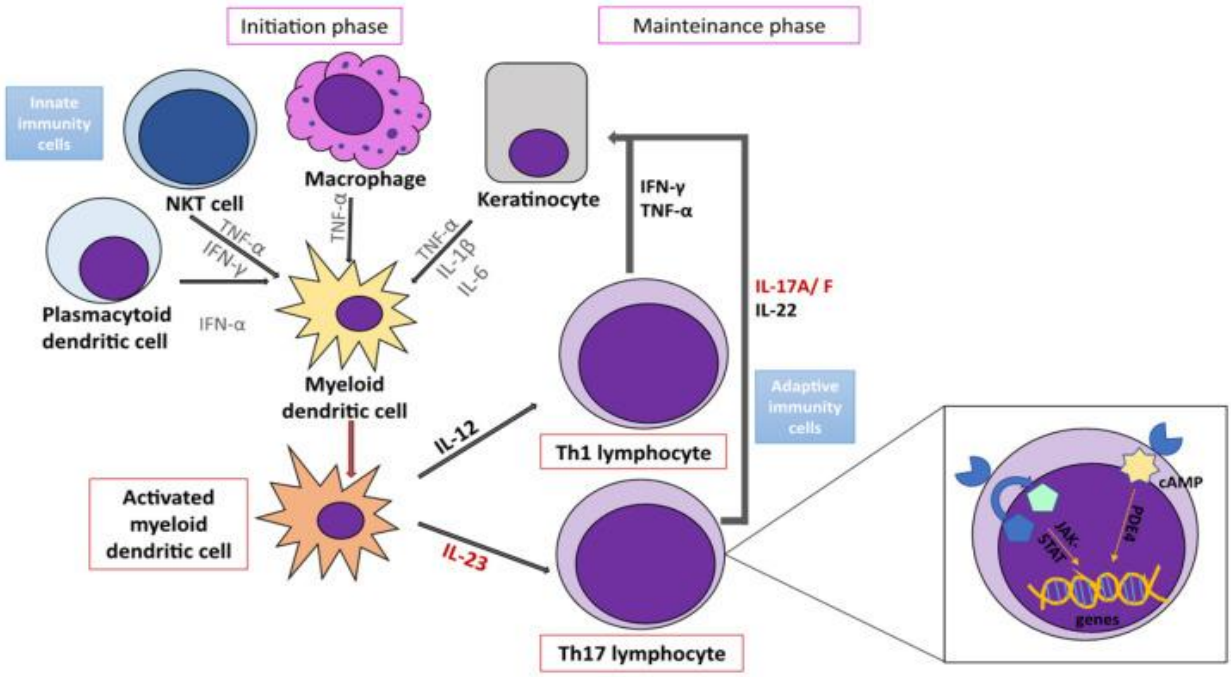

Figure (2.3): Psoriasis's immunopathogenesis: key effector cells and signaling pathways (Rendon & Schäkel, 2019)**.**

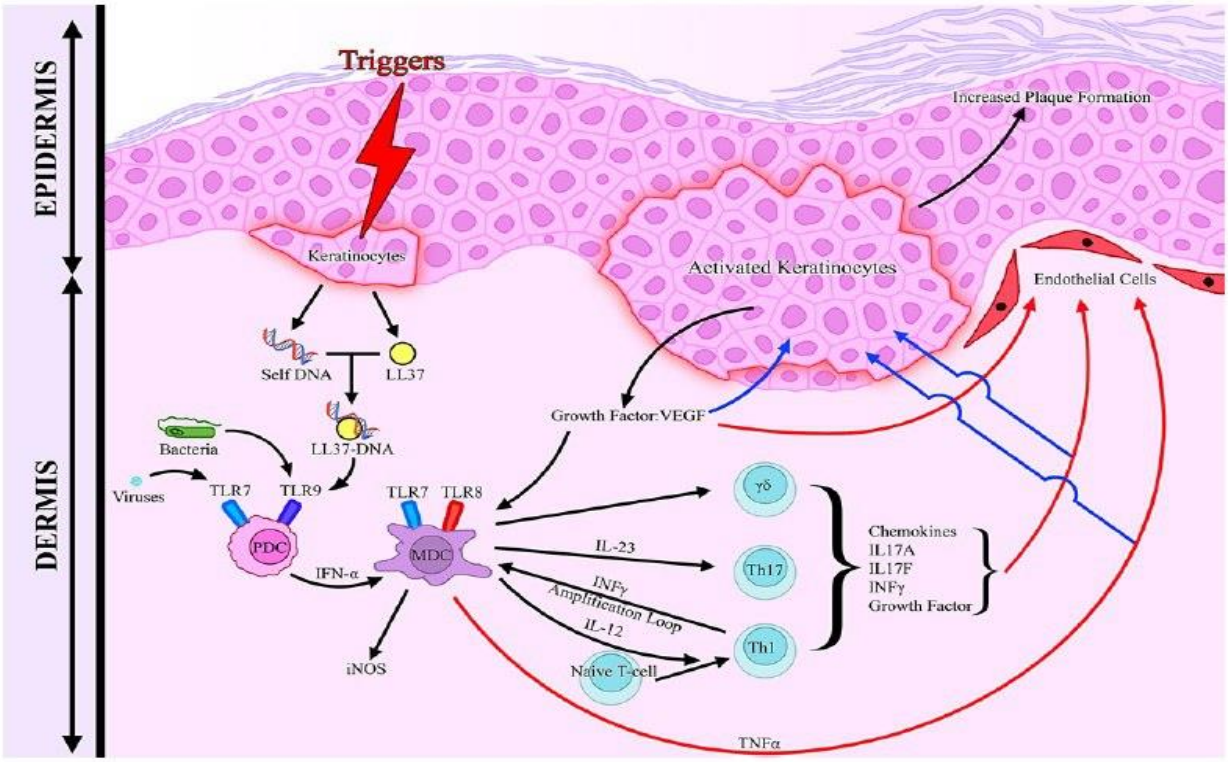

Figure (2.4): Pathophysiologic steps for psoriasis formation (Benhadou *et al*., 2019).

2.7.1 Primary Inflammatory Cells in Psoriasis

2.7.1.1. Dendritic Cells

Psoriasis is a complex disease, but dendritic cells (DCs) are a key player due to their role as a bridge between the innate and adaptive immune systems. They serve as professional antigen-presenting cells (APCs), aiding in T lymphocyte activation and differentiation and boosting inflammation via cytokine and chemokine production . Psoriasis development is aided by the presence of dermal plasmacytoid and myeloid DCs in addition to epidermal Langerhans cells (Samotij *et al*., 2020).

Disease is triggered when plasmacytoid dendritic cells (pDCs) attach to a combination of keratinocyte DNA and antimicrobial peptide LL-37 (Wang & Bai, 2020). Then, in response, they secrete copious quantities of IFN type I, especially IFN-γ, which promotes the development of myeloid-derived suppressor cells (mDCs) and the activation of T lymphocytes, setting in motion the inflammatory cascade that ultimately results in the psoriatic phenotype. Experimental blocking of this cytokine inhibited the formation of skin lesions, confirming that pDCs contribute to the pathophysiology of the illness as the principal source of IFN-γ in the skin. Psoriatic lesional skin has a higher concentration of pDCs compared to normal skin (Mahil *et al*., 2016).

Myeloid dendritic cells (mDCs) may be identified by the x integrin CD11γ they express, and they can be further subdivided into two groups based on the blood dendritic cell antigen (BDCA) levels they produce. Psoriatic skin has an equal number of BDCA-1-positive (CD1γ+) or "resident" DCs, which, as mature APCs, are responsible for local presentation of antigen to T cells. When effective antipsoriatic medication (such as etanercept, infliximab, or UVB phototherapy) is administered, the quantity of BDCA-1-negative (CD1γ) or "inflammatory" DC (iDC) decreases from their 30-fold rise in the lesional dermis. These cells, also known as TiP-DC (from TNF-/iNOS producing), produce TNF-α and inducible nitric oxide synthase (iNOS), as well as IL-6, IL-12, IL-20, and IL-23; they are crucial in

maintaining and enhancing psoriatic inflammation, primarily through activating Th17 cells and regulating the IL-17 response (Wang & Bai, 2020).

Psoriasis is still poorly understood, despite the fact that Langerhans cells (LCs) may present antigens in regional lymph nodes. They may have a significant role in preserving tolerance to cutaneous antigens. Although there is no difference in the absolute amount of LCs between lesional and nonlesional psoriatic and healthy skin epidermis, their decreased mobility and subsequent retention within the lesional epidermis contributes to the immune response problem (Chiricozzi *et al*., 2018).

2.7.1.2 Lymphocytes

Different subpopulations of T lymphocytes support the pathophysiology of the illness through aberrant cellular activation, production of pro-inflammatory cytokines, and mobilization of immune cells (Nilmare. *et al*., 2016; Schön, 2019b). Most of the lymphocytes in the skin have the alpha-beta T-cell receptor (α-TCR), and these include the helper (CD4+) and cytotoxic (CD8+) T cells. T cells, namely CD8+ in the epidermal and CD4+ in the perivascular portions of the upper dermal compartment, are elevated in psoriatic skin biopsies. In a study using SCID mice, dermal infiltration by CD4+ T lymphocytes was shown to be essential in developing the psoriatic phenotype after transplanting skin from a patient who had not been afflicted by the disease (Nomura *et al*., 2014).

The time at which CD8+ T cells enter the epidermis is also critical, since cell depletion may halt or impair disease progression (Di Meglio *et al*., 2016). Psoriatic cells express cutaneous lymphocyte antigen (CLA), which binds to E-selectin on skin capillaries, allowing some CD4+ and CD8+ T lymphocytes, which are also abundant in the patients' blood, to exit the circulation and enter the skin. CD8+ cells reach the epidermis via binding to type IV collagen in the basal membrane through 11 integrin (refers to the integrin known as integrin alpha 1 beta 1 (α1β1). Integrins are a family of cell surface receptors that play a crucial role in cell adhesion, signaling, and migration. Integrin alpha 1 beta 1 is a specific combination of integrin

subunits, and the "11" designation indicates the specific alpha and beta subunits that make up this integrin) or VLA-1 (from very late antigen-, VLA-1 is another term used to refer to the same integrin, integrin alpha 1 beta 1 (11 integrin). VLA-1 is expressed on the surface of certain immune cells, including T cells. VLA-1 facilitates the interaction between T cells and components of the extracellular matrix, allowing T cells to migrate and infiltrate tissues.). Significant infiltration of CD4+ and CD8+ T cells into the lesional epidermis and dermis is achieved through the aforementioned processes (Conrad *et al*., 2007).

Cytokines released in cellular infiltrates of psoriatic skin lesions have identified several subpopulations of pathogenic lymphocytes. Thus, IFN-α, TNF-α, and IL-2 cytokine production recognizes Th1 cells, whose differentiation is regulated by IL-12. Psoriasis chronic inflammation is maintained in part by Th17 cells, which develop in response to IL-23, IL-1, TGF-α, and IL-6; they then release IL-17A, IL-17F, TNF-α, IL-21, IL-22, and IL-26. Th22 differentiates in response to TNF- and IL-6, and as a result, generates IL-22, IL-13, and IL-26 (Karczewski *et al*., 2016). Tγ1, Tγ17, and Tγ22 refer to cytotoxic T-cell subsetthat generate the same cytokines as their helper counterparts (Volarić *et al*., 2019). Cell cytotoxicity processes are also implicated in the effector actions of Tγ lymphocytes (Prager & Watzl, 2019).

Cytotoxic action ultimately leads to the death of target cells, which might occur through necrosis or apoptosis. Secretory processes mediate the release of cytotoxic molecules like perforin, granzymes, and granulysin from cytotoxic cells' cytoplasmatic granules, while nonsecretory methods involve the interaction of effector and target cell membrane molecules like FasL-Fas (Martínez-Lostao *et al*., 2015). Psoriasis patients' lesional skin and peripheral blood have been shown to have elevated levels of granzyme B, perforin, and granulysin (Vičić *et al*., 2016).

T lymphocyte subpopulations are functionally versatile, with the ability to switch from Th17 and Treg to Th1 or Tγ17 to Tγ1. Th9 and follicular CD3+CD4+CXCR5+ T cells, as well as other Th lymphocyte subpopulations, contribute to the pathogenesis of psoriasis by presumably amplifying preexisting

immunological processes, particularly the IL-17 pathway. Psoriasis damages regulatory CD4+CD25+ T-cells (Tregs), which normally regulate the growth of effector T lymphocytes by secreting inhibitory cytokines and causing apoptosis. Patients have less Tregs in their blood circulation compared to healthy controls (Owczarczyk-Saczonek *et al*., 2018).

Resident memory in tissues Psoriatic lesions tend to reappear in the same locations during flare-ups because T-cells (Trms) stay in the skin long after psoriatic alterations have faded away (Schön, 2019b). The IL-17 secreted by Trms mediates local inflammation, and these cells may be either CD8+ in the epidermis of psoriatic skin or CD4+ in the dermis (Saczonek *et al*., 2020).

Having both adaptive and innate immune features, gamma delta T cells share a T-cell receptor (Sato *et al*., 2020). Psoriasis is associated with two subpopulations of T-cells, cutaneous T lymphocytes and circulating V9V2 lymphocytes. Psoriatic skin has an increased number of dermal T lymphocytes. Like Th17 and Tc17 lymphocytes, these cells have the IL-23 receptor and react to stimulation by secreting IL-17 and IL-22, which in turn activates keratinocytes. Their significance in psoriasis pathogenesis was supported by the finding that -positive T lymphocytes generate much larger levels of IL-17 in the lesional dermis, compared to -negative cells. After proper systemic treatment, the number of V9V2 T lymphocytes in the blood of patients returns to normal, suggesting that these cells were rapidly recruited to inflamed tissue (Laggner *et al*., 2011).

The remaining nonclassical lymphocytes include NK and NKT cells, ILC cells, and so-called mucosal-associated invariant T (MAIT) lymphocytes, all of which release inflammatory cytokines and chemokines that have a role in the development of the illness (Plužarić *et al*., 2020).

2.7.1.3. NK and NKT Cells

Natural killer (NK) cells, following activation by interleukin (IL)-12, produce the cytokines interferon (IFN-α), tumor necrosis factor (TNF), and transforming

growth factor (TGF-α), and are responsible for the cytotoxic elimination of infected and injured cells. NK17 and NK22 cells, which produce IL-17 and IL-22, respectively, are recent discoveries (Polese *et al*., 2020). Psoriatic skin contains immature CD56bright cells, which, in contrast to the CD56dim subtype, produce cytokines more efficiently and have a lower cytotoxic potential. Natural Killer (NK) cells, T cells, and CD3 are all types of lymphocytes involved in the immune system, but they have different functions, origins, and receptors. (Batista *et al*., 2013).

Natural Killer (NK) cells, T cells, and CD3 are all types of lymphocytes involved in the immune system, but they have different functions, origins, and receptors. Here's a brief overview of each:

1. **Natural Killer (NK) Cells:**
    - **Function:** NK cells are a type of innate immune cell that plays a crucial role in the early defense against viral infections and certain types of cancer. They are responsible for recognizing and killing infected or abnormal cells.
    - **Origin:** NK cells originate from the bone marrow.
    - **Receptors:** NK cells express a variety of receptors, including killer cell immunoglobulin-like receptors (KIRs) and natural cytotoxicity receptors (NCRs), which allow them to detect abnormal cells without the need for prior sensitization.
2. **T Cells:**
    - **Function:** T cells are a type of lymphocyte that plays a central role in cell-mediated immunity. They are involved in recognizing and attacking cells infected with intracellular pathogens (such as viruses) and in coordinating immune responses.
    - **Origin:** T cells originate from the bone marrow but mature in the thymus gland, which is why they are called "T" cells.
    - **Receptors:** T cells express the CD3 complex, which is a set of proteins that are associated with the T-cell receptor (TCR). The TCR is responsible for

recognizing specific antigens presented by major histocompatibility complex (MHC) molecules on the surface of other cells.

3. **CD3:**
    - **CD3 Complex:** CD3 is a complex of proteins (CD3γ, CD3δ, CD3ε, and two ζ chains) that are associated with the T-cell receptor (TCR) on the surface of T cells.
    - **Function:** The CD3 complex is essential for the signal transduction that occurs when the TCR binds to a specific antigen presented by MHC molecules. This signal transduction is crucial for T cell activation and the initiation of an immune response.

Lesional NK cells expressing the CD69 activation marker secrete high levels of IFN-α and TNF-α, activating and stimulating keratinocytes through the production of CXCL10 and CCL5. This was shown in vitro (Ottaviani *et al*., 2006). The new NK cells were drawn to the region of inflammation because their chemokine receptors were expressed. Psoriatic lesions have been shown to have elevated chemerin expression, and there is evidence that this leads to the recruitment of CD56dim cells (Mariani & Roncucci, 2015). Researchers have shown that the circulating NK cell count in individuals with psoriasis is lower than that of healthy controls and that this decline is independent of the disease's clinical severity (Gardiner & Dunphy, 2011).

According to the study conducted by Duphny *et al*., NK cells are unable to properly degranulate and produce cytokines. The identification of KIR-receptor gene polymorphisms provided additional confirmation of the significance of NK cells in the etiology of psoriasis (from killer-cell immunoglobulin-like receptors) (Dunphy *et al*., 2017). It has been hypothesized that NK cells mediate the immune response at the site of psoriatic inflammation through cellular cytotoxicity mechanisms and cytokine production, then participate in the adaptive immune response through DC modulation, and finally perform immune regulation by killing immature or

overactive cells like macrophages and T lymphocytes; however, this hypothesis needs more study (Płoski *et al*., 2006).

Natural killer T-cells (NKTs) are special cells that share characteristics with T lymphocytes, namely their low -TCR diversity with those cells. The majority of NKT (iNKT) cells carry receptors for interleukin (IL)-12, IL-18, IL-23, IL-25, and IL-33. To produce the cytokines IFN- γ, TNF- α, IL-10, IL-4, IL-13, IL-17, and GM-CSF, NKT cells must first be activated by the detection of glycolipids by CD1d antigen-presenting molecules, which are analogous to MHC group I molecules. When fully developed, NKT1 cells emit large amounts of IFN-α, NKT2 cells release IL-4, and so-called NKT17 cells generate IL-17A, IL-17F, and IL-22 (Yip *et al*., 2019).

The chemokine receptors CXCR3, CCR5, and CCR6 are also expressed by NKT cells, which aids in their migration into the skin. The strength of the TCR signal may modulate the NKT cells' function. The CD1d molecule, when stimulated once, causes an increase in IFN-γ production, which aids in cytotoxicity through CD8+ T lymphocyte generation and NK cell activation, and when stimulated repeatedly, causes an increase in IL-10 production, which mediates the regulatory role of NKT cells. Although NKT cells are implicated in the pathogenesis of psoriasis, they are unlikely to play a pivotal role in this process (Krijgsman *et al*., 2018).

Coculturing NKT cells with CD1d+ keratinocytes has been shown to have a direct effect on IFN-γ production in vitro, and this finding was corroborated in vivo by the observation of considerably elevated CD1d expression in patients' lesional keratinocytes. Injecting activated iNKT cells into a transplant of normal patient skin causes psoriasis in SCID mice, according to a recent study (Nickoloff *et al*., 2000). While there are more iNKT cells in the skin of psoriatic patients than in the blood of healthy controls, the opposite is true in the skin. The presence of more severe inhibitory receptors on iNKT cells in the blood was linked with the severity of the illness (Curry *et al*., 2003). NKT cells interact with CD1d+ keratinocytes and

produce IFN-γ and other cytokines, which mobilize T17 lymphocytes, likely contributingo disease development in psoriasis (Ince *et al*., 2004).

2.7.1.4. Keratinocytes

In addition to their structural and protective roles, keratinocytes in the epidermis also have an immunological role (Mahil *et al*., 2016). Both the innate immune response, via the release of innate immune system chemicals like AMP, and the adaptive immunological response, through the recruitment of T cells to the inflammatory site, are mediated by keratinocytes. Psoriatic inflammation seeks out the epidermis because keratinocytes are receptor-bearing for most pathogenic cytokines. Psoriatic phenotypic development occurs because of excessive proliferation and inadequate differentiation during so-called regenerative maturation (Chiricozzi *et al*., 2018).

A unique keratinocyte response is triggered by the cytokine released by each kind of immune cell. Although keratinocytes express receptors for IL-17, IL-22, TNF- α, IL-19, and IL-20, IL-17 has the greatest impact on the epidermis, leading to epidermal hyperplasia and stimulating the production of additional pro-inflammatory molecules by keratinocytes and thereby amplifying the inflammatory process in the skin (Furue *et al*., 2020). In particular, keratinocytes produce a variety of pro-inflammatory chemicals in response to executive cytokines. These include cytokines (TNF-α, IL-1, IL-6, IL-17C, IL-19, IL-36), chemokines (CCL20, CXCL1, CXCL2, CXCL8-11), growth factors (EGF, VEGF), and AMP (Hirahara *et al*., 2016).

While keratinocytes may produce certain AMPs constitutively, epithelial damage triggers the release of chemotactic effector innate immunity molecules such as defensins and S100 proteins from keratinocytes, among the initiators of the psoriatic pathogenic process. However, in addition to their direct antimicrobial activity, AMPs also promote the production of cytokines (IL-6 and IL-10) and chemokines (CCL20, CXCL8, and CXCL10) by keratinocytes, which in turn mobilize neutrophils, Th1 lymphocytes, and macrophages, and CCL20, which

recruits mDCs and IL-17-producing cells to the site of inflammation (T. Takahashi & Yamasaki, 2020).

Increased AMPs levels in psoriasis successfully reduce after the use of systemic therapy. Keratinocyte's IL-1β affects the production of TNF-α, stimulates the activation of T lymphocytes, increases the expression of leukocyte selectins, and, together with IL-18, is involved in the differentiation of Th1 and Th17 lymphocytes. VEGF secreted by keratinocytes in an inflammation state promotes angiogenesis with the consequent formation of vascular plaque, while its excessive expression in the mouse skin leads to the formation of psoriatic lesions (Benhadou *et al*., 2020). Keratinocytes are seen as supporting players in the etiology of psoriasis in the previously established model. However, since their gene abnormalities have been discovered, the idea of aberrant keratinocyte biology has elevated them to the forefront (Fotiadou *et al*., 2018). Psoriasis may be triggered by the production of STAT3 in the epidermis of a transgenic mouse that has been exposed to IFN-α, IL-6, IL-20, IL-17A, and IL-22. When keratinocytes and immune cells interact, a psoriatic lesion form. The transcription factor STAT3 is thought to be a crucial connection in this process (Furue *et al*., 2020).

2.8 Interleukins (IL) 17 and 23

2.8.1 Interleukins (IL) 17

2.8.1.1 Family IL-17 Biology

There are six distinct types of IL-17 (IL-17A-IL-17F). In addition to IL-17A and IL-17F, IL-17C and IL-17E have been linked to the development of psoriasis (Mosca *et al*., 2021). The involvement of these four cytokines in psoriasis is further supported by the fact that their expression is elevated inside psoriatic skin lesions (Johnston *et al*., 2013). Lesional psoriatic skin had considerably higher protein levels of IL-17A, IL-17C, and IL-17F than nonlesional skin by factors of 6.7, 4.1, and 8, respectively (Johansen *et al*., 2009).

Approximately 50% of the sequence in IL-17A and IL-17F is identical, making them the most structurally similar IL-17 family members. In addition to its homodimer form, IL-17A also occurs as a heterodimer with IL-17F (IL-17A/ IL-17F) (X. Zhang *et al*., 2011). Not only that, but the heterodimeric receptor IL-17R (made up of IL-17RA and IL-17RC) binds IL-17A homodimer, IL-17F homodimer, and IL-17A/IL-17F heterodimer. However, compared to IL-17F homodimer, IL-17A homodimer is the most physiologically active isomer, activating downstream genes by a factor of 10-30 (Chiricozzi & Krueger, 2013; Maitra *et al*., 2007).

2.8.1.2 Role of Cytokines IL-17 in Psoriasis

The IL-17 pathway aids in host defense against extracellular fungus and bacteria under normal circumstances. IL-17A, in particular, connects the dormant innate immune system with the more advanced adaptive immune system. The production and gradients of chemokines induced by IL-17A trigger immunological responses at mucosal surfaces, where neutrophils are recruited. In reaction, neutrophils release IL-17, which then recruits even more neutrophils and further intensifies the response (Lin *et al*., 2011).

The IL-17 pathway is also critically important in the development and perpetuation of the psoriatic inflammatory loop. An immunologic cascade is set in motion by the adaptive immune system when a person with a genetic susceptibility receives a trigger for psoriasis. Th17 cells, which release IL-17 cytokines, are helped along in their processes of survival, differentiation, and activation by IL-23 (Armstrong & Read, 2020).

New evidence reveals that IL-17 is produced and released mostly by mast cells and neutrophils in psoriatic skin, rather than Th17 cells as was previously believed. Therapeutic approaches directed at IL-23 may be effective in psoriasis because they trigger the production of IL-17 by a specific subset of neutrophils and mast cells. IL-17 might also be produced by gamma-delta T-cells, natural killer cells, and innate lymphoid cells (Brembilla *et al*., 2018).

Psoriasis-related IL-17 acts on keratinocytes, endothelial cells, and immune cells as its downstream targets. Psoriasis-related cytokines, chemokines, and antimicrobial peptides are produced by keratinocytes as a consequence of IL-17's direct action on these cells. By releasing factors that encourage the creation of more inflammatory cells and IL-17-producing cells, keratinocytes contribute to the positive feedback loop. Although IL-17A and IL-17F both cause inflammation on their own in the psoriasis cascade, their combined effects are amplified. When both cytokines were blocked, inflammation was reduced in vitro to a larger extent than with either IL-17A or IL-17F inhibition alone . Furthermore, IL-17E promotes innate cellular recruitment and activation by upregulating genes involved in chemotaxis, thereby amplifying the inflammatory feedback loop. IL-17 upregulates pro-inflammatory effects in macrophages and dendritic cells and enhances procoagulant activity in endothelial cells (Robert *et al*., 2022; Yasuda *et al*., 2019).

IL-17 also combines synergistically with TNF-α to coregulate cytokine and keratinocyte genes involved in psoriasis, which is a different mechanism. Keratinocytes express TNF-α and IL-17 receptors. Synergistic or cumulative upregulation of inflammatory cytokines is the outcome of simultaneous stimulation of the two receptors. Over 350 IL-17/TNF-α coregulated genes are strongly expressed in psoriatic skin, providing more evidence for the existence of a causal link between these two factors (Chiricozzi *et al*., 2011).

2.8.1.3 The Comorbidities of Psoriasis and IL-17

The specific mechanism linking psoriasis to other conditions such as cardiovascular disease, metabolic syndrome, mental illness, inflammatory bowel disease, and obesity is unclear. Immune system alterations and dysfunction are hypothesized to be essential processes connecting these diseases. The IL-17 pathway is thought to regulate the inflammatory responses seen in both primary psoriatic skin disease and concomitant systemic illness, given its central involvement in psoriatic disease. Psoriasis has been linked to cardiovascular dysfunction, depression, and

obesity, and IL-17 may have a causative role in all three (Ababneh *et al*., 2020; Lieberman *et al*., 2011; Schwarz *et al*., 2019).

According to several studies, psoriasis and vascular dysfunction have been linked to IL-17. Overexpressing IL-17A in keratinocytes in mice led to psoriasis-like skin changes as well as elevated oxidative stress in the blood vessels, endothelial dysfunction, and arterial hypertension (Egeberg *et al*., 2020). In addition, studies have linked upstream components of the IL-17 pathway to vascular dysfunction. Increased amounts of IL-23 and IL-23R were found inside atherosclerotic plaques, and patients with carotid atherosclerosis had considerably higher plasma levels of IL-23 compared to controls (Huang *et al*., 2019). In addition, studies show that hypertension persons have a threefold rise in serum IL-17, suggesting that this cytokine mediates the crucial hypertensive response to angiotensin II (Schüler *et al*., 2019).

Conflicting study points to interleukin-17 (IL-17) as the immunologic connection between psoriasis and depression. Hypothesized mechanisms linking elevated IL-17 levels to depression include microglial activation, neuroinflammation mediated by chemokines and cytokines, and neuroinflammatory mediators (A. Abbas *et al*., 2015).

Furthermore, IL-17 may act as a mediator of the obesity-related feed-forward inflammatory loop. IL-6, which enables Th17 commitment by naive T cells, is produced by adipocytes and macrophages in visceral adipose tissue, exacerbating the inflammatory state of psoriasis. By causing more IL-6 to be made, IL-17 kicks off the positive feedback loop (Álvarez-Mon *et al*., 2021; Beurel *et al*., 2013). This mechanism helps explain why plasma IL-17 is higher in obese individuals than in lean controls. Inflammation in adipose tissue is maintained and adipocyte lipolysis is stimulated, leading researchers to propose that IL-17 mediates the association between obesity and psoriasis (Sumarac-Dumanovic *et al*., 2009).

2.8.2 Interleukin (IL) 23

2.8.2.1 Family

The IL-12 family includes the heterodimeric cytokine interleukin-23 (IL-23), which consists of the IL-12p40 subunit and a new p19 component. As a disulphide-linked compound with the polypeptide p19 binding protein p40, interleukin-23 is mostly produced by activated macrophages and dendritic cells (DCs) in peripheral organs (skin, intestinal mucosa, and lung) (Gerosa *et al*., 2008; Kleinschek *et al*., 2006; Lupardus & Garcia, 2008; McKenzie *et al*., 2006).

Colitis, gastritis, psoriasis, and arthritis are only few of the autoimmune inflammatory illnesses linked to the new pro-inflammatory cytokine interleukin-23. The capacity of IL-23 to produce IL-17 offers a distinct function compared to that of IL-12 in both the genesis and maintenance of autoimmune inflammation, despite their structural similarities and the ability of memory T cells to boost interferon-(IFN-α) production and proliferation. Prostaglandin E2, which stimulates inflammatory reactions, regulated DCs' production of the inflammatory cytokines IL-12 and IL-23 (Cauli *et al*., 2015; Sherlock & Cua, 2021).

T helper type 17 (Th17) cells are CD4+ T cells that secrete IL-17, a pro-inflammatory cytokine that stimulates the production of molecules like IL-1, IL-6, and tumor necrosis factor alpha. IL-12 is important for the differentiation of naive CD4+ T cells, while IL-23 is crucial for the proliferation and development of CD4+ CD45RO+ memory T cells in humans and CD4+ CD45RBlow in mice (Bastos *et al*., 2005; Belladonna *et al*., 2002).

The CD4+ T cells known as T helper type 17 (Th17) cells produce the pro-inflammatory cytokine IL-17. This cytokine promotes the production of molecules such as IL-1, IL-6, and tumor necrosis factor alpha. While interleukin-12 (IL-12) is essential for naïve CD4+ T cell differentiation, interleukin-23 (IL-23) is required for the expansion and maturation of memory T cells (CD4+ CD45RO+ in humans and CD4+ CD45RBlow in mice) (Iwakura & Ishigame, 2006; Kannan *et al*., 2017; Langrish *et al*., 2005).

By binding to the IL-23 receptor on Th17-committed cells and generating significant and persistent upregulation of IL-17, IL-23 stimulates the development of Th17-committed cells. The p40 component of IL-23 may act as a monomer, homodimer, or heterodimer with p19; both macrophages and DCs are major sources of its release. Although only IL-12R1 is shared by the IL-12 receptor heterodimer, both IL-23R and IL-12R1 are required for IL-23 signaling (Schinocca *et al*., 2021).

Lymphoid cells (such as and T cells), innate lymphoid cells, and myeloid cells (such as DCs, macrophages, and monocytes) all express the IL-23 receptor complex on their surface. Tyrosine residues in the intracellular domain of the IL-23R subunit are phosphorylated by Jak2 in response to IL-23 binding to its receptor complex, providing a docking site for STAT3 molecules, which are then phosphorylated, homodimerize, and translocate into the nucleus. Increased gene expression of IL17A, IL-17F, and IL-23R is indicative of Th17-specific cell differentiation, which is facilitated by Signal Transducer and Activator of Transcription 3 (STAT3) regulation of Retinoic Acid Receptor-Related Orphan Receptor Gamma t (RORγt) (Liang *et al*., 2013; Zenewicz & Flavell, 2011).

Tyk2-mediated phosphorylation of the intracellular domain of IL-12R1 is induced by IL-23 binding to its receptor, STAT4 is phosphorylated and STAT3-STAT4 heterodimers are formed, and the inhibitory subunit of nuclear factor kappa B alpha (IB) is degraded, leading to NF-B activation (Cheung *et al*., 2008; Yang *et al*., 2008).

2.8.2.2 IL-23 Structure, Receptor and Signaling Pathways

Interleukin-23 (IL-23) is composed of two subunits: a smaller α subunit called IL-23p19 with a molecular weight of 19,000, and a larger β subunit known as IL-12p40 with a molecular weight of 40,000. These subunits are connected by disulfide bonds to form a heterodimer with a fourfold helical core. The production of IL-23p19 occurs in various cell types, including antigen-presenting cells, T cells, and endothelial cells. On the other hand, IL-12p40 is mainly found in antigen-presenting

cells like monocytes, macrophages, and dendritic cells. To create biologically active IL-23, both IL-12p40 and IL-23p19 subunits must be synthesized within the same cell. IL-12 and IL-23 share the p40 subunit, which enables them to bind to the β1 receptor present on T cells and natural killer (NK) cells (Torti & Feldman, 2007).

The p19 subunit consists of four exons and three introns, and its gene is located on chromosome 12q13.2. In contrast, the p40 subunit is composed of eight exons and seven introns, encoded by a gene found on 11q1.3. The human p19 shares 70% structural similarity with the mouse p19 and shows homology with the p35 subunit of IL-12. Both p35 and p19 belong to the gp130-class of long-chain cytokines and exhibit structural resemblance to IL-6 and granulocyte colony-stimulating factor. Furthermore, the p40 subunit is comprised of three domains: D1, D2, and D3. The D1 domain is an S-type immunoglobulin-like fold that interacts with the D2 domain, while the D3 domain, along with other domains, forms the canonical cytokine binding homology region present in all class I cytokine receptors. This region is also found in non-signaling α receptors for IL-6 and ciliary neurotrophic factor (Beyer *et al*., 2008).

Interleukin-23 (IL-23) binds to the IL-23 receptor (IL-23R) and IL-12Rβ1, but not IL-12Rβ2. The IL-23R, which interacts with IL-23p19, consists of an extracellular N-terminal immunoglobulin-like domain and two cytokine receptor domains. It belongs to the haematopoietin receptor family. On the other hand, the IL-12Rβ1 subunit contains three fibronectin type III domains near the cell membrane and two cytokine receptor domains that interact with IL-12/23p40 (McGovern & Powrie, 2007; Noviello *et al*., 2021).

The schematic diagram in Figure (2.5) illustrates the composition of the interleukin-23 (IL-23) and IL-12 receptors, as well as the shared signal transduction pathway involving the activation of signal transducer and activator of transcription 4 (STAT4). The IL-12 receptor β1 (IL-12Rβ1) and IL-12Rβ2 consist of three fibronectin type III domains (depicted in yellow) and two cytokine receptor domains (shown in green), with an additional immunoglobulin-like domain (depicted in blue)

present in IL-12Rβ2. The IL-23R closely resembles IL-12Rβ2 but lacks the fibronectin type III domains (De Vosse *et al*., 2003).

The IL-23R chain is primarily expressed on activated memory T cells, as well as on NK cells, monocytes/macrophages, and dendritic cells (at lower levels). The IL-12Rβ1 chain has been observed on T cells, NK cells, and dendritic cells. Recent studies have demonstrated that the IL-12p40 homodimer stimulates the production of lymphotoxin-α in microglia and macrophages via IL-12Rβ1, but not IL-12Rβ2. Based on this information, it is hypothesized that IL-12Rβ1 plays a dominant role in autoimmune inflammation compared to IL-12Rβ2. These findings suggest that IL-23 may initiate an autocrine loop within the innate immune system, resulting in the production of various inflammatory mediators (Schmitt *et al*., 2021).

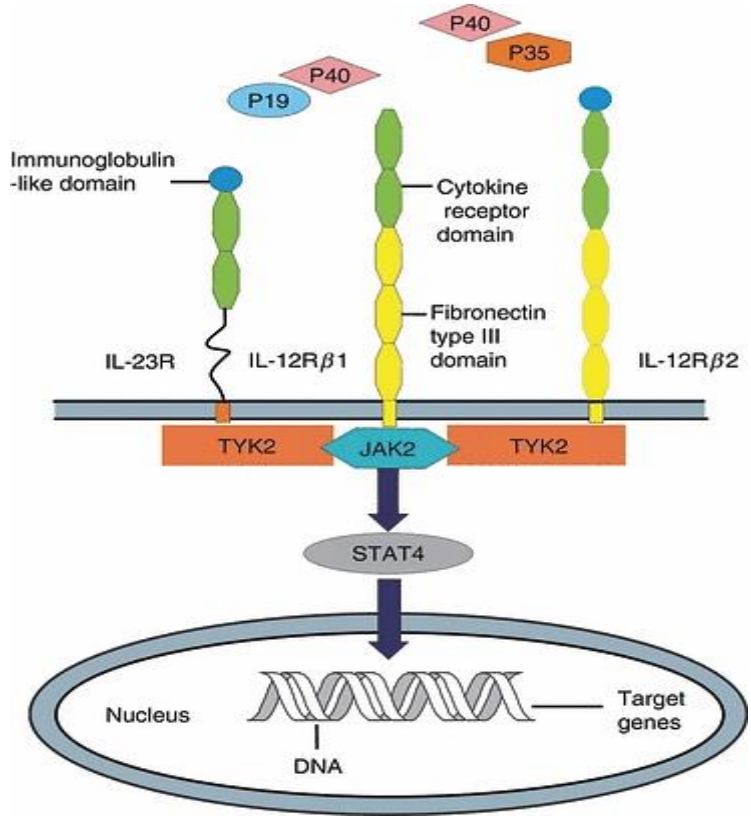

Figure (2.5): The schematic diagram of the composition for the interleukin-23 (IL-23) and IL-12 receptors, as well as the shared signal transduction pathway involving the activation of signal transducer and activator of transcription 4 (STAT4) (Tang *et al*., 2012)**.**

2.8.2.3 Role of IL-23 in Psoriasis

Interleukin-23 is a key factor in psoriasis, an autoimmune skin disorder (IL-23). Dendritic cells, macrophages, and T cells are all sources of this pro-inflammatory cytokine. Th17 cells, a subset of T cells, are formed and maintained in part via the mediation of IL-23. Among the cytokines that Th17 cells generate are IL-17, IL-22, and IL-23 receptor (IL-23R). In psoriasis, these cytokines are crucial in triggering inflammation and immunological responses (McGovern & Powrie, 2007; Noviello *et al*., 2021).

Th17 cells in psoriasis respond to IL-23 by increasing their production of IL-17 and IL-22. It is due in part to these cytokines, especially IL-17, that immune cells such as neutrophils and dendritic cells are recruited and activated in the skin. They also affect keratinocytes, the most common skin cell type, causing them to proliferate abnormally and generate more inflammatory chemicals. IL-23 not only keeps Th17 cells going, but it also helps them live longer and produce more cytokines. Psoriasis is characterized by immunological dysregulation and persistent inflammation, both of which are maintained by a positive feedback loop involving IL-23 and Th17 cells (Benhadou *et al*., 2018; Fitch *et al*., 2007).

Therapeutic approaches that aim to inhibit IL-23 production have shown great promise in the treatment of psoriasis. Clinical studies have demonstrated that IL-23 inhibitors, such as monoclonal antibodies that block the IL-23p19 subunit, may reduce skin lesions and improve symptoms of psoriasis. Psoriasis-related inflammation and aberrant cell development are reduced by these treatments because they suppress IL-23, hence disrupting the IL-23/Th17 axis (Fotiadou *et al*., 2018).

2.9 Toll-Like Receptors (TLRs)

2.9.1 Toll-Like Receptors TLR-4

The innate and adaptive immune responses are both initiated by members of the Toll-like receptor (TLR) family (Liu *et al*., 2012). Toll-interleukin-1 (TIR) domains in the cytosol stimulate downstream signaling pathways, and the

ectodomain of this highly conserved family of transmembrane proteins is characterized by leucine-rich repeats. Pathogen-associated molecular pattern (PAMP) molecules, like endotoxin lipopolysaccharide (LPS) (Bettoni *et al*., 2008), and danger-associated molecular pattern (DAMP) molecules, like heat shock proteins, extracellular matrix degradation products, and high-mobility group box-1 (HMGB-1) protein, are recognized by the extracellular domain. The TLR4 Activation Pathways are shown in Figure (2.6) (Sauer *et al*., 2014).

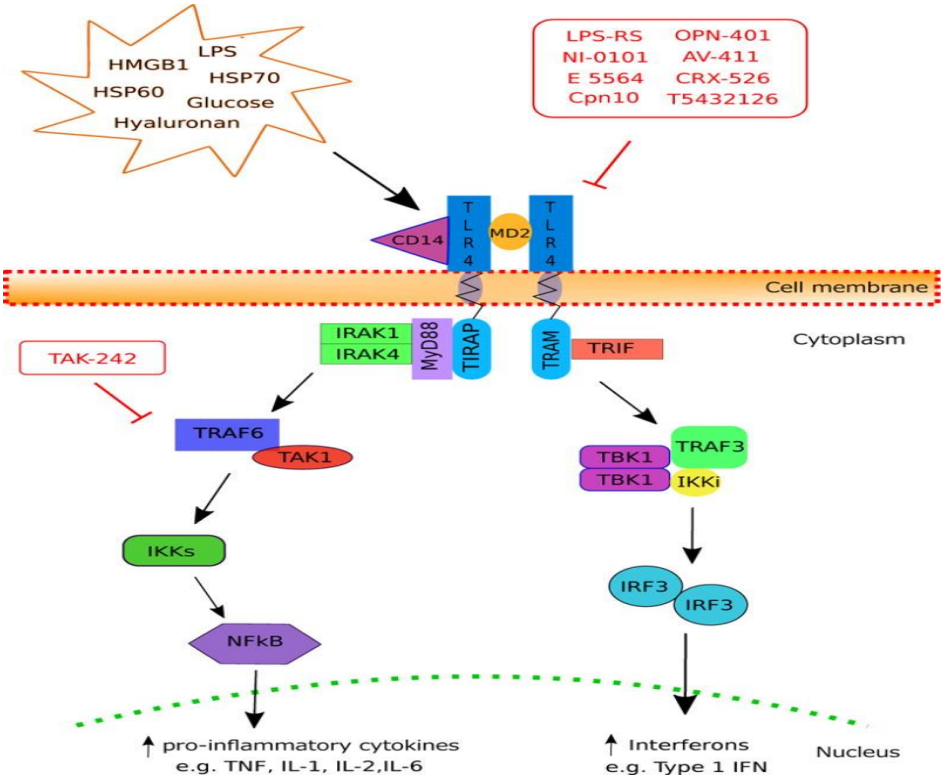

Figure (2.6): Ways in which TLR4 becomes activated (Bruno *et al*., 2018)**.**

2.9.1.1 Role of TLR-4 in Psoriasis

Toll-like receptor 4 (TLR4) is a member of the Toll-like receptor family, and its involvement in the pathogenesis of psoriasis, an autoimmune skin disorder, has been established. TLR4 plays a role in recognizing and responding to various microbial components, particularly lipopolysaccharide (LPS), a component of bacterial cell walls. While TLR4's role in psoriasis is not as extensively studied as TLR7, there is evidence to suggest its involvement in the disease (Smith *et al*., 2016).

Psoriasis is an autoimmune skin disease, and Toll-like receptor 4 (TLR4), another member of the Toll-like receptor family, has been linked to its development. Lipopolysaccharide (LPS), a component of bacterial cell walls, is recognized and responded to by TLR4, among other microbial components. The function of TLR4 in psoriasis has not been investigated to the same extent as that of TLR7, however there is some evidence to support its relevance (Piipponen *et al*., 2020).

Moreover, TLR4 signaling may promote the differentiation and activation of Th17 cells, a subset of T cells that produce high levels of pro-inflammatory cytokines such as interleukin-17 (IL-17). Th17 cells and IL-17 have been implicated in the pathogenesis of psoriasis, contributing to the hyperproliferation of keratinocytes and the chronic inflammation in affected skin areas (Fitch *et al*., 2007).

The NLRP3 inflammasome is a molecular complex that is essential for the generation of pro-inflammatory cytokines like IL-1, and it may be activated in response to TLR4 activation. Additional evidence for a role for TLR4 in psoriasis comes from the activation of the NLRP3 inflammasome. The NLRP3 inflammasome is a molecular complex that is essential for the generation of pro-inflammatory cytokines like IL-1, and it may be activated in response to TLR4 activation. Additional evidence for a role for TLR4 in psoriasis comes from the activation of the NLRP3 inflammasome (Swanson *et al*., 2019).

2.9.1.2 Distribution of TLR4

Endothelial cells, myocytes, thyroid cells, endometrial cells, mesangial cells, adipocytes, and fibroblasts are only few of the peripheral cell types that express TLR4 in addition to antigen-presenting cells. Expression may change in response to lipopolysaccharide (LPS) or pro-inflammatory cytokines. TLR4 expression is highest on CNS resident macrophages and microglial cells, with lower levels on astrocytes and other macroglial cells (Vaure & Liu, 2014). Not only are TLR4 expressed on primary sensory neurons, but also on CGRP and TRPV1-expressing

neurons (neurons that express the transient receptor potential cation channel subfamily V) (Wadachi & Hargreaves, 2006)

2.9.1. 3 Activation

Membrane microdomains rich in cholesterol and sphingomyelin are called lipid rafts, and TLR4 is known to reside there either constitutively or in response to ligand binding. To allow ligand binding at the TLR4 site and begin recruitment of intracellular TIR-adaptor molecules, TLR4 dimerizes with the co-receptor myeloid differentiation protein 2 (MD-2). Also located in lipid rafts and participating in some but not all TLR4 activation is cluster of differentiation 14 (CD14). TLR4 dimerization, the first step in its signaling cascade, is aided by the decreased diffusion rates seen in lipid rafts (Schmitz & Orsó, 2002; Triantafilou *et al*., 2011)

2.9.1.4 Signaling

When TLR4 is activated, it triggers two key intracellular signaling pathways: the TIR-domain containing adapter-inducing interferon (IFN-α)- (TRIF) route and the myeloid differentiation primary response 88 (MyD88)-dependent pathway. MyD88 and TIR domain-containing adaptor protein (TIRAP) mediate the MyD88-dependent pathway, which in turn induces NF-kB translocation and the expression of pro-inflammatory cytokines like tumor necrosis factor alpha (TNF-α), interleukin (IL)-1, IL-2, and interleukin (IL)-6, and type I IFN (INF) genes like TNF and IL-12 (Ma *et al*., 2018). Through IFN regulatory factor 3 (IRF-3), TRIF and the TRIF-related adaptor molecule (TRAM) activate type 1 IFN genes and delay NF-kB (Roy *et al*., 2016). Inflammatory cytokine and type 1 IFN production are kept in check by these pathways' coordinated activation and inhibition(Lu *et al*., 2008).

2.9.2 Toll-Like Receptors TLR-7

2.9.2.1 TLR-7 Definition

The pattern recognition receptor (PRR) known as Toll-like receptor 7 (TLR7) is essential to the body's innate immune defenses. It is a receptor in the Toll-like receptor family, which helps identify pathogens and sets off immune responses. TLR7 is adept at identifying virally generated single-stranded RNA molecules (D. Li & Wu, 2021).

Endosomes, which are subcellular structures, are where TLR7 is predominantly found. Nuclear factor kappa B (NF-B) and interferon regulatory factors are activated as part of a signaling cascade initiated by TLR7 upon recognition of viral RNA (IRFs). Many immune response mediators, including inflammatory cytokines and type I interferons, are produced in response to this activation (Vijay, 2018).

Dendritic cells, macrophages, and B cells are only a few of the cell types that express TLR7. The development of adaptive immune responses and the identification and elimination of viral infections depends on its activation. Autoimmune illnesses and persistent viral infections are only two examples of immune-related disorders linked to TLR7 dysfunction or dysregulation (Chang *et al*., 2006).

2.9.2.2 The Role of TLR 7 in Psoriasis

Psoriasis is an inflammatory skin ailment characterized by persistent inflammation and aberrant skin cell development, and Toll-like receptor 7 (TLR7) has been linked to the pathophysiology of the disease. TLR7's significance in psoriasis is currently being investigated, although preliminary findings show it may play a significant impact (Jeon *et al*., 2017).

Plasmacytoid dendritic cells (pDCs) are an immune cell type hypothesized to trigger the release of type I interferons (IFNs) and other pro-inflammatory cytokines upon activation through TLR7. Psoriasis' inflammatory response is aided by these immune mediators, which spur the growth of keratinocytes (skin cells) and draw in more immune cells to the sites of inflammation (Bencze *et al*., 2021).

Additionally, TLR7 activation may stimulate the production of various chemokines and cytokines that attract and activate immune cells, such as T cells and neutrophils, which are known to play a significant role in psoriasis pathogenesis. TLR7 signaling can also modulate the differentiation and function of regulatory T cells (Tregs), essential in maintaining immune tolerance and preventing excessive inflammation (Lowes *et al*., 2014).

Furthermore, studies have shown that certain genetic variations in the TLR7 gene may increase the susceptibility to psoriasis. These genetic variations can affect the expression and function of TLR7, potentially influencing the inflammatory response and disease development. While the specific role of TLR7 in psoriasis is still being explored, its activation and downstream immune responses appear to contribute to the chronic inflammation, altered immune cell function, and abnormal skin cell growth observed in psoriasis. Understanding the involvement of TLR7 in psoriasis pathogenesis may provide insights into potential therapeutic targets for the disease (Harden *et al*., 2015).

Chapter Three
Materials and Methods

Chapter Three
Materials and Methods

3.1 Patients

This study includes 90 participant subjects. Fifty of them were psoriasis (19 were male and 31 were female), and 40 subjects were control (people that were apparently healthy); the male was 14, and the female was 26. The age range of psoriasis patients was 36.62 ± 2.09 years, and the control was 34.37 ± 2.42 years that undergo the unit of Dermatology in the Hospital of Imam Al-Hussein City in Karbala province, Iraq during a period from December 2022 to April 2023. Psoriasis patients were diagnosed by dermatologist as psoriasis (the patients were newly diagnosed were taken in study.

3.1.1 Sample collection

A 5 ml of blood samples were withdrawn from each psoriasis patient and control subjects to determine the levels of IL17, IL-23, TLR-4, and TLR-7. Serum sample was collected and transported to another tube or to plane tube and freezes at -37^{0}C for used.

3.1.2 Inclusion and Exclusion Criteria

A) Inclusion Criteria

1. Healthy patients who underwent the clinical dermatology department
2. Patients who are newly diagnosed with psoriasis.
3. Patients who are not under any treatment.

B) Exclusion Criteria

1. Pregnant women
2. Patients with chronic diseases (celiac + autoimmune)
3. Patients who received treatment for psoriasis

3.1.3 Study Design and Sampling Technique

1. **Study Design:** Observational case-control study
2. **Sampling Technique:** Convenience Sampling

The methodology and sample collection are shown in the diagram below:

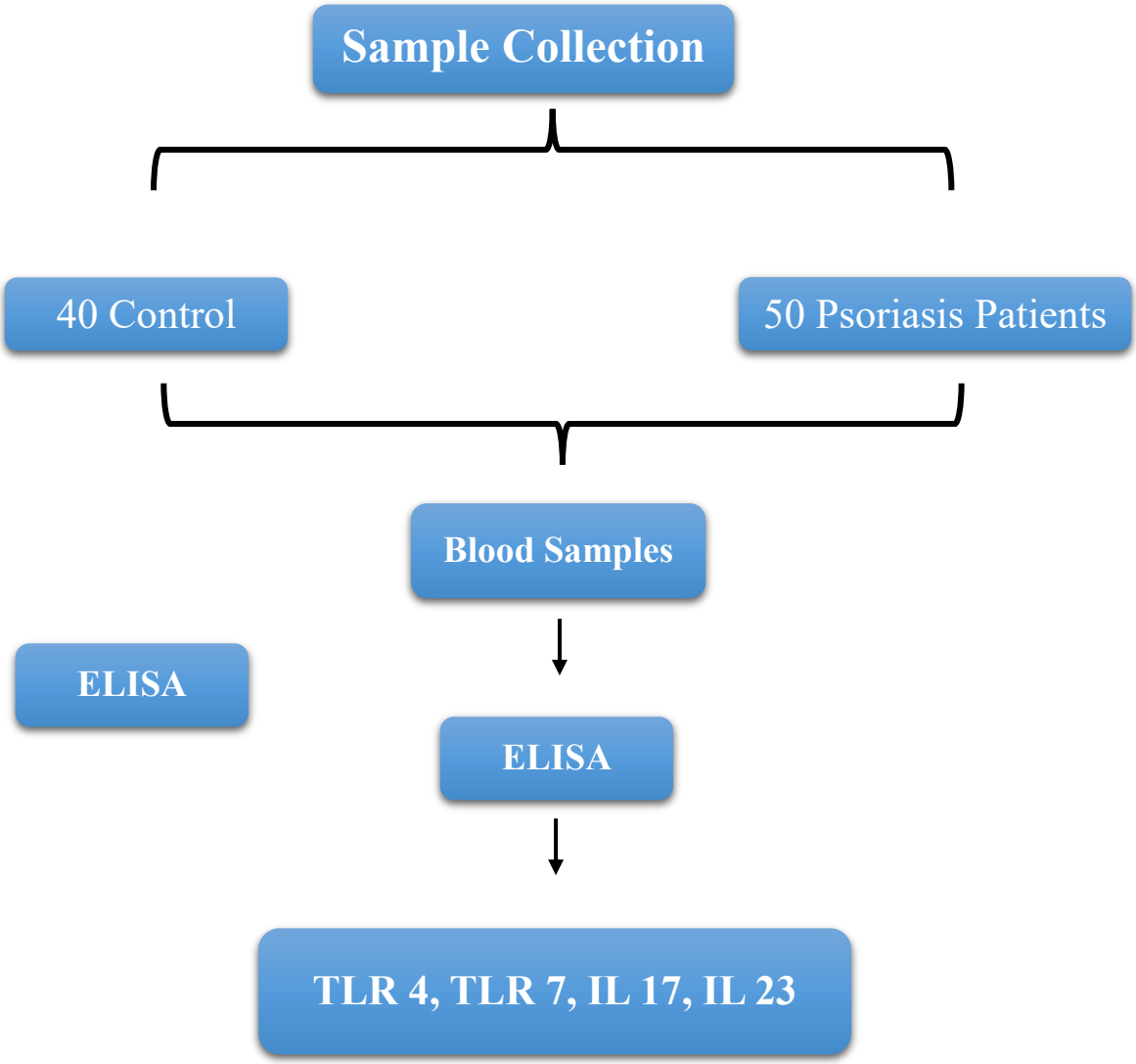

Figure (3.1): The Study Design

3.1.4 Score of psoriasis

The Psoriasis Area and Severity Index (PASI) scoring system assesses four body regions: the head (h), the upper extremities (u), the trunk (t) and the lower extremities (l) (Mattei *et al*., 2014).

Table (3.1): Erythema, scaling, and induration are graded in each region, and a combined score ranging from 0 to 72 is calculated as the psoriasis Area Severity Index (PASI) (Mattei *et al*., 2014)**.**

Body Area	Thickness 0-4	Scaling 0-4	Erythema 0-4	x Area 0-6	Total
Head	a	b	c	d (a+b+c) x 0.1	=A
Upper limbs	e	f	g	h (e + f + g) x 0.2	=B
Trunk	i	j	k	I (I + j + k) x 0.3	=C
Lower limbs	m	n	o	p (m + n + o)	=D
				PASI = A + B + C + D	
Severity 0 = none 1 = mild 2 = moderate 3 = severe 4 = very severe		Area 0 = no involvement 1 =0 <10% 2 = 10 < 30% 3 = 30 <50% 4 = 50 <70% 5 = 70 <90% 6 = 90 <1005		Axillae = upper limb Neck/ buttocks = trunk Genito-femoral = lower limb	

3.2 Materials

3.2.1 The Equipment

The laboratory equipment and instruments used in this study are listed in Table (3.2).

Table (3.2): Equipment and instruments

Equipment	Company	Origin
Bench centrifuge	Hettich	(Germany)
Deep freezer	GFL	(Germany)
Distillator (Water distiller)	GFL	(Germany)
EDTA tubes	AFCO	(Jordan)
ELISA instrument system	Biotek	(USA)
Micropipettes	Slammed	(Germany)
Micropipette tips	BIOBASIC	(Canada)
Micro titer plate reader– spectrophotometer	Human	(Germany)
Syringes	MEDECO	(UAE)
Vortex	Gemmy	(Taiwan)
Water bath	Memmert	(Germany)
IL-17 Kit	Cloud-clone corps	(USA)
IL-23 Kit	Elabscience	(USA)
TLR 4 Kit	Elabscience	(USA)
TLR 7 Kit	Cloud-clone corps	(USA)

3.3 Methods

3.3.1 Enzyme-Linked Immunosorbent Assay (ELISA)

The principle of the sandwich enzyme-linked immunosorbent assay (ELISA) technique has been widely recognized for its effectiveness in detecting antigens. It had offered higher sensitivity compared to direct binding assays, typically exhibiting 2 to 5 times greater sensitivity. (Mir *et al*., 2020)

In this technique, specific 'capture' antibodies were immobilized in the wells of microtiter plates. The plates were then incubated with test solutions containing the antigen of interest. Unbound antigens were subsequently washed away, and an enzyme-conjugated antibody that recognized a different antigen region (referred to as the 'developing reagent') was added, followed by another incubation step. Excess unconjugated antibody was washed out, and a substrate was introduced into the wells. Upon further incubation, the substrate underwent hydrolysis in the presence of the enzyme conjugate. The extent of substrate hydrolysis was indirectly proportional to the quantity of antigen present in the test solution (Sakamoto *et al*., 2018).

By employing this sandwich ELISA technique, researchers and diagnosticians can accurately detect and quantify specific antigens of interest, providing valuable insights into various scientific and medical applications.

3.3.2 Interleukin 17 (IL17) and Toll-Like-Receptor 7 (TLR-7)

3.3.2.1 Reagents and materials provided.

The materials of the interleukin 17 (IL 17) and Toll-Like-Receptor 7 (TLR-7) and reagents are shown in Table (3.3).

Table (3.3): The agents and their quantity for IL-17 and TLR 7.

Reagents	Quantity	Reagents	Quantity
Pre-coated, ready-to-use 96-well strip plate	1	Plate sealer for 96 wells	4
Standard	2	Standard Diluent	1×20mL
Detection Reagent A	1×120µL	Assay Diluent A	1×12mL
Detection Reagent B	1×120µL	Assay Diluent B	1×12mL
TMB Substrate	1×9mL	Stop Solution	1×6mL
Wash Buffer (30 × concentrate)	1×20mL	Instruction manual	1

3.3.2.2 Reagent Preparation

1. The kit components and samples had to be brought to room temperature (18-25°C) before use. If the kit was not fully utilized at once, only the necessary strips and reagents for the current experiment were removed while keeping the remaining ones and reagents in the required conditions.
2. Standard - The Standard had to be reconstituted by adding 1.0 mL of standard diluent. It was allowed to rest at room temperature for 10 minutes without agitation to prevent foaming. The concentration of the standard in the stock solution was 1,000 pg/mL. Seven tubes were prepared, each containing 0.5 mL of standard diluent, and a double dilution series was created as depicted in the diagram. Each tube was thoroughly mixed before transferring it to the next one. Seven points of diluted standard were established, including concentrations of 1,000 pg/mL, 500 pg/mL, 250 pg/mL, 125 pg/mL, 62.5 pg/mL, 31.2 pg/mL, and 15.6 pg/mL. The last Eppendorf (E.P.) tube containing Standard Diluent was the blank with a 0 pg/mL concentration, as shown in Figure (3.2).

3. Detection reagent A and detection reagent B - Before use, the stock detection reagents A and B were briefly spun or centrifuged. They were diluted 100-fold with assay diluents A and B, respectively, to achieve the working concentration.
4. Wash solution - 20 ml of the concentrated wash solution (30×) was diluted with 580 mL of deionized or distilled water to prepare 600 mL of the diluted Wash Solution (1×).
5. TMB substrate - Using sterilized tips, the required amount of the solution was aspirated, and any residual solution was avoided from being returned into the vial.

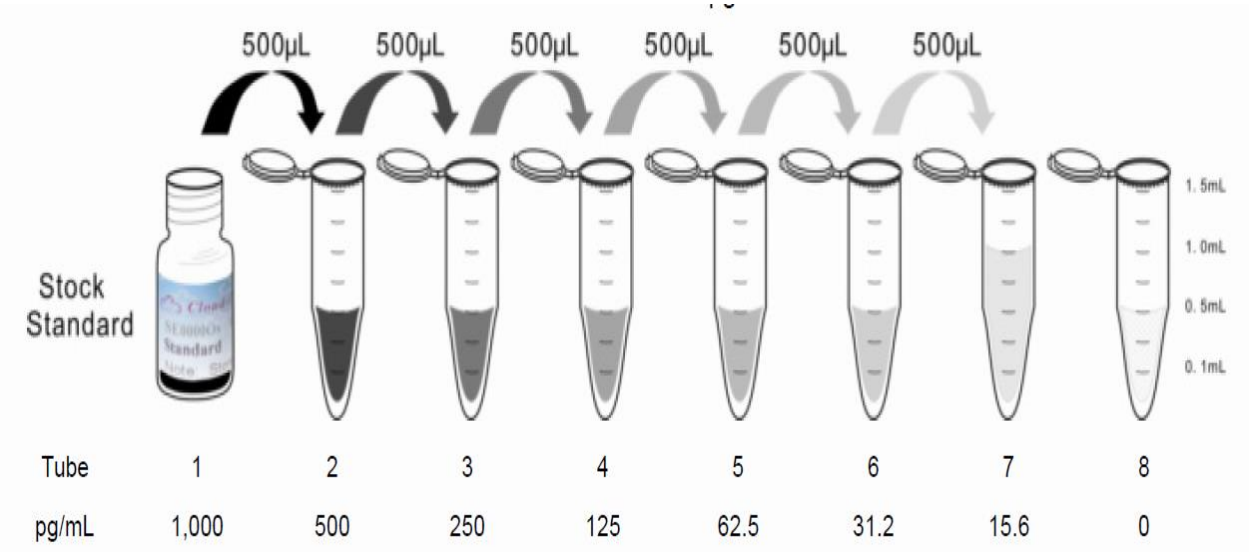

Figure (3.2): The E.P. tubes for Standard Diluent preparation of IL-17 and TLR-7

3.3.2.3 Sample Preparation

1. The samples' concentration had to be predicted before the assay. If the values fell outside the standard curve range, users had to determine the optimal dilutions of their samples for their specific experiments. The samples had to be diluted using PBS.

2. Due to the potential impact of certain chemicals, ELISA results could be affected unexpectedly when using tissue or cell extraction samples prepared with chemical lysis buffers.

3.3.2.4 Assay Procedure

1. Wells was allocated for the diluted standard, blank, and sample. A total of 7 wells were prepared for the standard dilutions, while one was designated for the blank. Each well received 100 µL of the respective standard dilutions, blank, and samples, following the instructions provided for reagent preparation. The plate was covered with a plate sealer and incubated at 37°C for 1 hour.
2. The liquid in each well was carefully removed without performing any washing steps.
3. Next, 100 µL of the working solution of detection reagent A was added to each well. The plate was covered with a plate sealer and incubated at 37°C for 1 hour.
4. The solution in each well was aspirated, and then 350 µL of 1× wash solution was added to each well using a squirt bottle, multi-channel pipette, manifold dispenser, or auto washer. The plate was left undisturbed for 1-2 minutes for proper washing. The remaining liquid was removed from all wells by gently tapping the plate onto absorbent paper. A total of 3 wash cycles were performed. After the final wash, any residual wash buffer was removed by aspirating or decanting the solution. The plate was inverted and gently tapped against absorbent paper to remove excess liquid.
5. Subsequently, 100 µL of the working solution of detection reagent B was added to each well. The plate was covered with a plate sealer and incubated at 37°C for 30 minutes.
6. The aspiration/wash process was repeated five times, following the steps described in Step 4.
7. Next, 90 µL of Substrate Solution was added to each well. The plate was covered with a new plate sealer and incubated at 37°C for 10-20 minutes (not exceeding 30

minutes). The plate was protected from light during this step. The addition of Substrate Solution resulted in the liquid turning blue.

8. Following the incubation, 50 µL of Stop Solution was added to each well. The addition of Stop Solution caused the liquid to turn yellow. The plate was gently tapped on the side to ensure thorough mixing if the color change appeared uneven.

3.3.2.5 Test Principle

The microplate included in the kit had been pre-coated with an antibody explicitly targeting IL17. Subsequently, standards or samples were introduced into the respective microplate wells along with a biotin-conjugated antibody specific to IL17. Following that, each microplate well received Avidin conjugated to Horseradish Peroxidase (HRP), which was allowed to incubate. Upon addition of the TMB substrate solution, only those wells containing IL17 and TLR-7, biotin-conjugated antibody, and enzyme-conjugated Avidin exhibited a noticeable color change. The enzyme-substrate reaction was halted by introducing a sulphuric acid solution, and the resulting color change was measured using a spectrophotometer at a wavelength of 450nm ± 10nm. By comparing the optical density (O.D.) of the samples to the standard curve, the concentration of IL17 within the samples could be determined.

3.3.2.6 Calculation of Results

The duplicate readings for each standard, control, and sample were averaged, and the average optical density (O.D.) of the zero standard was subtracted. A standard curve was constructed, with IL17 concentration plotted on the y-axis and absorbance on the x-axis. The points on the curve were fitted with a best-fit curve using regression analysis. If the samples had been diluted, the concentration obtained from the standard curve needed to be multiplied by the dilution factor.

To simplify the calculations, the O.D. value of the standard is plotted on the x-axis against the known concentration of the standard on the y-axis, even though the concentration is the independent variable and the O.D. value is the dependent

variable. However, worth noting that the O.D. values of the standard curve may vary due to factors such as assay conditions (e.g., operator, pipetting technique, washing technique, or temperature effects). Therefore, plotting the logarithm of the data was recommended to establish a standard curve for each test. The typical standard curve provided below in Figure 3.3 is for reference purposes only for IL-17 and TLR-7 in Figure (3.4).

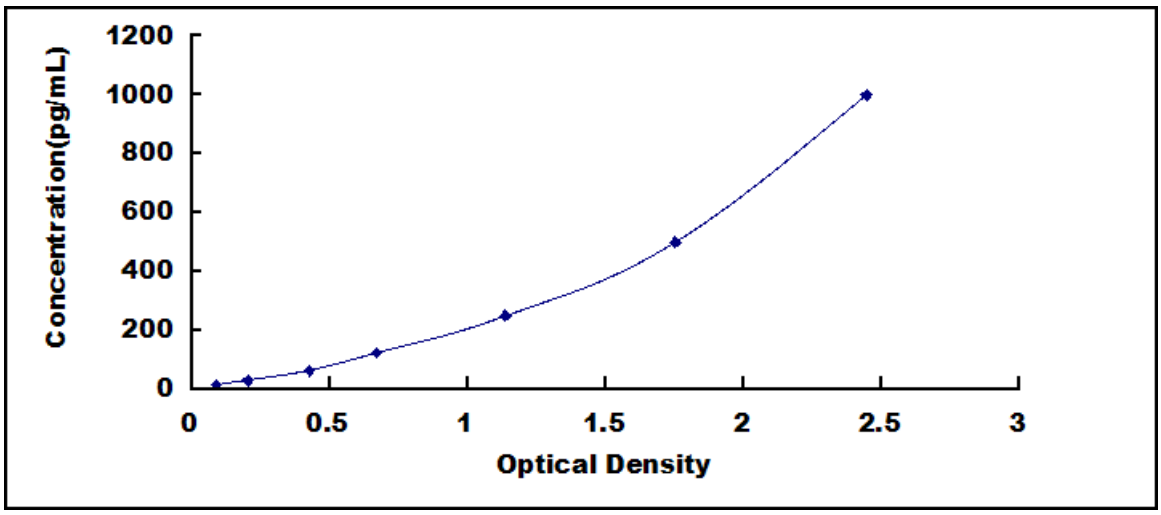

Figure (3.3): Typical Standard Curve for IL17, Human ELISA.

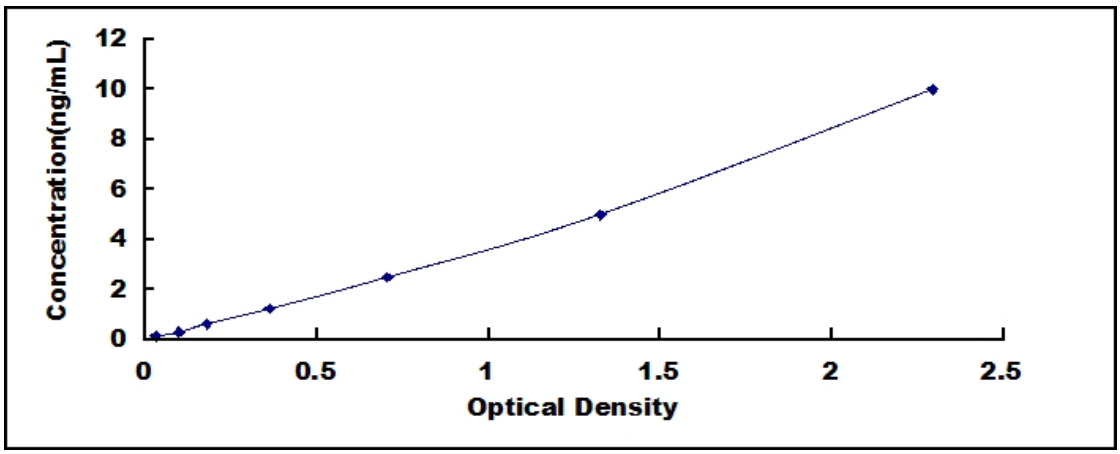

Figure (3.4): Typical Standard Curve for TLR-7, Human ELISA.

3.3.2.7 Detection Range

The IL-17 concentration detection range for the ELISA assay was 15.6-1,000 pg/mL. The standard curve concentrations utilized in the ELISA experiments included

concentrations of 1,000 pg/mL, 500 pg/mL, 250 pg/mL, 125 pg/mL, 62.5 pg/mL, 31.2 pg/mL, and 15.6 pg/mL.

The detection range of TLR-7 concentration in this ELISA assay was 0.156-10 ng/mL. The standard curve concentrations employed for the ELISA consisted of 10 ng/mL, 5 ng/mL, 2.5 ng/mL, 1.25 ng/mL, 0.625 ng/mL, 0.312 ng/mL, and 0.156 ng/mL.

3.3.3 Interleukin 23 (IL-23) and Toll-Like-Receptor 4 (TLR-4)

3.3.3.1 Test Principle

The ELISA kit employed the Sandwich-ELISA principle to detect Human IL-23 and TLR-4. The micro-ELISA plate provided in the kit had been pre-coated with an antibody specific to Human IL-23 and TLR-4. Samples or standards were added to the wells of the micro-ELISA plate, where they interacted with the specific antibody. Subsequently, a biotinylated detection antibody specific for Human IL-23 and TLR-4 and Avidin-Horseradish Peroxidase (HRP) conjugate were successively added to each well and incubated. Unbound components were washed away, and a substrate solution was added to the wells. Only those wells containing Human IL-23 and TLR-4, the biotinylated detection antibody, and the Avidin-HRP conjugate exhibited a blue color.

The enzyme-substrate reaction was terminated by adding a stop solution, resulting in a yellow color change. The samples' optical density (O.D.) was measured using a spectrophotometer at a wavelength of 450 nm ± 2 nm. The O.D. value was directly proportional to the concentration of Human IL-23 and TLR-4. By comparing the O.D. of the samples to the standard curve, the concentration of Human IL-23 in the samples could be calculated.

3.3.3.2 Reagent preparation

1. The reagents were brought to room temperature (18-25℃) before use. If the kit was not used entirely in one assay, only the necessary strips and reagents were removed for the current experiment. In contrast, the remaining strips and reagents were stored according to the required conditions.

2. To prepare the Wash Buffer, 30 mL of Concentrated Wash Buffer was diluted with 720 mL of deionized or distilled water, resulting in 750 mL of Wash Buffer. If crystals formed in the concentrate, it was gently warmed in a 40℃-water bath and mixed until the crystals dissolved.

3. The Standard working solution was prepared by centrifuging the standard at 10,000×g for 1 minute. Then, 1.0 mL of Reference Standard & Sample Diluent was added, and the mixture was allowed to stand for 10 minutes. After complete dissolution, the solution was thoroughly mixed with a pipette. This reconstitution step yielded a working solution with a 2500 pg/mL concentration. Alternatively, 1 mL of reference standard & sample diluent was added, the mixture was allowed to stand for 1-2 minutes, and then thoroughly mixed with a low-speed vortex meter to remove any bubbles generated during vortexing. Serial dilutions were made as needed, following the recommended dilution gradient: 2500, 1250, 625, 312.500, 156.250, 78.130, 39.06, 0 pg/mL. The dilution process involved adding 500 µL of Reference Standard & Sample Diluent to each of the 7 E.P. tubes and then transferring 500 µL of the working solution from the previous tube to the subsequent tube. The last tube was blank and was not filled with the solution of the prior tube. The gradient diluted standard working solution was prepared just before use. This procedure of IL-23 and TLR-4 is shown in Figure (3.5)

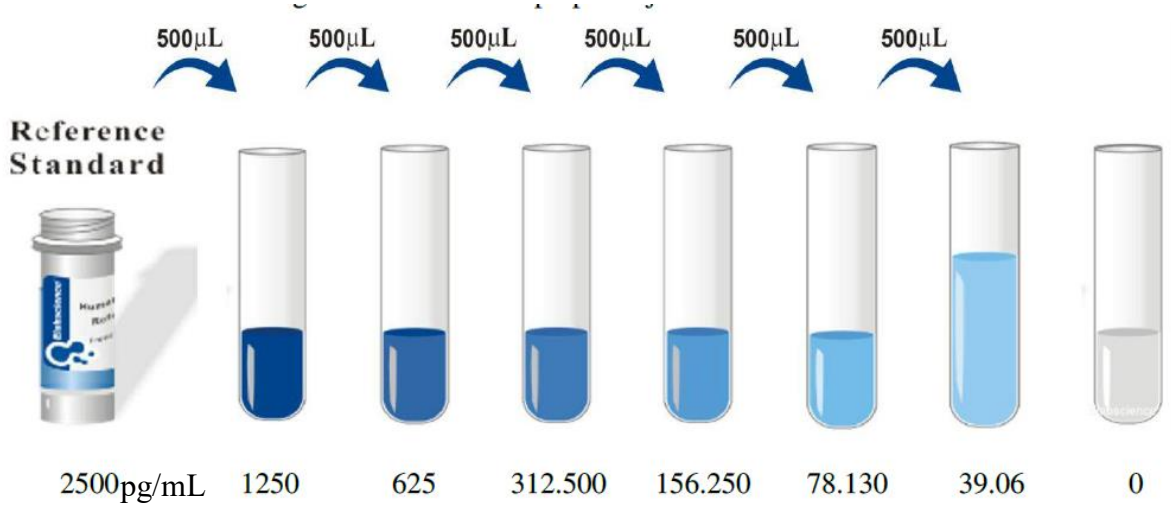

Figure (3.5): The E.P. tubes for Standard Diluent preparation of IL-23 and TLR-4.

4. The Biotinylated Detection Ab working solution was prepared by calculating the required amount for the experiment (100 µL/well). A slightly more significant amount than estimated was prepared. The Concentrated Biotinylated Detection Ab was centrifuged at 800×g for 1 minute and then diluted with Biotinylated Detection Ab Diluent to obtain a 1× working solution (Concentrated Biotinylated Detection Ab: Biotinylated Detection Ab Diluent = 1:99). The working solution was prepared just before use.

5. The Concentrated HRP Conjugate working solution, an HRP conjugated avidin, was prepared by calculating the required amount for the experiment (100 µL/well). A slightly more significant amount than estimated was prepared. The Concentrated HRP Conjugate was centrifuged at 800×g for 1 minute and then diluted with HRP Conjugate Diluent to obtain a 1× working solution (Concentrated HRP Conjugate: HRP Conjugate Diluent = 1:99). The working solution was prepared just before use.

3.3.3.3 Assay Procedure

1. The appropriate wells for diluted standard, blank, and sample were determined. Then, 100 µL of each standard, blank, and sample dilution were added to their

respective wells. It was recommended to assay all samples and standards in duplicate. The plate was covered with the provided sealer and incubated for 90 minutes at 37°C. Care was taken to add the solutions to the bottom of the micro-ELISA plate wells, avoiding contact with the inside wall to minimize foaming.

2. The liquid was decanted from each well without washing. Immediately after, 100 µL of Biotinylated Detection Ab working solution was added to each well. The plate was covered with a new sealer and incubated for 1 hour at 37°C.

3. The solution was decanted from each well, and 350 µL of wash buffer was added to each well. The plate was soaked for 1 minute, and then the solution was aspirated or decanted from each well, followed by gently patting the plate dry against clean absorbent paper. This wash step was repeated three times. Note: A microplate washer could be used for this and subsequent wash steps. The tested strips were used immediately after the wash step, ensuring that the wells did not dry out.

4. Each well was added to 100 µL of HRP Conjugate working solution. The plate was covered with a new sealer and incubated for 30 minutes at 37°C.

5. The solution was decanted from each well, and the wash process was repeated five times, as performed in step 3.

6. Ninty microliter (90 µL) of Substrate Reagent was added to each well. The plate was covered with a new sealer and incubated for approximately 15 minutes at 37°C while protecting it from light. It was noted that the reaction time could be adjusted based on the observed color change, but it should not exceed 30 minutes. The Microplate Reader was preheated for approximately 15 minutes before measuring the optical density (O.D.).

7. Fifty microliters (50 µL) of Stop Solution was added to each well, ensuring the stop solution was added in the same order as the substrate solution.

8. Each well's optical density (O.D. value) was determined at 450 nm using a microplate reader, measuring all wells simultaneously.

3.3.3.4 Range Detection

The ELISA assays for IL-23 and TLR-4 have specific detection ranges and sensitivities. For IL-23, the detection range spans from 39.06 to 2500 pg/mL, with a sensitivity as low as 23.44 pg/mL. The concentrations used for the standard curve were 31.25, 62.5, 125, 250, 500, 1000, and 2000 pg/mL. On the other hand, the TLR-4 assay has a detection range of 31.25 to 2000 pg/mL, with a sensitivity of 18.75 pg/mL.

The standard curve concentrations employed for TLR-4 were 39.06, 78.130, 156.250, 312.500, 625, 1250, and 2500 pg/mL. These ranges and sensitivities accurately quantify IL-23 and TLR-4 concentrations in samples, providing valuable information for various study and diagnostic applications.

3.3.3.5 Calculation of results

The duplicate readings for each standard and sample were averaged, and the average zero standard optical density was subtracted. A four-parameter logistic curve was plotted on a logarithmic scale, with the standard concentration on the x-axis and the O.D. values on the y-axis. If a sample's O.D. value exceeded the standard curve's upper limit, it was retested using an appropriate dilution. The actual concentration was calculated by multiplying the computed concentration by the dilution factor.

Since the O.D. values of the standard curve could vary depending on various assay conditions (such as the operator, pipetting technique, washing technique, or temperature effects), it was recommended for the operator to establish a standard curve for each test. A typical standard curve and data were provided in Figure (3.6) for IL-23 and Figure (3.7) for TLR-4 for reference purposes only.

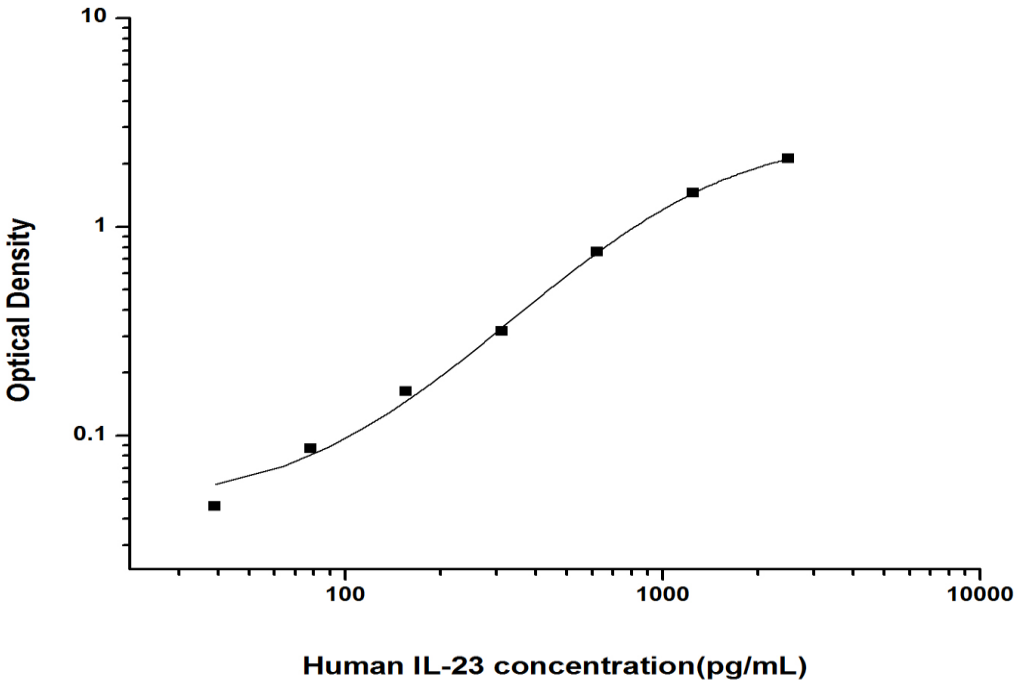

Figure (3.6): Typical Standard Curve for IL23, Human ELISA.

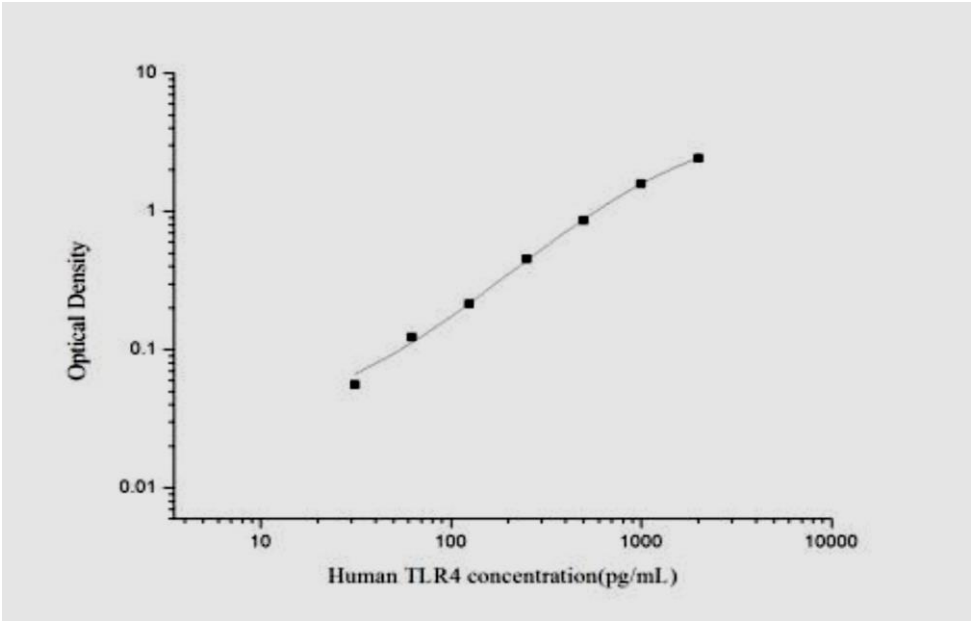

Figure (3.7): Typical Standard Curve for TLR-4, Human ELISA.

3.4 Statistical Analysis

The collected data was analyzed using the Statistical Packages for Social Sciences-version 28 (SPSS-28). The data were summarized using various descriptive measures, including percentages, means, standard deviations, and ranges (minimum-maximum values). Statistical tests such as the student's t-test were employed for independent means to determine the significance of differences in means for quantitative data. In contrast, the Paired t-test was utilized for paired observations or dependent means. For qualitative data, the chi-square test was used. Spearman's rank correlation coefficient (Spearman rho) was calculated to examine the correlation between variables. The scattering distribution curve was employed to visualize the correlation pattern. In assessing statistical significance, a p-value equal to or less than 0.05 was considered the threshold. This comprehensive statistical analysis allowed for exploring relationships, comparisons between groups, and identifying significant findings, providing a rigorous and evidence-based interpretation of the data (Moore *et al*., 2021).

Chapter Four

Results and Discussion

4.1 Demography

Table 4.1 provides an overview of the age distribution and gender composition among control subjects and patients with psoriasis. The table includes mean age values with standard deviations (Age: Control = 34.37 ± 2.42, Psoriasis =36.62 ± 2.09), gender distribution with counts and percentages, and associated p-values.

For age distribution, the mean age of control subjects is 34.37 years with a standard deviation of 2.42, while psoriasis patients have a mean age of 36.62 years with a standard deviation of 2.09. The p-value associated with the age distribution (0.850) indicates that there is no statistically significant difference in age between the control and psoriasis groups, as the p-value is greater than the significance threshold of 0.05.

The age distribution shows that In the control group, 14 individuals (35.0%) are male, and 26 individuals (65.0%) are female. In the psoriasis group, 19 individuals (38.0%) are male, and 31 individuals (62.0%) are female. The p-values associated with the gender distribution between control and psoriasis groups are 0.058 for males and 0.090 for females. While the p-value for males is slightly below the conventional significance level of 0.05, it is important to note that p-values close to 0.05 may indicate a trend but do not necessarily imply a strong statistical significance. The overall Comparison shows that p-value (0.850) mentioned at the end of the table likely pertains to an overall comparison or summary statistic related to age distribution.

Table (4.1): Age distribution of control subjects and psoriasis patients.

		Control	Psoriasis	*p*-value
Age		34.37 ± 2.42	36.62 ± 2.09	0.850
sex	Male	14 (35.0%)	19 (38.0%)	0.058
	Female	26 (65.0%)	31 (62.0%)	0.090
		p-value	0.850	
*** Independent T-Test is significant at the 0.05 level**				

The information states there were no significant difference between the mean age of psoriasis patients and the control. This implies that the age difference between the two groups was not statistically significant despite the higher mean age in the psoriasis patients. The age range of the control subjects was broader than that of the psoriasis patients. This means that the control group included individuals of a broader range of ages than the psoriasis patients, who likely fell within a narrower age range.

This study, a recruited control from a more extensive age range to ensure that all age groups were well represented. This more excellent age range in the control group may have resulted in a broader age distribution compared to the psoriasis patients. The selection criteria for people with psoriasis and control participants may have affected the age distribution. Due to the study's intention to include only newly diagnosed patients, the age range of psoriasis patients may be shorter than that of control people. In general, psoriasis were a chronic skin disorder that grows and persists over time. This might result in a more significant proportion of elderly psoriasis patients compared to the control. The size of the study's sample might affect the observed disparities in age distribution. A bigger sample size might offer a more precise depiction of the population's age distribution.

Psoriasis often begins before age 40, with around one-third of instances appearing before the age of 20 years, as mentioned by (Parisi *et al*., 2013). Griffiths

& Barker, 2007) and (Kampe *et al*., 2022; Neimann *et al*., 2006) found that type I psoriasis is most significant before age 40, accounting for roughly 75% of all psoriasis cases. Although psoriasis may manifest at any age, most patients appear before the age of 35 years (Thomas, 2012).

Although psoriasis may occur at any age, it is far less common in children than adults. Age at the beginning seems to display two peaks: one between 30 and 39 years and another between 50 and 69 years (Parisi *et al*., 2013). In addition, the average age of onset for Japanese patients is almost 39 years older than the worldwide norm (Kawada *et al*., 2003). In the United States, psoriasis is known to occur at various ages, with the typical age of onset for the first occurrence lying between 15 and 20 years (Langley *et al*., 2005).

Studies showed that psoriasis may occur throughout a person's lifespan, with a higher prevalence in some age groups, particularly before age 40 and throughout the early and middle adult years. Understanding the age range of psoriasis onset assists healthcare practitioners in developing age-specific diagnostic, therapeutic, and management techniques (Thomas *et al*., 2012).

Variables such as the demography of the study population, the prevalence of psoriasis, and the overall distribution of the sexes in the study population, may account for these data. Multiple variables, including the demographics of the community from which study participants were recruited, might impact the sex distribution of a study. It was possible that the fact that in this study was performed in an area or region with a larger number of females contributed to a higher frequency and percentage of females in both the control and psoriasis patient groups.

Results recognized that psoriasis affects both men and females. Its incidence might vary between patients with psoriasis and control. The prevalence of psoriasis in similar study population is comparable across males and females, and there may be a similar number of males and female psoriasis patients. The inclusion and exclusion criteria for participant selection were not impacted by sex.

Psoriasis has a significant global prevalence, impacting roughly 125 million people globally. The illness is prevalent in the Caucasian population, with men and women being equally affected (Langley *et al*., 2005). In addition, the prevalence of psoriasis in the general population is between 2% and 3% and is evenly divided across men and women (Duarte *et al*., 2012). In addition, Thomas *et al*. underlined that psoriasis affects both sexes equally (Thomas *et al*., 2012).

Abbas *et al*. (O. Abbas *et al*., 2013) reported that the patient cohort consisted of 36 females (51.4% of the total) and 34 males (48.6% of the total), resulting in a female-to-male ratio of 1:1. (Dogra & Yadav, 2010) investigation confirmed the continuous male-to-female ratio found among psoriasis patients. In addition, several studies in Western countries have consistently shown no significant Sex differences in the incidence of psoriasis among patients.

a study in 2022, conducted by Carole Guillet *et al.* agreed with this study. Their primary purpose was to examine possible sex-dependent variations in the presentation of psoriasis among patients. This investigation aimed to determine whether there were differences in the incidence, prevalence, and clinical symptoms of psoriasis on the skin between persons of different sexes. The studies used a rigorous technique that included enrolling a broad sample of male and female psoriasis patients. Various sources, including medical records, clinical exams, and patient self-reports, were used to obtain data. The incidence and prevalence of psoriasis did not vary significantly between men and females, according to the study's conclusions, which were based on a thorough examination of the collected data. Both sexes were equally susceptible to getting skin diseases. In addition, the cutaneous manifestations and clinical aspects of psoriasis were the same in male and female patients. These results show that, in this particular investigation, Sex did not substantially alter the skin-related elements of psoriasis (Guillet *et al*., 2022).

4.2 BMI Classification

The classification of body mass index (BMI Kg/m^2) is as follows: Below 18.5 is classified as Underweight, 18.5 – 24.9 was classified as healthy weight, 25.0 – 29.9 is classified as overweight, and 30.0 and above is classified as Obesity (Nuttall, 2015; Pengpid & Peltzer, 2021). The results of BMI in this study were shown in table (3.2). The BMI analysis shows a highly significant difference between the classifications underweight, healthy weight, overweight, and obesity for control and psoriasis patients. For control, it was shown that 58.82% of them were obese, 23.53% of them were overweight, 8.82% of them were healthy, and the same percentage were underweighted.

Table (4.2): Body mass index (BMI Kg/m^2) of control subjects and psoriasis patients.

Groups	Classifications	Mean	Standard Deviation	Minimum	Maximum	*p*-value
Control	**Underweight**	17.8383	0.06033	17.78	17.96	<0.001*
	Healthy Weight	20.3030	0.60718	19.10	21.05	
	Overweight	28.0864	0.51638	25.00	29.30	
	Obesity	34.8533	1.02718	30.04	49.03	
Psoriasis	**Underweight**	17.3292	0.48003	15.42	17.96	<0.001*
	Healthy Weight	22.9075	0.39035	19.10	24.61	
	Overweight	27.0825	.25721	25.26	29.30	
	Obesity	35.4755	1.43207	30.04	49.03	
*One-way ANOVA test at a significant difference level of ≤0.05.						

Thirty four percent were obese among psoriasis patients, 30% of them were overweight, 26% of them were healthy, and 10% of them were underweight. No significant difference was reported between the BMI of control subjects and psoriasis patients at *p*–value 0.955.

The BMI data analysis revealed a very significant difference between the BMI classes (underweight, healthy weight, overweight, and obesity) for both control and psoriasis patients. This suggested that the distribution of BMI categories varied

significantly between the two groups. Despite the considerable variation in BMI category distribution, statistical analysis revealed no significant difference in BMI between control and psoriasis patients. In other words, the average BMI of controls and psoriasis patients didn't vary considerably.

The absence of a statistically significant difference in average BMI between control participants and psoriasis patients shows that, on average, both groups had comparable body weight features. Even though the percentage distribution of BMI categories varied between the two groups, the total BMI values did not change substantially. The lack of a statistically significant difference in average BMI does not always indicate that BMI is unrelated to psoriasis. Additional study and analysis may be required to investigate possible links between BMI and psoriasis.

Consistent with a 2017 study by Sobhan *et al*., data supported the hypothesis that overweight, and obesity were more frequent among persons with different skin disorders, including psoriasis, than healthy ones. Their study aimed to examine the possible relationship between obesity and psoriasis severity. The study analyzed the body mass index (BMI), waist circumference, age, and sex of psoriasis patients classified as mild, moderate, or severe. Comparing the mean values of BMI, waist circumference, age, and sex across patients with mild, moderate, and severe psoriasis did not indicate any statistically significant differences. These results suggested that these specific factors did not display major differences between psoriasis severity levels (Sobhan & Farshchian, 2017).

4.3 Severity of Psoriasis

The statistical analysis indicated a significant variation in disease severity among psoriasis patients, with the majority (54.44%) exhibiting moderate symptoms and the remainder (45.56%) displaying severe signs. Despite this disparity in illness severity distribution, the study revealed a statistically significant difference between

the two groups (p = 0.0461). These results had important implications for comprehending the severity range of psoriasis in afflicted people. The substantially more significant proportion of moderate instances highlighted the prevalence of milder symptoms, which may had significant consequences for patient management and treatment strategies. On the other hand, severe instances necessitate heightened vigilance since patients with more severe symptoms may need more intense and specialist treatment.

Analyzing several variables that may have contributed to this result was crucial. A bigger sample size might gave more solid insights into the illness severity distribution. In addition, the psoriasis patients variety of psoriasis symptoms complicates the categorization of individuals into various severity categories, resulting in the possibility of overlapping symptomatology.

In addition, the absence of statistical significance does not undermine the clinical importance of the observed heterogeneity in illness severity. It is essential to recognize the possible effect of other variables on psoriasis severity, including genetic predisposition, environmental triggers, lifestyle, and treatment history. Unaccounted-for confounding factors may have contributed to the reported results (van Acht *et al*., 2022).

4.4 Comparison of Moderate and Severe Psoriasis

The age range of psoriasis patients is divided into five age groups for moderate and severe cases, as illustrated in table (4.3). These groups were divided into 2-15 years, 16-25 years, 26-35 years, 36-51 years, and Above 51 years. A significant difference was found between the moderate and severe psoriasis patients for all groups. There was a significant difference between the psoriasis severity groups for total psoriasis patients (moderate and severe). From observation, the severe psoriasis patients were older than moderate in the age groups of 16 -25 years and 36 – 51

years, while the moderate psoriasis patients were older than severe in the age groups of 2 – 15 years, 26 - 36 years, and above 51 years.

Table (4.3): Age group distribution of psoriasis patients

Age groups	Patients	N	Mean± SD	*p*-value
2-15 year	**Moderate**	2	13.50 ± 0.50	NA
	Sever	1	13	
16-25 year	**Moderate**	5	18.40 ± 1.12	0.13845
	Sever	7	21.14 ± 1.28	
26-35 year	**Moderate**	3	30.00 ± 2.08	0.230698
	Sever	3	27.00 ± 0.12	
36-51 year	**Moderate**	10	44.50 ± 1.42	0.788874
	Sever	14	45.00 ± 1.16	
Above 51 years	**Moderate**	3	63.33 ± 5.66	0.423887
	Sever	2	57.50 ± 2.50	
Total	**Moderate**	23	36.69 ± 3.45	< 0.001*
	Sever	27	36.55 ± 2.58	
*** Independent T-Test is significant at the 0.05 level** **NA: Non- Available statistically.**				

The socio-demographic characteristics of psoriasis patients were distributed according to the disease severity and presented in table (4.4). The moderate patients were more than the severe psoriasis patients. The moderate percentage is higher than the severe patients. The severe patients were older than moderate with no significant difference. The moderate psoriasis patients had a higher minimum and maximum age than the severe psoriasis patients.

The body mass index comparison between the severe and moderate psoriasis patients classified according to obesity into underweight, healthy weight, overweight, and obese. It was shown that the psoriasis patients with severe symptoms had a significantly higher BMI than those with moderate symptoms.

Table (4.4): Socio-demographic characteristics of moderate and severe psoriasis patients.

Socio-demographic Characteristics		Moderate	Severe	*p*-value
Sex	**Male**	9	10	0.879192
	Female	14	17	
BMI	**Underweight**	17.23 ± 1.21	17.72	<0.001*
	Healthy Weight	23.78 ± 0.56	22.47 ± 1.66	
	Overweight	27.34 ± 1.17	26.85 ± 0.95	
	Obesity	33.73 ± 3.90	36.96 ± 5.91	
	Total	26.47 ± 6.01	27.51 ± 6.95	
*** Independent T-Test is significant at the 0.05 level**				

This study showed that the age differences between people with severe and mild psoriasis may be attributable to genetic predisposition, lifestyle decisions, and environmental variables. Also, the severity of psoriasis may change with age, which may explain the age-related discrepancies (Alexis & Blackcloud, 2014; Kamiya *et al*., 2019).

The higher BMI in individuals with severe psoriasis might be attributable to several variables. Due to their illness, people with severe psoriasis may engage in less physical activity, leading to weight gain. In addition, obesity and severe psoriasis may share some risk factors (Armstrong *et al*., 2012).

The study by Li *et al*. is to compare the clinical features of two groups of Chinese psoriasis patients who differed mainly by their BMI (BMI). The study includes a comprehensive data review from 208 people diagnosed with psoriasis. Patients who are overweight or obese are placed in one group, while those with a healthy weight were placed in another. Also, compared to psoriasis patients with normal BMI levels (p>0.05), those with overweight or obesity had a significantly

greater incidence of comorbidities such as fatty liver, hyperlipidemia, hyperuricemia, and impaired liver function. Using linear regression analysis, the authors found a clear correlation between PASI scores and body mass index (*p*=0.016). This statistical evidence highlights the connection between psoriasis severity and increased body mass index. Patients with psoriasis who are overweight or obese are at a higher risk for acquiring metabolic comorbidities and have psoriatic lesions that are more severe on average. Therefore, it is inferred that a thorough assessment of patients' body mass index (BMI) is necessary for those with psoriasis. People who are overweight or obese and have psoriasis may need to lose weight or use other weight management strategies to reduce their risk of metabolic problems. These results add much to our understanding of how psoriasis, body mass index, and health outcomes are interconnected(Li *et al*., 2023).

This study indicates that the increased incidence of smoking among psoriasis patients with severe psoriasis may be attributable to the fact that smoking is a risk factor for psoriasis and may aggravate the illness. Individuals with severe psoriasis may be more likely to engage in harmful behaviors like smoking.

The scholarly reviewed by Naldi explores the complex relationship between smoking and various health conditions, highlighting the role of genetic, environmental, and social factors. The main addictive component in tobacco, nicotine, is responsible for the habit-forming nature of tobacco products. Smoking is a significant risk factor for various diseases, including cardiovascular ailments, respiratory disorders, cancer, and global mortality. The review also highlights the association between smoking and immune-related inflammatory conditions, such as psoriasis. Smoking influences the onset of psoriasis, with a higher risk for smokers consuming 1-14 cigarettes per day and more for those consuming 25 or more. Smoking also affects the clinical severity of psoriasis and its treatment responsiveness and contributes to comorbidities like cardiovascular disease, inflammatory bowel disease, and various cancers. The review explores potential

pathophysiological mechanisms underlying the association between psoriasis and smoking, including oxidative stress, interactions with signaling pathways, and vascular influences (Naldi, 2016).

In this study, the increased stress experienced by individuals with severe psoriasis may result from the psychological load of managing a more severe and possibly debilitating skin disease. Stress was a recognized cause of psoriasis flare-ups so it may aggravate the severity of the illness in certain instances.

An agreement is found with this study is conducted by Tribó *et al*., 2019. According to the studies conducted by Tribó *et al.,* 2019, psoriasis is more than just an annoying skin illness; it's also associated with severe psychological and physiological complications. The role of stress and emotional disturbances in developing and exacerbating psoriasis has come into focus. A total of 300 people with psoriasis are evaluated to see if there was an association between the severity of the condition and their levels of stress and mood changes. Validated questionnaires that assessed things like stress and emotional state. The effect that psoriasis has on the lives of those who have it was also measured in this study. The results of this study revealed a correlation between the severity of psoriasis and emotional distress and negative impacts on participants' quality of life ratings. The severity of the disease was found to be directly correlated with the increased risk of depression as measured by several essential depression assessment tools, including the Montgomery-Asberg Depression Rating Scale, the Hamilton Rating Scale, and the Hospital Anxiety and Depression Scale for Depression. The relevance of the correlation between depressive symptoms, anxious states, self-perceived stress, and psoriasis severity cannot be overstated. It highlights the need to consider patients' mental health when developing a care plan for psoriasis. To improve the well-being and results of people dealing with psoriasis, it is crucial to identify and treat the psychological elements of the illness (Tribó *et al*., 2019).

In this study, psoriasis may influence patients' healthy habits and food choices; for example, those with severe psoriasis may consume more processed foods. People with severe psoriasis may react to their illness or manage stress by making poor food choices.

The study by Garbicz *et al*. focused on psoriasis, a chronic inflammatory skin condition with multiple etiological factors, including dietary considerations. The study suggests that dietary modifications can improve a patient's quality of life by reducing skin lesions and mitigating the risk of concurrent health issues. One recommendation is a low-energy diet for overweight patients, which can help manage psoriasis symptoms. The study also emphasizes the importance of dietary fat composition, suggesting a reduction in saturated fatty acids and a preference for polyunsaturated fatty acids from the omega-3 family. Other study also recommended the inclusion of antioxidants like vitamin A, vitamin C, vitamin E, carotenoids, flavonoids, and selenium in diet therapy. Vitamin D supplementation is also recommended, as it affects immune regulation. The study also explores alternative dietary approaches, such as gluten-free, vegetarian, and Mediterranean diets, which could positively impact psoriasis treatment (Garbicz *et al*., 2022).

Kanda *et al*.'s reviewed focuses on psoriasis, a persistent inflammatory skin condition with comorbidities like obesity, diabetes, dyslipidemia, cardiovascular disorders, and inflammatory bowel diseases. Psoriasis patients often have dietary imbalances, with increased fat consumption and reduced fish and dietary fiber intake. Nutrition plays a crucial role in psoriasis development and progression. Consumption of saturated fatty acids, simple sugars, red meat, and alcohol can exacerbate psoriasis by activating pathways involved in inflammation. Conversely, certain nutrients and dietary elements, such as n-3 polyunsaturated fatty acids, vitamin D, vitamin B12, short-chain fatty acids, selenium, genistein, dietary fibers, and probiotics, can mitigate psoriasis by suppressing inflammatory pathways or promoting regulatory T

cell induction. Imbalances in gut microbiota and vitamin D and selenium deficiencies further contribute to psoriasis progression (Kanda *et al*., 2020b).

Muzumdar and Rothe literature reviewed examine the use of nutrition and dietary supplements in psoriasis management. While these interventions are widely used, their effectiveness is not uniformly conclusive. The review indicated that caloric restriction, particularly in overweight or obese individuals, has a consistent positive impact on reducing psoriatic activity. The evidence surrounding other dietary supplements and interventions was less clear and lacks consistency. The review emphasizes the need for more extensive, extended study studies to establish a more comprehensive understanding of how dietary interventions can effectively manage psoriasis and alleviate symptoms. While caloric restriction shows promise, further study is needed to understand nutrition's role in psoriasis management better and potentially offer alternatives to pharmaceutical treatments (Muzumdar & Rothe, 2022).

4.5 Immune Markers

This work is essential to evaluating immune markers, notably IL-17, and IL-23, TLR-4, and TLR-7. Table (4.5) displays the comparative study of these characteristics between the control group and psoriasis patients. All the immune markers were within the normal range.

These results suggest that these immune marker variables may play a role in the etiology of psoriasis. The greater levels reported in individuals with psoriasis may reflect their role in disease genesis and progression. The determine of higher IL-17, and IL-23, TLR-4, and TLR-7 levels in psoriasis patients are relative to healthy controls implies that these proteins may serve as disease biomarkers. In addition, these findings provide light on the immunological systems and genetic factors that contribute to psoriasis.

In this research, an examination of immune marker variables found that psoriasis patients had substantially elevated levels of IL-17, and IL-23, TLR-4, and TLR-7 compared to healthy controls (p – values= <0.001, 0.003, <0.001, <0.001, respectively). These results add to the expanding body of information about the immunopathogenesis of psoriasis. More study is required to define the exact functions of these immune marker markers and their interactions in psoriasis to further our knowledge and treatment of this complicated illness.

Table (4.5): Comparison between control subjects and psoriasis patients for TLR 7, TLR 4, IL 17, and IL 23.

Markers	Groups	Mean	Std. Deviation	*p*-value
TLR-4	Control	233.7154	35.71082	<0.001*
	Psoriasis	647.5158	139.30081	
TLR-7	Control	1.4736	0.24200	0.003*
	Psoriasis	3.3694	0.62321	
IL17	Control	178.8261	38.17535	<0.001*
	Psoriasis	510.4492	128.29269	
IL23	Control	344.2801	52.64646	<0.001*
	Psoriasis	764.7995	130.29179	
*** Independent T-Test is significant at the 0.05 level**				

The results of this study support the hypothesis that IL-23 plays an essential role in the onset of psoriasis and is connected with the activation of innate immunity. The blood levels of IL-23 in psoriasis patients and controls have produced contradictory findings in prior study, indicating that IL-23 may have a localized impact on psoriatic lesions (Campanati *et al*., 2021).

The elevated levels of IL-17, and IL-23, TLR-4, and TLR-7 in psoriasis patients imply that these biomarkers may have a role in the etiology of the illness.

These higher levels may reflect their role in the origin and evolution of psoriasis, suggesting that they are possible biomarkers for the disease.

The findings of this study demonstrate a significant elevation in the levels of IL-17, IL-23, TLR-4, and TLR-7 in psoriasis patients compared to healthy controls. This investigation has the potential to advance our comprehension of the immunopathogenesis of psoriasis, thereby guiding the development of personalized therapeutic interventions.

The comparative study between the control and psoriasis patients of moderate and severe diseases for immune markers IL-17, and IL-23, TLR-4, and TLR-7 are shown in tables (4.6), (4.7), (4.8), and (4.9), respectively. The analysis showed a highly significant difference in the levels of immune markers (IL-17, and IL-23, TLR-4, and TLR-7) between the control and psoriasis patients of moderate and severe psoriasis patients. The control always showed a lower level, while the levels increased in moderate, and higher levels were shown in severe psoriasis patients.

Table 4.6 presents the IL-17 levels among control subjects and psoriasis patients categorized into moderate and severe groups. The data include the number of participants (N), the mean IL-17 levels with standard deviation (Mean ± SD), and the associated p-values.

In the control group, the IL-17 levels were observed to be 178.82 ± 6.03. A statistically significant difference was found when comparing the control group to both the moderate psoriasis group (506.16 ± 31.52, $p < 0.001$*) and the severe psoriasis group (514.09 ± 20.77, $p < 0.001$*). This indicates a substantial increase in IL-17 levels in both moderate and severe psoriasis patients compared to the control group.

These results suggest a potential correlation between IL-17 levels and the severity of psoriasis, highlighting the immunological alterations associated with this skin disorder. The statistical significance, as denoted by the low p-values,

underscores the robustness of the observed differences in IL-17 levels across the study groups.

Table 4.7 provides an overview of IL-23 levels in control subjects and psoriasis patients stratified into moderate and severe categories. In the control group, the mean IL-23 level was 344.28 ± 8.32. A statistically significant difference was observed when comparing the control group to both the moderate psoriasis group (753.12 ± 24.36, $p < 0.001$*) and the severe psoriasis group (778.51 ± 28.36, $p < 0.001$*). These results indicate a substantial elevation in IL-23 levels in both moderate and severe psoriasis patients in comparison to the control group.

The findings suggest a potential association between IL-23 levels and the severity of psoriasis, underscoring the immunological variations inherent in this dermatological condition. The significance of the observed differences is highlighted by the low p-values, emphasizing the statistical robustness of the detected variations in IL-23 levels across the studied cohorts.

Table 4.8 presents the TLR-4 levels in control individuals and patients with psoriasis. In the control group, the mean TLR-4 level was 233.71 ± 5.64. A statistically significant difference was observed when comparing the control group to both the moderate psoriasis group (647.03 ± 37.02, $p < 0.001$*) and the severe psoriasis group (657.93 ± 19.13, $p < 0.001$*). These findings indicate a notable increase in TLR-4 levels in both moderate and severe psoriasis patients in comparison to the control group.

The results suggest a potential correlation between TLR-4 levels and the severity of psoriasis, highlighting the immunological alterations associated with this skin disorder. The statistical significance, as indicated by the low p-values, underscores the robustness of the observed differences in TLR-4 levels across the study groups.

Table 4.9 illustrates the TLR-7 levels. In the control group, the mean TLR-7 level was 1.47 ± 0.03. A statistically significant difference was observed when

comparing the control group to both the moderate psoriasis group (3.35 ± 0.11, $p < 0.001$*) and the severe psoriasis group (3.38 ± 0.13, $p < 0.001$*). These results indicate a substantial elevation in TLR-7 levels in both moderate and severe psoriasis patients compared to the control group. The findings suggest a potential association between TLR-7 levels and the severity of psoriasis, emphasizing the immunological variations inherent in this dermatological condition. The statistical significance, as indicated by the low p-values, underscores the robustness of the observed differences in TLR-7 levels across the study groups.

Table (4.6): The IL-17 levels for control, moderate, and severe psoriasis patients.

		N	Mean ± SD	*p*-value
IL 17	Control	40	178.82 ± 6.03	<0.001*
	Moderate Psoriasis	23	506.16 ± 31.52	
	Severe Psoriasis	27	514.09 ± 20.77	

Table (4.7): The IL-23 levels for control, moderate, and severe psoriasis patients.

		N	Mean	*p*-value
IL 23	Control	40	344.28 ± 8.32	<0.001*
	Moderate Psoriasis	23	753.12 ± 24.36	
	Severe Psoriasis	27	778.51 ± 28.36	

Table (4.8): The TLR-4 levels for control, moderate, and severe psoriasis patients.

		N	Mean ± SD	*p*-value
TLR 4	Control	40	233.71 ± 5.64	<0.001*
	Moderate Psoriasis	23	647.03 ± 37.02	
	Severe Psoriasis	27	657.93 ± 19.13	

Table (4.9): The TLR-7 levels for control, moderate, and severe psoriasis patients.

		N	Mean	*p*-value
TLR 7	Control	40	1.47 ± 0.03	<0.001*
	Moderate Psoriasis	23	3.35 ± 0.11	
	Severe Psoriasis	27	3.38 ± 0.13	

This study shows a significant difference in the levels of immunological markers (IL-17, and IL-23, TLR-4, and TLR-7) between control people and psoriasis patients, exceptionally moderate and severe. Consistently lower levels of these immunological markers in control people compared to psoriasis patients, particularly those with severe psoriasis, are consistent with the psoriasis was characterized by dysregulated immune responses and chronic inflammation.

Interleukin-17 (IL-17) and interleukin-23 (IL-23) are pro-inflammatory cytokines directly connected with psoriasis etiology. IL-23 has a role in the development and maintenance of IL-17-producing Th17 cells. In psoriasis, both IL-17 and IL-23 contribute to the inflammatory cascade. Prior study has repeatedly shown higher levels of IL-17 and IL-23 in psoriatic lesions and the circulation of psoriasis patients, providing support for the present results (Hawkes *et al*., 2018; Menter *et al*., 2021).

TLR-4 and TLR-7 are essential components of the innate immune system, involved in recognizing pathogen-associated molecular patterns (PAMPs) and the induction of immune responses. TLR 4 and TLR 7 recognize some pathogens, such as bacteria and viruses. These receptors are often hyperactive in psoriasis, increasing immune response. This data is consistent with prior study demonstrating elevated TLR 4 and TLR 7 activation in psoriatic lesions, contributing to psoriasis-specific chronic inflammation (Georgescu *et al*., 2019).

TLRs were crucial innate immune system components, functioning as receptors for pattern recognition that identify microbial components and activate immunological responses. According to a previous study, TLR7 and TLR4 activation may contribute to the chronic inflammatory process found in psoriasis. This theory is supported by the fact that people living with psoriasis have greater blood levels of TLR7 and TLR4 than healthy controls. This data implies that these receptors may play a role in the identification of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) present in psoriatic lesions, resulting in an abnormal immune response (Janeway & Medzhitov, 2002; Janssens & Beyaert, 2003; Kawai & Akira, 2011; Takeuchi & Akira, 2010).

In addition, the study offerd evidence that the overexpression of TLR7 and TLR4 in individuals with psoriasis may stimulate the production of pro-inflammatory cytokines and chemokines. TLR activation in the skin may induce the generation of cytokines, including IL-17, IL-23, and TNF-, which are known to play crucial roles in the pathogenesis of psoriasis. These cytokines' elevated levels lead to the growth of keratinocytes, the recruitment of immune cells, and the creation of psoriatic plaques. In addition, the interaction between TLRs and cytokines may generate a positive feedback loop that sustains the inflammatory response and contributes to the chronicity of illness (Fitch *et al*., 2007; Lee & Moon, 2023).

The results of this study also align with a previous study by (Smith *et al*., 2016), suggesting that TLR7 and TLR4 signaling may be involved in the development and progression of psoriasis. Other studies have reported the presence of TLR7 and TLR4 in psoriatic skin lesions, indicating their localization and potential roles in psoriasis immunopathogenesis. The higher serum levels of these TLRs in psoriasis patients support the hypothesis that systemic immune dysregulation involving TLR activation may contribute to the disease's widespread manifestations (Bacharewicz *et al*., 2014; Chen *et al*., 2013; L. Sun *et al*., 2019).

This study's findings have significant clinical implications. Targeting the TLR7 and TLR4 pathways may constitute a unique strategy for treating psoriasis. By regulating TLR signaling, reducing disease severity and symptomatology may be feasible by attenuating the pro-inflammatory response (El-Zayat *et al*., 2019; Lai *et al*., 2017; Santos-Sierra, 2021).

Hassoon *et al.* indicated the blood levels of IL-17 in psoriasis patients and their possible association with disease severity (Hassoon *et al*., 2014). According to the study of Oliveira *et al*., Th17 cells and their accompanying cytokines, notably IL-17, play a crucial role in the pathogenesis of psoriasis (Oliveira *et al*., 2015). In prior local investigations done in Iraq and Egypt, IL-17A levels in psoriasis patients were shown to be considerably greater than in healthy controls (A. Abbas *et al*., 2015; Abdel-Mawla *et al*., 2013; Sabri *et al*., 2015). A study by (Kampe *et al*., 2022) indicated that blood levels of IL-17 were associated with the severity of psoriasis, indicating its role in promoting the inflammatory response.

The high expression of IL-17 in psoriatic lesions showed that it plays a crucial role in fostering an inflammatory milieu. IL-17 induces the overexpression of pro-inflammatory mediators, including IL-6, IL-8, and ICAM-1 in keratinocytes, allowing lymphocyte infiltration inside the epidermis and attracting neutrophils through chemokine induction. Notably, psoriasis is distinguished by a mixed Th1 and Th17 inflammatory response, with both T cell subsets capable of generating illness independently. Th17 seems to be the primary regulator of psoriasis inflammation, especially in terms of promoting epidermal activation (Afzali *et al*., 2007)

(Johansen *et al*., 2009) Stated that IL-17A is prominently prevalent in psoriasis-affected skin, with much greater concentrations compared to non-psoriatic skin, according to several studies. A researcher (Arican *et al*., 2005) reported that the increased levels of IL-17A in the skin have also been connected to the severity of psoriasis symptoms. Other researchers such as (Chiricozzi *et al*., 2011; Martin *et al*.,

2013; Nestle *et al*., 2009) have shown that IL-17A engages in a feedback loop, signaling to skin cells and the immune system, which eventually contributes to the psoriasis symptoms.

Interest in Th17 cells gained momentum when psoriasis patients were found to have elevated circulating Th17 cells and increased cutaneous Th17 cells in lesional skin compared to non-lesional skin (Lowes *et al*., 2008; Zhang *et al*., 2009). Th17 cells are primarily responsible for producing IL-17A and IL-17F, and their dysregulation is associated with autoimmune and inflammatory conditions (Housseau *et al*., 2014; Miossec *et al*., 2009) . Psoriatic plaques have been found to contain a higher number of Th17 cells (Harper *et al*., 2009). Additionally, other T cell populations, such as CD8+ cells, have been implicated in IL-17A production within psoriatic lesions, further emphasizing the intricate involvement of various immune cell subsets in the disease process (Benham *et al*., 2013; Dowlatshahi *et al*., 2013; Res *et al*., 2010).

The present study were consistent with previous study (Nickoloff *et al*., 2000; Singh *et al*., 2017; Yen *et al*., 2006), which also reported increased IL-17 levels in psoriasis patients.

Following these results, the current investigation revealed that considerably greater IL-23 levels in early psoriatic lesions, suggesting its possible role in the earliest stages of psoriasis development. Earlier studies on the blood levels of IL-23 in psoriasis patients and healthy controls yielded contradictory findings. Some investigations found no significant changes in IL-23 blood levels between psoriasis patients and healthy controls, suggesting that IL-23 may be engaged exclusively in the lesion skin or the first stages of psoriasis development (Takahashi *et al*., 2010; Takahashi & Yamasaki, 2020).

The investigation of the function of IL-23 in psoriasis, specifically its potential as an early mediator in the production of psoriatic lesions and its role in boosting

innate immunity (El-Hadidi *et al*., 2014). Multiple studies have presents higher IL-23 expression in psoriatic lesions, both at the level of mRNA and in terms of overproduction by dermal dendritic cells and keratinocytes (Gordon *et al*., 2015; Mosca *et al*., 2021; Res *et al*., 2010) . In addition, several cell types, including Th-17, CD8+ T, and natural killer T cells, have been identified as producing IL-23 (K. Eyerich *et al*., 2009; S. Eyerich *et al*., 2009)

Intriguingly, psoriasis medication, including conventional and biologic systemic therapies, had been linked to IL-23 downregulation in psoriatic patients (Di Cesare *et al*., 2009; Di Meglio *et al*., 2014; Johnson-Huang *et al*., 2012).

4.6 Correlation of immune markers with socio-demographic characteristics

Table 4.10 outlines the correlation between immune markers and socio-demographic characteristics, including age, sex, severity of psoriasis, and BMI classification. The table includes indicates the significance levels of correlation coefficients (Spearman's rho)

The IL-17 shows that there is a statistically significant positive correlation between IL-17 levels and age (p – value = 0.0275*) and severity of psoriasis (p – value = 0.0085*). Additionally, there is a negative correlation with BMI classification (p – value = 0.0141*).

The IL-23 levels show a statistically significant positive correlation with severity of psoriasis (p – value = 0.0433*) and BMI classification (p – value = 0.037*).

TLR-4 levels exhibit a statistically significant positive correlation with age (p – value = 0.612), sex (p – value = 0.0066*), severity of psoriasis (p – value = 0.0199*), and BMI classification (p – value = 0.007*).

TLR-7 levels display a statistically significant positive correlation with age (p – value = 0.904) and sex (p – value = 0.0083*). There is no significant correlation

with severity of psoriasis, while a significant negative correlation is observed with BMI classification (p – value = 0.002*).

The results suggest intricate associations between immune markers and socio-demographic factors in psoriasis patients. Notably, IL-17 and IL-23 levels correlate with both the severity of psoriasis and BMI classification. TLR-4 and TLR-7 levels exhibit correlations with age, sex, severity of psoriasis, and BMI classification, indicating potential links between these immune markers and the examined socio-demographic characteristics in the context of psoriasis.

Table (4.10): Correlation of immune markers with socio-demographic characteristics

Markers	Age	Sex	Severity	BMI Classification
IL-17	0.0275*	0.898	0.0085*	0.0141*
IL-23	0.903	0.964	0.0433*	0.037*
TLR-4	0.612	0.0066*	0.0199*	0.007*
TLR-7	0.904	0.0083*	0.170	0.002*
* Spearman's rho Correlation is significant at the 0.05 level				

Given the literature on the role of these indicators in the etiology of psoriasis, the absence of significant associations between the majority of immune marker markers and socio-demographic variables. According to previous study, IL-17, IL-23, TLR-4, and TLR-7 were crucial in the inflammatory processes that cause psoriasis (Bacharewicz *et al*., 2014; Boutet *et al*., 2018). In addition, socio-demographic characteristics, such as age, sex, and lifestyle behaviors, have been associated with differences in disease severity response in psoriasis patients. As a result, the primary hypothesised of the study was that specific immune markers may demonstrate associations with certain socio-demographic factors (Petito *et al*., 2020).

The intricacy of psoriasis as a multifaceted illness is a possible reason for the absence of meaningful connections. Genetic, environmental, and immune factors impact psoriasis. The interplay of these variables may result in distinct individual illness presentations, making it difficult to establish definite connections with particular biomarkers. In the setting of complex genetic and environmental interactions, the sample size of the study may have affected its statistical ability to find significant relationships (Alshobaili *et al*., 2010; Griffiths & Barker, 2007; Raharja *et al*., 2021).

An exception to the absence of correlations was detecting a substantial link between BMI and TLR-4 and TLR-7. These results were good because it implies a possible association between body mass index and the expression of these immune markers in psoriasis patients. Previous studies agreed with our findings (Alshobaili *et al*., 2010; Fatani *et al*., 2002; Sun *et al*., 2010), which indicated obesity as a risk factor for the onset and progression of psoriasis. Due to obesity-induced chronic low-grade inflammation, Adipose tissue may generate pro-inflammatory cytokines, such as IL-17 and IL-23. This study suggested the relatioship between BMI and TLR-4 and TLR-7 may provide more light on the relationship between obesity, immunological dysregulation, and the pathogenesis of psoriasis.

Conclusions & Recommendations

Conclusion

This comprehensive inquiry delved into diverse facets of psoriasis, encompassing demographic characteristics, lifestyle parameters, and immune markers. Several salient observations emerged from the investigation:

1. The prevalence of psoriasis was notably higher among patients relative to control participants, and no statistically significant disparities were discerned in mean age, gender distribution, or BMI categories between the two cohorts.

2. Noteworthy was the absence of a significant distinction in the severity of psoriasis symptoms between moderate and severe cases. Immunomarker variables, namely IL-17, IL-23, TLR-4, and TLR-7, emerged as potential candidates for biomarkers indicative of psoriasis disease. These immune markers are conjectured to play a pivotal role in modulating the impact of socio-demographic factors on psoriasis. Patients with psoriasis exhibited markedly elevated levels of immunological markers (IL-17, IL-23, TLR-4, TLR-7) in severe cases, followed by moderate cases, in comparison to their healthy counterparts.

Recommendation

1. Investigate and study the psoriasis in children and pregnant women .
2. Study the genetic mutation of IL-17 among patient with psoriasis .
3. Investigate and study a role of IL-12 in patient with psoriasis .

References

Ababneh, M., Al Ayed, M. Y., Robert, A. A., Al Dawish, M. A., Abboud, H., Labreuche, J., Arauz, A., Bryer, A., Lavados, P. G. M., Massaro, A., Collazos, M. M., Steg, P. G., Yamout, B. I., Vicaut, E., Amarenco, P., Munoz Collazos, M., Steg, P. G., Yamout, B. I., Vicaut, E., … Qasim, A. N. (2020). Peripheral arterial disease, primary care management in a Spanish health centre. *Atherosclerosis*, *12*(1).

Abbas, A., Gregersen, I., Holm, S., Daissormont, I., Bjerkeli, V., Krohg-Sørensen, K., Skagen, K. R., Dahl, T. B., Russell, D., Almås, T., Bundgaard, D., Alteheld, L. H., Rashidi, A., Dahl, C. P., Michelsen, A. E., Biessen, E. A., Aukrust, P., Halvorsen, B., & Skjelland, M. (2015). Sinterleukin 23 levels are increased in carotid atherosclerosis possible role for the interleukin 23/interleukin 17 axis. *Stroke*, *46*(3). https://doi.org/10.1161/STROKEAHA.114.006516

Abbas, O., Itani, S., Ghosn, S., Kibbi, A. G., Fidawi, G., Farooq, M., Shimomura, Y., & Kurban, M. (2013). Acrodermatitis continua of hallopeau is a clinical phenotype of DITRA: Evidence that it is a variant of pustular psoriasis. *Dermatology*, *226*(1). https://doi.org/10.1159/000346572

Abdel-Mawla, M. Y., Abulmajd, Y., Soliman, M., Amer, A., & Nasr, M. (2013). Serum Interleukin (IL)-17 in Psoriasis. *Journal of American Science*, *9*(12), 229–232.

Abrams, J. R., Kelley, S. L., Hayes, E., Kikuchi, T., Brown, M. J., Kang, S., Lebwohl, M. G., Guzzo, C. A., Jegasothy, B. V., Linsley, P. S., & Krueger, J. G. (2000). Blockade of T lymphocyte costimulation with cytotoxic T lymphocyte-associated antigen 4-immunoglobulin (CTLA4Ig) reverses the cellular pathology of psoriatic plaques, including the activation of keratinocytes, dendritic cells, and endothelial cells. *Journal of Experimental Medicine*, *192*(5). https://doi.org/10.1084/jem.192.5.681

Afzali, B., Lombardi, G., Lechler, R. I., & Lord, G. M. (2007). The role of T helper 17 (Th17) and regulatory T cells (Treg) in human organ transplantation and autoimmune disease. In *Clinical and Experimental Immunology* (Vol. 148, Issue 1). https://doi.org/10.1111/j.1365-2249.2007.03356.x

Ahlehoff, O., Gislason, G. H., Charlot, M., Jørgensen, C. H., Lindhardsen, J., Olesen, J. B., Abildstrøm, S. Z., Skov, L., Torp-Pedersen, C., & Hansen, P. R. (2011). Psoriasis is associated with clinically significant cardiovascular risk: A Danish nationwide cohort study. *Journal of Internal Medicine*, *270*(2). https://doi.org/10.1111/j.1365-2796.2010.02310.x

Ainali, C., Valeyev, N., Perera, G., Williams, A., Gudjonsson, J. E., Ouzounis, C. A., Nestle, F. O., & Tsoka, S. (2012). Transcriptome classification reveals molecular subtypes in psoriasis. *BMC Genomics*, *13*(1). https://doi.org/10.1186/1471-2164-13-472

Alexis, A. F., & Blackcloud, P. (2014). Psoriasis in skin of color: Epidemiology, genetics, clinical presentation, and treatment nuances. *Journal of Clinical and Aesthetic Dermatology*, *7*(11).

Alshobaili, H. A., Shahzad, M., Al-Marshood, A., Khalil, A., Settin, A., & Barrimah, I. (2010). Genetic background of psoriasis. *International Journal of Health Sciences*, *4*(1).

Álvarez-Mon, M. A., Gómez-Lahoz, A. M., Orozco, A., Lahera, G., Diaz, D., Ortega, M. A., Albillos, A., Quintero, J., Aubá, E., Monserrat, J., & Álvarez-Mon, M. (2021). Expansion of CD4 T lymphocytes expressing interleukin 17 and tumor necrosis factor in patients with major depressive disorder. *Journal of Personalized Medicine*, *11*(3). https://doi.org/10.3390/jpm11030220

Alwan, W., & Nestle, F. O. (2015). Pathogenesis and treatment of psoriasis: Exploiting pathophysiological pathways for precision medicine. *Clinical and Experimental Rheumatology*, *33*.

Anand, S., Gupta, P., Bhardwaj, R., Narang, T., Dogra, S., Minz, R. W., Saikia, B., & Chhabra, S. (2017). Is psoriasis an autoimmune disease? Interpretations from an immunofluorescence-based study. *Journal of Cutaneous Pathology*, *44*(4). https://doi.org/10.1111/cup.12891

Anandarajah, A. P., & Ritchlin, C. T. (2009). The diagnosis and treatment of early psoriatic arthritis. In *Nature Reviews Rheumatology* (Vol. 5, Issue 11). https://doi.org/10.1038/nrrheum.2009.210

Anonymous. (2012). Research Symposium Rheumatology and Dermatology 2011. *Zeitschrift Fur Rheumatologie*, *71*(SUPPL. 1).

Arakawa, A., Siewert, K., Stöhr, J., Besgen, P., Kim, S. M., Rühl, G., Nickel, J., Vollmer, S., Thomas, P., Krebs, S., Pinkert, S., Spannagl, M., Held, K., Kammerbauer, C., Besch, R., Dornmair, K., & Prinz, J. C. (2015). Melanocyte antigen triggers autoimmunity in human psoriasis. *Journal of Experimental Medicine*, *212*(13). https://doi.org/10.1084/jem.20151093

Arican, O., Murat, A., Sezai, S., & Pinar, C. (2005). Serum levels of TNF-alpha, IFN-gamma, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. *Mediators of Inflammation*, *2005*(5), 273–279.

Armstrong, A. W., Harskamp, C. T., & Armstrong, E. J. (2012). The association between psoriasis and obesity: A systematic review and meta-

analysis of observational studies. In *Nutrition and Diabetes* (Vol. 2, Issue DECEMBER). https://doi.org/10.1038/nutd.2012.26

Armstrong, A. W., & Read, C. (2020). Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review. In *JAMA - Journal of the American Medical Association* (Vol. 323, Issue 19). https://doi.org/10.1001/jama.2020.4006

Ayala, F. (2007). Clinical presentation of psoriasis. *Reumatismo*, *59*(SUPPL. 1). https://doi.org/10.4081/reumatismo.2007.1s.40

Bacharewicz, J., Reduta, T., & Flisiak, I. (2014). The role of Toll-like receptors in skin diseases. *Dermatology Review*, *4*. https://doi.org/10.5114/dr.2014.45126

Backel, K., & Cain, C. (2017). Skin as a marker of general feline health: Cutaneous manifestations of infectious disease. In *Journal of Feline Medicine and Surgery* (Vol. 19, Issue 11). https://doi.org/10.1177/1098612X17735764

Bastos, K. R. B., De Moraes, L. D. D. V., Zago, C. A., Marinho, C. R. F., Russo, M., Alvarez, J. M. M., & Lima, M. R. D. I. (2005). Analysis of the activation profile of dendritic cells derived from the bone marrow of interleukin-12/interleukin-23-deficient mice. *Immunology*, *114*(4). https://doi.org/10.1111/j.1365-2567.2005.02118.x

Batista, M. D., Ho, E. L., Kuebler, P. J., Milush, J. M., Lanier, L. L., Kallas, E. G., York, V. A., Chang, D., Liao, W., Unemori, P., Leslie, K. S., Maurer, T., & Nixon, D. F. (2013). Skewed distribution of natural killer cells in psoriasis skin lesions. In *Experimental Dermatology* (Vol. 22, Issue 1). https://doi.org/10.1111/exd.12060

Belladonna, M. L., Renauld, J.-C., Bianchi, R., Vacca, C., Fallarino, F., Orabona, C., Fioretti, M. C., Grohmann, U., & Puccetti, P. (2002). IL-23 and IL-12 Have Overlapping, but Distinct, Effects on Murine Dendritic Cells. *The Journal of Immunology*, *168*(11). https://doi.org/10.4049/jimmunol.168.11.5448

Ben Abdallah, H., Johansen, C., & Iversen, L. (2021). Key Signaling Pathways in Psoriasis: Recent Insights from Antipsoriatic Therapeutics. *Psoriasis: Targets and Therapy*, *Volume 11*. https://doi.org/10.2147/ptt.s294173

Bencze, D., Fekete, T., & Pázmándi, K. (2021). Type i interferon production of plasmacytoid dendritic cells under control. In *International Journal of Molecular Sciences* (Vol. 22, Issue 8). https://doi.org/10.3390/ijms22084190

Benhadou, F., Glitzner, E., Brisebarre, A., Swedlund, B., Song, Y., Dubois, C., Rozzi, M., Paulissen, C., del Marmol, V., Sibilia, M., & Blanpain, C.

(2020). Epidermal autonomous VEGFA/Flt1/Nrp1 functions mediate psoriasis-like disease. *Science Advances*, *6*(2). https://doi.org/10.1126/sciadv.aax5849

Benhadou, F., Mintoff, D., Schnebert, B., & Thio, H. (2018). Psoriasis and Microbiota: A Systematic Review. *Diseases*, *6*(2). https://doi.org/10.3390/diseases6020047

Benhadou, F., Mintoff, Di., & Del Marmol, V. (2019). Psoriasis: Keratinocytes or Immune Cells - Which Is the Trigger? In *Dermatology* (Vol. 235, Issue 2). https://doi.org/10.1159/000495291

Benham, H., Norris, P., Goodall, J., Wechalekar, M. D., FitzGerald, O., Szentpetery, A., Smith, M., Thomas, R., & Gaston, H. (2013). Th17 and Th22 cells in psoriatic arthritis and psoriasis. *Arthritis Research and Therapy*, *15*(5). https://doi.org/10.1186/ar4317

Bettoni, I., Comelli, F., Rossini, C., Granucci, F., Giagnoni, G., Peri, F., & Costa, B. (2008). Glial TLR4 receptor as new target to treat neuropathic pain: Efficacy of a new receptor antagonist in a model of peripheral nerve injury in mice. *GLIA*, *56*(12). https://doi.org/10.1002/glia.20699

Beurel, E., Harrington, L. E., & Jope, R. S. (2013). Inflammatory T helper 17 cells promote depression-like behavior in mice. *Biological Psychiatry*, *73*(7). https://doi.org/10.1016/j.biopsych.2012.09.021

Beyer, B. M., Ingram, R., Ramanathan, L., Reichert, P., Le, H. V., Madison, V., & Orth, P. (2008). Crystal Structures of the Pro-Inflammatory Cytokine Interleukin-23 and Its Complex with a High-Affinity Neutralizing Antibody. *Journal of Molecular Biology*, *382*(4). https://doi.org/10.1016/j.jmb.2008.08.001

Blauvelt, A. (2007). New concepts in the pathogenesis and treatment of psoriasis: Key roles for IL-23, IL-17A and TGF-β1. *Expert Review of Dermatology*, *2*(1). https://doi.org/10.1586/17469872.2.1.69

Blauvelt, A. (2008). T-helper 17 cells in psoriatic plaques and additional genetic links between IL-23 and psoriasis. In *Journal of Investigative Dermatology* (Vol. 128, Issue 5). https://doi.org/10.1038/jid.2008.85

Boutet, M. A., Nerviani, A., Gallo Afflitto, G., & Pitzalis, C. (2018). Role of the IL-23/IL-17 axis in psoriasis and psoriatic arthritis: The clinical importance of its divergence in skin and joints. In *International Journal of Molecular Sciences* (Vol. 19, Issue 2). https://doi.org/10.3390/ijms19020530

Brembilla, N. C., Senra, L., & Boehncke, W. H. (2018). The IL-17 family of cytokines in psoriasis: IL-17A and beyond. In *Frontiers in Immunology* (Vol. 9, Issue AUG). https://doi.org/10.3389/fimmu.2018.01682

Bruno, K., Woller, S. A., Miller, Y. I., Yaksh, T. L., Wallace, M., Beaton, G., & Chakravarthy, K. (2018). Targeting toll-like receptor-4 (TLR4)-an emerging therapeutic target for persistent pain states. In *Pain* (Vol. 159, Issue 10). https://doi.org/10.1097/j.pain.0000000000001306

Campanati, A., Marani, A., Martina, E., Diotallevi, F., Radi, G., & Offidani, A. (2021). Psoriasis as an immune-mediated and inflammatory systemic disease: From pathophysiology to novel therapeutic approaches. In *Biomedicines* (Vol. 9, Issue 11). https://doi.org/10.3390/biomedicines9111511

Cauli, A., Piga, M., Floris, A., & Mathieu, A. (2015). Current perspective on the role of the interleukin-23/interleukin-17 axis in inflammation and disease (chronic arthritis and psoriasis). *ImmunoTargets and Therapy*. https://doi.org/10.2147/itt.s62870

Chandran, V., & Raychaudhuri, S. P. (2010). Geoepidemiology and environmental factors of psoriasis and psoriatic arthritis. *Journal of Autoimmunity*, *34*(3). https://doi.org/10.1016/j.jaut.2009.12.001

Chang, J. H., McCluskey, P. J., & Wakefield, D. (2006). Toll-like receptors in ocular immunity and the immunopathogenesis of inflammatory eye disease. In *British Journal of Ophthalmology* (Vol. 90, Issue 1). https://doi.org/10.1136/bjo.2005.072686

Chen, L., Guo, S., Ranzer, M. J., & Dipietro, L. A. (2013). Toll-like receptor 4 has an essential role in early skin wound healing. *Journal of Investigative Dermatology*, *133*(1). https://doi.org/10.1038/jid.2012.267

Cheung, P. F. Y., Wong, C. K., & Lam, C. W. K. (2008). Molecular Mechanisms of Cytokine and Chemokine Release from Eosinophils Activated by IL-17A, IL-17F, and IL-23: Implication for Th17 Lymphocytes-Mediated Allergic Inflammation. *The Journal of Immunology*, *180*(8). https://doi.org/10.4049/jimmunol.180.8.5625

Chiricozzi, A., Guttman-Yassky, E., Suárez-Farĩas, M., Nograles, K. E., Tian, S., Cardinale, I., Chimenti, S., & Krueger, J. G. (2011). Integrative responses to IL-17 and TNF-α in human keratinocytes account for key inflammatory pathogenic circuits in psoriasis. *Journal of Investigative Dermatology*, *131*(3). https://doi.org/10.1038/jid.2010.340

Chiricozzi, A., & Krueger, J. G. (2013). IL-17 targeted therapies for psoriasis. In *Expert Opinion on Investigational Drugs* (Vol. 22, Issue 8). https://doi.org/10.1517/13543784.2013.806483

Chiricozzi, A., Romanelli, P., Volpe, E., Borsellino, G., & Romanelli, M. (2018). Scanning the Immunopathogenesis of Psoriasis. *International*

Journal of Molecular Sciences, *19*(1). https://doi.org/10.3390/ijms19010179

Christophers, E. (2001). Psoriasis - Epidemiology and clinical spectrum. In *Clinical and Experimental Dermatology* (Vol. 26, Issue 4). https://doi.org/10.1046/j.1365-2230.2001.00832.x

Conrad, C., Boyman, O., Tonel, G., Tun-Kyi, A., Laggner, U., De Fougerolles, A., Kotelianski, V., Gardner, H., & Nestle, F. O. (2007). α1β1 integrin is crucial for accumulation of epidermal T cells and the development of psoriasis. *Nature Medicine*, *13*(7). https://doi.org/10.1038/nm1605

Conrad, C., & Gilliet, M. (2018). Psoriasis: from Pathogenesis to Targeted Therapies. In *Clinical Reviews in Allergy and Immunology* (Vol. 54, Issue 1). https://doi.org/10.1007/s12016-018-8668-1

Curry, J. L., Qin, J. Z., Robinson, J., & Nickoloff, B. J. (2003). Reactivity of resident immunocytes in normal and prepsoriatic skin using an ex vivo skin-explant model system. *Archives of Pathology and Laboratory Medicine*, *127*(3). https://doi.org/10.5858/2003-127-0289-roriin

De Vosse, E. Van, Lichtenauer-Kaligis, E. G. R., Van Dissel, J. T., & Ottenhoff, T. H. M. (2003). Genetic variations in the interleukin-12/interleukin-23 receptor (β1) chain, and implications for IL-12 and IL-23 receptor structure and function. In *Immunogenetics* (Vol. 54, Issue 12). https://doi.org/10.1007/s00251-002-0534-9

Di Cesare, A., Di Meglio, P., & Nestle, F. O. (2009). The IL-23Th17 axis in the immunopathogenesis of psoriasis. In *Journal of Investigative Dermatology* (Vol. 129, Issue 6). https://doi.org/10.1038/jid.2009.59

Di Meglio, P., Villanova, F., Navarini, A. A., Mylonas, A., Tosi, I., Nestle, F. O., & Conrad, C. (2016). Targeting CD8+ T cells prevents psoriasis development. *Journal of Allergy and Clinical Immunology*, *138*(1). https://doi.org/10.1016/j.jaci.2015.10.046

Di Meglio, P., Villanova, F., & Nestle, F. O. (2014). Psoriasis. *Cold Spring Harbor Perspectives in Medicine*, *4*(8). https://doi.org/10.1101/cshperspect.a015354

Dogra, S., & Yadav, S. (2010). Psoriasis in India: Prevalence and pattern. In *Indian Journal of Dermatology, Venereology and Leprology* (Vol. 76, Issue 6). https://doi.org/10.4103/0378-6323.72443

Dowlatshahi, E. A., Van Der Voort, E. A. M., Arends, L. R., & Nijsten, T. (2013). Markers of systemic inflammation in psoriasis: A systematic review and meta-analysis. *British Journal of Dermatology*, *169*(2). https://doi.org/10.1111/bjd.12355

Duarte, G. V., Faillace, C., & Freire De Carvalho, J. (2012). Psoriatic arthritis. In *Best Practice and Research: Clinical Rheumatology* (Vol. 26, Issue 1). https://doi.org/10.1016/j.berh.2012.01.003

Dunphy, S. E., Sweeney, C. M., Kelly, G., Tobin, A. M., Kirby, B., & Gardiner, C. M. (2017). Natural killer cells from psoriasis vulgaris patients have reduced levels of cytotoxicity associated degranulation and cytokine production. *Clinical Immunology*, *177*. https://doi.org/10.1016/j.clim.2015.10.004

Eder, L., Chandran, V., Pellett, F., Pollock, R., Shanmugarajah, S., Rosen, C. F., Rahman, P., & Gladman, D. D. (2011). IL13 gene polymorphism is a marker for psoriatic arthritis among psoriasis patients. *Annals of the Rheumatic Diseases*, *70*(9). https://doi.org/10.1136/ard.2010.147421

Egeberg, A., Gisondi, P., Carrascosa, J. M., Warren, R. B., & Mrowietz, U. (2020). The role of the interleukin-23/Th17 pathway in cardiometabolic comorbidity associated with psoriasis. In *Journal of the European Academy of Dermatology and Venereology* (Vol. 34, Issue 8). https://doi.org/10.1111/jdv.16273

El-Hadidi, H., Samir, N., Shaker, O. G., & Otb, S. (2014). Estimation of tissue and serum lipocalin-2 in psoriasis vulgaris and its relation to metabolic syndrome. *Archives of Dermatological Research*, *306*(3). https://doi.org/10.1007/s00403-013-1414-x

Ellinghaus, E., Stuart, P. E., Ellinghaus, D., Nair, R. P., Debrus, S., Raelson, J. V., Belouchi, M., Tejasvi, T., Li, Y., Tsoi, L. C., Onken, A. T., Esko, T., Metspalu, A., Rahman, P., Gladman, D. D., Bowcock, A. M., Helms, C., Krueger, G. G., Koks, S., … Franke, A. (2012). Genome-wide meta-analysis of psoriatic arthritis identifies susceptibility locus at REL. *Journal of Investigative Dermatology*, *132*(4). https://doi.org/10.1038/jid.2011.415

El-Zayat, S. R., Sibaii, H., & Mannaa, F. A. (2019). Toll-like receptors activation, signaling, and targeting: an overview. *Bulletin of the National Research Centre*, *43*(1). https://doi.org/10.1186/s42269-019-0227-2

Eyerich, K., Pennino, D., Scarponi, C., Foerster, S., Nasorri, F., Behrendt, H., Ring, J., Traidl-Hoffmann, C., Albanesi, C., & Cavani, A. (2009). IL-17 in atopic eczema: Linking allergen-specific adaptive and microbial-triggered innate immune response. *Journal of Allergy and Clinical Immunology*, *123*(1). https://doi.org/10.1016/j.jaci.2008.10.031

Eyerich, S., Eyerich, K., Pennino, D., Carbone, T., Nasorri, F., Pallotta, S., Cianfarani, F., Odorisio, T., Traidl-Hoffmann, C., Behrendt, H., Durham, S. R., Schmidt-Weber, C. B., & Cavani, A. (2009). Th22 cells represent a distinct human T cell subset involved in epidermal immunity and

remodeling. *Journal of Clinical Investigation*, *119*(12). https://doi.org/10.1172/JCI40202

Fatani, M. I., Abdulghani, M. M., & Al-Afif, K. A. (2002). Psoriasis in the eastern Saudi Arabia. *Saudi Medical Journal*, *23*(2).

Fitch, E., Harper, E., Skorcheva, I., Kurtz, S. E., & Blauvelt, A. (2007). Pathophysiology of psoriasis: Recent advances on IL-23 and TH17 cytokines. In *Current Rheumatology Reports* (Vol. 9, Issue 6). https://doi.org/10.1007/s11926-007-0075-1

Fotiadou, C., Lazaridou, E., Sotiriou, E., & Ioannides, D. (2018). Targeting IL-23 in psoriasis: current perspectives. *Psoriasis: Targets and Therapy*, *Volume 8*. https://doi.org/10.2147/ptt.s98893

Furue, M., Furue, K., Tsuji, G., & Nakahara, T. (2020). Interleukin-17A and keratinocytes in psoriasis. In *International Journal of Molecular Sciences* (Vol. 21, Issue 4). https://doi.org/10.3390/ijms21041275

Garbicz, J., Całyniuk, B., Górski, M., Buczkowska, M., Piecuch, M., Kulik, A., & Rozentryt, P. (2022). Nutritional therapy in persons suffering from psoriasis. In *Nutrients* (Vol. 14, Issue 1). https://doi.org/10.3390/nu14010119

Gardiner, C. M., & Dunphy, S. (2011). NK cells and psoriasis. In *Journal of Biomedicine and Biotechnology* (Vol. 2011). https://doi.org/10.1155/2011/248317

Georgescu, S. R., Tampa, M., Caruntu, C., Sarbu, M. I., Mitran, C. I., Mitran, M. I., Matei, C., Constantin, C., & Neagu, M. (2019). Advances in understanding the immunological pathways in Psoriasis. In *International Journal of Molecular Sciences* (Vol. 20, Issue 3). https://doi.org/10.3390/ijms20030739

Gerosa, F., Baldani-Guerra, B., Lyakh, L. A., Batoni, G., Esin, S., Winkler-Pickett, R. T., Consolaro, M. R., De Marchi, M., Giachino, D., Robbiano, A., Astegiano, M., Sambataro, A., Kastelein, R. A., Carra, G., & Trinchieri, G. (2008). Differential regulation of interleukin 12 and interleukin 23 production in human dendritic cells. *Journal of Experimental Medicine*, *205*(6). https://doi.org/10.1084/jem.20071450

Gladman, D. D., Antoni, C., Mease, P., Clegg, D. O., & Nash, O. (2005). Psoriatic arthritis: Epidemiology, clinical features, course, and outcome. *Annals of the Rheumatic Diseases*, *64*(SUPPL. 2). https://doi.org/10.1136/ard.2004.032482

Gordon, K. B., Duffin, K. C., Bissonnette, R., Prinz, J. C., Wasfi, Y., Li, S., Shen, Y.-K., Szapary, P., Randazzo, B., & Reich, K. (2015). A Phase 2 Trial of Guselkumab versus Adalimumab for Plaque Psoriasis. *New*

England Journal of Medicine, *373*(2). https://doi.org/10.1056/nejmoa1501646

Gottlieb, A. B., Lebwohl, M., Shirin, S., Sherr, A., Gilleaudeau, P., Singer, G., Solodkina, G., Grossman, R., Gisoldi, E., Phillips, S., Neisler, H. M., & Krueger, J. G. (2000). Anti-CD4 monoclonal antibody treatment of moderate to severe psoriasis vulgaris: Results of a pilot, multicenter, multiple-dose, placebo-controlled study. *Journal of the American Academy of Dermatology*, *43*(4). https://doi.org/10.1067/mjd.2000.107945

Griffiths, C. E., & Barker, J. N. (2007). Pathogenesis and clinical features of psoriasis. *Lancet (London, England)*, *370*(9583), 263–271. https://doi.org/10.1016/S0140-6736(07)61128-3

Griffiths, C. E. M., Christophers, E., Barker, J. N. W. N., Chalmers, R. J. G., Chimenti, S., Krueger, G. G., Leonardi, C., Menter, A., Ortonne, J. P., & Fry, L. (2007). A classification of psoriasis vulgaris according to phenotype. *British Journal of Dermatology*, *156*(2). https://doi.org/10.1111/j.1365-2133.2006.07675.x

Guillet, C., Seeli, C., Nina, M., Maul, L. V., & Maul, J.-T. (2022). The impact of gender and sex in psoriasis: What to be aware of when treating women with psoriasis. *International Journal of Women's Dermatology*, *8*(2). https://doi.org/10.1097/jw9.0000000000000010

Gullick, N. J., Evans, H. G., Church, L. D., Jayaraj, D. M., Filer, A., Kirkham, B. W., & Taams, L. S. (2010). Linking power doppler ultrasound to the presence of Th17 cells in the rheumatoid arthritis joint. *PLoS ONE*, *5*(9). https://doi.org/10.1371/journal.pone.0012516

Harden, J. L., Krueger, J. G., & Bowcock, A. M. (2015). The immunogenetics of Psoriasis: A comprehensive review. In *Journal of Autoimmunity* (Vol. 64). https://doi.org/10.1016/j.jaut.2015.07.008

Hart, P. H., Gorman, S., & Finlay-Jones, J. J. (2011). Modulation of the immune system by UV radiation: More than just the effects of vitamin D? In *Nature Reviews Immunology* (Vol. 11, Issue 9). https://doi.org/10.1038/nri3045

Hassoon, H. J., Risan, F. A., & Abdul-Muhaimen, N. (2014). Estimation the concentration of IL-23, and IL-17A in the sera of patients with psoriasis in Baghdad city. *Iraqi Journal of Biotechnology*, *13*(2).

Hawkes, J. E., Yan, B. Y., Chan, T. C., & Krueger, J. G. (2018). Discovery of the IL-23/IL-17 Signaling Pathway and the Treatment of Psoriasis. *The Journal of Immunology*, *201*(6). https://doi.org/10.4049/jimmunol.1800013

Hirahara, K., Eberle, F. C., Brück, J., Holstein, J., & Ghoreschi, K. (2016). Recent advances in understanding psoriasis. In *F1000Research* (Vol. 5). https://doi.org/10.12688/f1000research.7927.1

Housseau, F., Geis, A., Thiele-Orberg, E., & Llosa, N. (2014). Interleukin-17 and type 17 helper T cells in cancer management and research. *ImmunoTargets and Therapy*. https://doi.org/10.2147/itt.s56529

Hu, P., Wang, M., Gao, H., Zheng, A., Li, J., Mu, D., & Tong, J. (2021). The Role of Helper T Cells in Psoriasis. In *Frontiers in Immunology* (Vol. 12). https://doi.org/10.3389/fimmu.2021.788940

Huang, P., Zinselmeyer, B., Saunders, B. T., Swartz, M. A., Kim, B. S., & Randolph, G. J. (2019). Interleukin-17 Drives Interstitial Entrapment of Tissue Lipoproteins in Experimental Psoriasis. *The Journal of Immunology*, *202*(1_Supplement). https://doi.org/10.4049/jimmunol.202.supp.133.5

Icen, M., Crowson, C. S., McEvoy, M. T., Dann, F. J., Gabriel, S. E., & Maradit Kremers, H. (2009). Trends in incidence of adult-onset psoriasis over three decades: A population-based study. *Journal of the American Academy of Dermatology*, *60*(3). https://doi.org/10.1016/j.jaad.2008.10.062

Ince, M. N., Harnisch, B., Xu, Z., Lee, S. K., Lange, C., Moretta, L., Lederman, M., & Lieberman, J. (2004). Increased expression of the natural killer cell inhibitory receptor CD85j/ILT2 on antigen-specific effector CD8 T cells and its impact on CD8 T-cell function. *Immunology*, *112*(4). https://doi.org/10.1046/j.1365-2567.2004.01907.x

Iwakura, Y., & Ishigame, H. (2006). The IL-23/IL-17 axis in inflammation. In *Journal of Clinical Investigation* (Vol. 116, Issue 5). https://doi.org/10.1172/JCI28508

Janeway, C. A., & Medzhitov, R. (2002). Innate immune recognition. In *Annual Review of Immunology* (Vol. 20). https://doi.org/10.1146/annurev.immunol.20.083001.084359

Janssens, S., & Beyaert, R. (2003). Role of Toll-Like Receptors in Pathogen Recognition. In *Clinical Microbiology Reviews* (Vol. 16, Issue 4). https://doi.org/10.1128/CMR.16.4.637-646.2003

Jeon, Y. J., Sah, S. K., Yang, H. S., Lee, J. H., Shin, J., & Kim, T. Y. (2017). Rhododendrin inhibits toll-like receptor-7-mediated psoriasis-like skin inflammation in mice. *Experimental and Molecular Medicine*, *49*(6). https://doi.org/10.1038/emm.2017.81

Johansen, C., Usher, P. A., Kjellerup, R. B., Lundsgaard, D., Iversen, L., & Kragballe, K. (2009). Characterization of the interleukin-17 isoforms and

receptors in lesional psoriatic skin. *British Journal of Dermatology*, *160*(2). https://doi.org/10.1111/j.1365-2133.2008.08902.x

Johnson-Huang, L. M., Lowes, M. A., & Krueger, J. G. (2012). Putting together the psoriasis puzzle: An update on developing targeted therapies. In *DMM Disease Models and Mechanisms* (Vol. 5, Issue 4). https://doi.org/10.1242/dmm.009092

Johnston, A., Fritz, Y., Dawes, S. M., Diaconu, D., Al-Attar, P. M., Guzman, A. M., Chen, C. S., Fu, W., Gudjonsson, J. E., McCormick, T. S., & Ward, N. L. (2013). Keratinocyte Overexpression of IL-17C Promotes Psoriasiform Skin Inflammation. *The Journal of Immunology*, *190*(5). https://doi.org/10.4049/jimmunol.1201505

Kamiya, K., Kishimoto, M., Sugai, J., Komine, M., & Ohtsuki, M. (2019). Risk factors for the development of psoriasis. In *International Journal of Molecular Sciences* (Vol. 20, Issue 18). https://doi.org/10.3390/ijms20184347

Kampe, T., Dorko, E., Rimárová, K., Houžvičková, A., Baloghová, J., Baranová, Z., Madleňák, M., & Rohoň, I. (2022). PREVALENCE OF CARDIOVASCULAR RISK FACTORS IN PATIENTS WITH PSORIASIS. *Central European Journal of Public Health*, *30*. https://doi.org/10.21101/cejph.a6806

Kanda, N. (2021). Psoriasis: Pathogenesis, comorbidities, and therapy updated. In *International Journal of Molecular Sciences* (Vol. 22, Issue 6). https://doi.org/10.3390/ijms22062979

Kanda, N., Hoashi, T., & Saeki, H. (2020a). Nutrition and psoriasis. In *International Journal of Molecular Sciences* (Vol. 21, Issue 15). https://doi.org/10.3390/ijms21155405

Kanda, N., Hoashi, T., & Saeki, H. (2020b). Nutrition and psoriasis. In *International Journal of Molecular Sciences* (Vol. 21, Issue 15). https://doi.org/10.3390/ijms21155405

Kannan, A. K., Su, Z., Gauvin, D. M., Lippert, S. E., Marie, H. P., McGaraughty, S. P., Kort, M. E., Scott, V. E., & Gauld, S. B. (2017). IL-23 induces regulatory T cell plasticity with implications for inflammatory skin diseases. *The Journal of Immunology*, *198*(1_Supplement). https://doi.org/10.4049/jimmunol.198.supp.220.13

Karczewski, J., Dobrowolska, A., Rychlewska-Hańczewska, A., & Adamski, Z. (2016). New insights into the role of T cells in pathogenesis of psoriasis and psoriatic arthritis. In *Autoimmunity* (Vol. 49, Issue 7). https://doi.org/10.3109/08916934.2016.1166214

Kastelein, R. A., Hunter, C. A., & Cua, D. J. (2007). Discovery and biology of IL-23 and IL-27: Related but functionally distinct regulators of inflammation. In *Annual Review of Immunology* (Vol. 25). https://doi.org/10.1146/annurev.immunol.22.012703.104758

Kawada, J. I., Kimura, H., Ito, Y., Hara, S., Iriyama, M., Yoshikawa, T., & Morishima, T. (2003). Systemic cytokine responses in patients with influenza-associated encephalopathy. *Journal of Infectious Diseases*, *188*(5). https://doi.org/10.1086/377101

Kawai, T., & Akira, S. (2011). Toll-like Receptors and Their Crosstalk with Other Innate Receptors in Infection and Immunity. In *Immunity* (Vol. 34, Issue 5). https://doi.org/10.1016/j.immuni.2011.05.006

Kim, G. K., & del Rosso, J. Q. (2010). Drug-provoked psoriasis: Is it drug induced or drug aggravated? understanding pathophysiology and clinical relevance. *Journal of Clinical and Aesthetic Dermatology*, *3*(1).

Kim, H. O., Kang, S. Y., Kim, J. C., Park, C. W., & Chung, B. Y. (2021). Pediatric psoriasis: From new insights into pathogenesis to updates on treatment. In *Biomedicines* (Vol. 9, Issue 8). https://doi.org/10.3390/biomedicines9080940

Kimmel, G. W., & Lebwohl, M. (2018). *Psoriasis: Overview and Diagnosis*. https://doi.org/10.1007/978-3-319-90107-7_1

Kleinschek, M. A., Muller, U., Brodie, S. J., Stenzel, W., Kohler, G., Blumenschein, W. M., Straubinger, R. K., McClanahan, T., Kastelein, R. A., & Alber, G. (2006). IL-23 Enhances the Inflammatory Cell Response in Cryptococcus neoformans Infection and Induces a Cytokine Pattern Distinct from IL-12 . *The Journal of Immunology*, *176*(2). https://doi.org/10.4049/jimmunol.176.2.1098

Krijgsman, D., Hokland, M., & Kuppen, P. J. K. (2018). The role of natural killer T cells in cancer-A phenotypical and functional approach. In *Frontiers in Immunology* (Vol. 9, Issue FEB). https://doi.org/10.3389/fimmu.2018.00367

Krueger, J. G., Fretzin, S., Suárez-Fariñas, M., Haslett, P. A., Phipps, K. M., Cameron, G. S., McColm, J., Katcherian, A., Cueto, I., White, T., Banerjee, S., & Hoffman, R. W. (2012). IL-17A is essential for cell activation and inflammatory gene circuits in subjects with psoriasis. *Journal of Allergy and Clinical Immunology*, *130*(1). https://doi.org/10.1016/j.jaci.2012.04.024

Laggner, U., Di Meglio, P., Perera, G. K., Hundhausen, C., Lacy, K. E., Ali, N., Smith, C. H., Hayday, A. C., Nickoloff, B. J., & Nestle, F. O. (2011). Identification of a Novel Proinflammatory Human Skin-Homing Vγ9Vδ2

T Cell Subset with a Potential Role in Psoriasis. *The Journal of Immunology*, *187*(5). https://doi.org/10.4049/jimmunol.1100804

Lai, C. Y., Su, Y. W., Lin, K. I., Hsu, L. C., & Chuang, T. H. (2017). Natural Modulators of Endosomal Toll-Like Receptor-Mediated Psoriatic Skin Inflammation. In *Journal of Immunology Research* (Vol. 2017). https://doi.org/10.1155/2017/7807313

Langley, R. G. B., Krueger, G. G., & Griffiths, C. E. M. (2005). Psoriasis: Epidemiology, clinical features, and quality of life. *Annals of the Rheumatic Diseases*, *64*(SUPPL. 2). https://doi.org/10.1136/ard.2004.033217

Langrish, C. L., Chen, Y., Blumenschein, W. M., Mattson, J., Basham, B., Sedgwick, J. D., McClanahan, T., Kastelein, R. A., & Cua, D. J. (2005). IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. *Journal of Experimental Medicine*, *201*(2). https://doi.org/10.1084/jem.20041257

Lee, B.-W., & Moon, S.-J. (2023). Inflammatory Cytokines in Psoriatic Arthritis: Understanding Pathogenesis and Implications for Treatment. *International Journal of Molecular Sciences*, *24*(14). https://doi.org/10.3390/ijms241411662

Levine, N. (2000). Cutaneous manifestations of infectious diseases. *Consultant*, *40*(13). https://doi.org/10.1007/978-1-4614-0688-4_7

Lew, W., Bowcock, A. M., & Krueger, J. G. (2004). Psoriasis vulgaris: Cutaneous lymphoid tissue supports T-cell activation and "Type 1" inflammatory gene expression. In *Trends in Immunology* (Vol. 25, Issue 6). https://doi.org/10.1016/j.it.2004.03.006

Li, D., & Wu, M. (2021). Pattern recognition receptors in health and diseases. In *Signal Transduction and Targeted Therapy* (Vol. 6, Issue 1). https://doi.org/10.1038/s41392-021-00687-0

Li, J., Chen, X., Liu, Z., Yue, Q., & Liu, H. (2007). Expression of Th17 cytokines in skin lesions of patients with psoriasis. *Journal of Huazhong University of Science and Technology - Medical Science*, *27*(3). https://doi.org/10.1007/s11596-007-0329-1

Li, L., Liu, K., Duan, X., Xu, L., Yang, Q., & Liu, F. (2023). A Comparison of Clinical Characteristics in Overweight/Obese and Normal Weight Patients with Psoriasis Vulgaris: A Bicentric Retrospective Observational Study. *Clinical, Cosmetic and Investigational Dermatology*, *16*. https://doi.org/10.2147/CCID.S411636

Liang, D., Zuo, A., Shao, H., Born, W. K., O'Brien, R. L., Kaplan, H. J., & Sun, D. (2013). IL-23 Receptor Expression on γδ T Cells Correlates with

Their Enhancing or Suppressive Effects on Autoreactive T Cells in Experimental Autoimmune Uveitis. *The Journal of Immunology*, *191*(3). https://doi.org/10.4049/jimmunol.1300626

Lieberman, J. A., Hammond, F. M., Barringer, T. A., Norton, H. J., Goff, D. C., Bockenek, W. L., & Scelza, W. M. (2011). Comparison of coronary artery calcification scores and National Cholesterol Education Program guidelines for coronary heart disease risk assessment and treatment paradigms in individuals with chronic traumatic spinal cord injury. *Journal of Spinal Cord Medicine*, *34*(2). https://doi.org/10.1179/107902611X13019162562548

Lin, A. M., Rubin, C. J., Khandpur, R., Wang, J. Y., Riblett, M., Yalavarthi, S., Villanueva, E. C., Shah, P., Kaplan, M. J., & Bruce, A. T. (2011). Mast Cells and Neutrophils Release IL-17 through Extracellular Trap Formation in Psoriasis. *The Journal of Immunology*, *187*(1). https://doi.org/10.4049/jimmunol.1100123

Liu, T., Gao, Y. J., & Ji, R. R. (2012). Emerging role of Toll-like receptors in the control of pain and itch. In *Neuroscience Bulletin* (Vol. 28, Issue 2). https://doi.org/10.1007/s12264-012-1219-5

Lowes, M. A., Bowcock, A. M., & Krueger, J. G. (2007). Pathogenesis and therapy of psoriasis. In *Nature* (Vol. 445, Issue 7130). https://doi.org/10.1038/nature05663

Lowes, M. A., Kikuchi, T., Fuentes-Duculan, J., Cardinale, I., Zaba, L. C., Haider, A. S., Bowman, E. P., & Krueger, J. G. (2008). Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. *Journal of Investigative Dermatology*, *128*(5). https://doi.org/10.1038/sj.jid.5701213

Lowes, M. A., Suárez-Fariñas, M., & Krueger, J. G. (2014). Immunology of psoriasis. In *Annual Review of Immunology* (Vol. 32). https://doi.org/10.1146/annurev-immunol-032713-120225

Lu, Y. C., Yeh, W. C., & Ohashi, P. S. (2008). LPS/TLR4 signal transduction pathway. In *Cytokine* (Vol. 42, Issue 2). https://doi.org/10.1016/j.cyto.2008.01.006

Lupardus, P. J., & Garcia, K. C. (2008). The Structure of Interleukin-23 Reveals the Molecular Basis of p40 Subunit Sharing with Interleukin-12. *Journal of Molecular Biology*, *382*(4). https://doi.org/10.1016/j.jmb.2008.07.051

Ma, B., Yang, Y., Li, Z., Zhao, D., Zhang, W., Jiang, Y., & Xue, D. (2018). Modular bioinformatics analysis demonstrates that a Toll-like receptor signaling pathway is involved in the regulation of macrophage

polarization. *Molecular Medicine Reports*, *18*(5). https://doi.org/10.3892/mmr.2018.9486

Mahil, S. K., Capon, F., & Barker, J. N. (2016). Update on psoriasis immunopathogenesis and targeted immunotherapy. In *Seminars in Immunopathology* (Vol. 38, Issue 1). https://doi.org/10.1007/s00281-015-0539-8

Maitra, A., Shen, F., Hanel, W., Mossman, K., Tocker, J., Swart, D., & Gaffen, S. L. (2007). Distinct functional motifs within the IL-17 receptor regulate signal transduction and target gene expression. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(18). https://doi.org/10.1073/pnas.0611589104

Mariani, F., & Roncucci, L. (2015). Chemerin/chemR23 axis in inflammation onset and resolution. In *Inflammation Research* (Vol. 64, Issue 2). https://doi.org/10.1007/s00011-014-0792-7

Marina, S., Semkova, K., Guleva, D., & Kazandjieva, J. (2013). Acute generalized exanthematous pustulosis (AGEP): a literature review. *Scripta Scientifica Medica*, *45*(4). https://doi.org/10.14748/ssm.v45i4.226

Marrakchi, S., Guigue, P., Renshaw, B. R., Puel, A., Pei, X.-Y., Fraitag, S., Zribi, J., Bal, E., Cluzeau, C., Chrabieh, M., Towne, J. E., Douangpanya, J., Pons, C., Mansour, S., Serre, V., Makni, H., Mahfoudh, N., Fakhfakh, F., Bodemer, C., … Smahi, A. (2011). Interleukin-36–Receptor Antagonist Deficiency and Generalized Pustular Psoriasis. *New England Journal of Medicine*, *365*(7). https://doi.org/10.1056/nejmoa1013068

Martin, D. A., Towne, J. E., Kricorian, G., Klekotka, P., Gudjonsson, J. E., Krueger, J. G., & Russell, C. B. (2013). The emerging role of IL-17 in the pathogenesis of psoriasis: Preclinical and clinical findings. In *Journal of Investigative Dermatology* (Vol. 133, Issue 1). https://doi.org/10.1038/jid.2012.194

Martínez-Lostao, L., Anel, A., & Pardo, J. (2015). How Do Cytotoxic Lymphocytes Kill Cancer Cells? *Clinical Cancer Research*, *21*(22). https://doi.org/10.1158/1078-0432.CCR-15-0685

Mattei, P. L., Corey, K. C., & Kimball, A. B. (2014). Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI): The correlation between disease severity and psychological burden in patients treated with biological therapies. *Journal of the European Academy of Dermatology and Venereology*, *28*(3). https://doi.org/10.1111/jdv.12106

McCormick, T., Ayala-Fontanez, N., & Soler, D. (2016). Current knowledge on psoriasis and autoimmune diseases. *Psoriasis: Targets and Therapy*. https://doi.org/10.2147/ptt.s64950

McGovern, D., & Powrie, F. (2007). The IL23 axis plays a key role in the pathogenesis of IBD. In *Gut* (Vol. 56, Issue 10). https://doi.org/10.1136/gut.2006.115402

McKenzie, B. S., Kastelein, R. A., & Cua, D. J. (2006). Understanding the IL-23-IL-17 immune pathway. *Trends in Immunology*, *27*(1). https://doi.org/10.1016/j.it.2005.10.003

Menter, A., Krueger, G. G., Paek, S. Y., Kivelevitch, D., Adamopoulos, I. E., & Langley, R. G. (2021). Interleukin-17 and Interleukin-23: A Narrative Review of Mechanisms of Action in Psoriasis and Associated Comorbidities. In *Dermatology and Therapy* (Vol. 11, Issue 2). https://doi.org/10.1007/s13555-021-00483-2

Miossec, P., Korn, T., & Kuchroo, V. K. (2009). Interleukin-17 and Type 17 Helper T Cells. *New England Journal of Medicine*, *361*(9). https://doi.org/10.1056/nejmra0707449

Mir, M. A., Mehraj, U., Nisar, S., & Qayoom, H. (2020). Enzyme linked immunosorbent assay (ELISA). In *Immunoglobulins, Magic Bullets and Therapeutic Antibodies*. https://doi.org/10.4049/jimmunol.109.1.129

Moore, D. S., McCabe, G. P., Craig, B. A., McCabe, G. P., & Craig, B. A. (2021). Introduction to the Practice of Statistics. In *Macmillan Learning* (9th Ed.). Macmillan Learning.

Morizane, S., & Gallo, R. L. (2012). Antimicrobial peptides in the pathogenesis of psoriasis. *Journal of Dermatology*, *39*(3). https://doi.org/10.1111/j.1346-8138.2011.01483.x

Mosca, M., Hong, J., Hadeler, E., Hakimi, M., Liao, W., & Bhutani, T. (2021). The Role of IL-17 Cytokines in Psoriasis. *ImmunoTargets and Therapy*, *Volume 10*. https://doi.org/10.2147/itt.s240891

Muzumdar, S., & Rothe, M. J. (2022). Nutrition and psoriasis. *Clinics in Dermatology*, *40*(2). https://doi.org/10.1016/j.clindermatol.2021.10.005

N., A.-F., D.C., S., & T.S., M. (2016). Current knowledge on psoriasis and autoimmune diseases. *Psoriasis: Targets and Therapy*, *6*.

Naldi, L. (2016). Psoriasis and smoking: Links and risks. In *Psoriasis: Targets and Therapy* (Vol. 6). https://doi.org/10.2147/PTT.S85189

Neimann, A. L., Shin, D. B., Wang, X., Margolis, D. J., Troxel, A. B., & Gelfand, J. M. (2006). Prevalence of cardiovascular risk factors in patients with psoriasis. *Journal of the American Academy of Dermatology*, *55*(5). https://doi.org/10.1016/j.jaad.2006.08.040

Nestle, F. O., Kaplan, D. H., & Barker, J. (2009). Psoriasis. *The New England Journal of Medicine*, *361*(5), 496–509. https://doi.org/10.1056/NEJMra0804595

Nickoloff, B. J., Bonish, B., Huang, B. B., & Porcelli, S. A. (2000). Characterization of a T cell line bearing natural killer receptors and capable of creating psoriasis in a SCID mouse model system. *Journal of Dermatological Science*, *24*(3). https://doi.org/10.1016/S0923-1811(00)00120-1

Nomura, T., Kabashima, K., & Miyachi, Y. (2014). The panoply of αβT cells in the skin. In *Journal of Dermatological Science* (Vol. 76, Issue 1). https://doi.org/10.1016/j.jdermsci.2014.07.010

Noviello, D., Mager, R., Roda, G., Borroni, R. G., Fiorino, G., & Vetrano, S. (2021). The IL23-IL17 Immune Axis in the Treatment of Ulcerative Colitis: Successes, Defeats, and Ongoing Challenges. In *Frontiers in Immunology* (Vol. 12). https://doi.org/10.3389/fimmu.2021.611256

Nuttall, F. Q. (2015). Body mass index: Obesity, BMI, and health: A critical review. *Nutrition Today*, *50*(3), 117–128. https://doi.org/10.1097/NT.0000000000000092

Oliveira, P. S. S. De, Cardoso, P. R. G., Lima, E. V. D. A., Pereira, M. C., Duarte, A. L. B. P., Pitta, I. D. R., Rêgo, M. J. B. D. M., & Pitta, M. G. D. R. (2015). IL-17A, IL-22, IL-6, and IL-21 serum levels in plaque-type psoriasis in Brazilian patients. *Mediators of Inflammation*, *2015*. https://doi.org/10.1155/2015/819149

Onoufriadis, A., Simpson, M. A., Pink, A. E., Di Meglio, P., Smith, C. H., Pullabhatla, V., Knight, J., Spain, S. L., Nestle, F. O., Burden, A. D., Capon, F., Trembath, R. C., & Barker, J. N. (2011). Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. *American Journal of Human Genetics*, *89*(3). https://doi.org/10.1016/j.ajhg.2011.07.022

Ottaviani, C., Nasorri, F., Bedini, C., de Pità, O., Girolomoni, G., & Cavani, A. (2006). CD56brightCD16- NK cells accumulate in psoriatic skin in response to CXCL10 and CCL5 and exacerbate skin inflammation. *European Journal of Immunology*, *36*(1). https://doi.org/10.1002/eji.200535243

Owczarczyk-Saczonek, A., Czerwińska, J., & Placek, W. (2018). The role of regulatory T cells and anti-inflammatory cytokines in psoriasis. *Acta Dermatovenerologica Alpina, Pannonica et Adriatica*, *27*(1). https://doi.org/10.15570/actaapa.2018.4

Parisi, R., Iskandar, I. Y. K., Kontopantelis, E., Augustin, M., Griffiths, C. E. M., & Ashcroft, D. M. (2020). National, regional, and worldwide epidemiology of psoriasis: Systematic analysis and modelling study. *The BMJ*, *369*. https://doi.org/10.1136/bmj.m1590

Parisi, R., Symmons, D. P. M., Griffiths, C. E. M., & Ashcroft, D. M. (2013). Global epidemiology of psoriasis: A systematic review of incidence and prevalence. *Journal of Investigative Dermatology*, *133*(2). https://doi.org/10.1038/jid.2012.339

Pengpid, S., & Peltzer, K. (2021). Overweight and obesity among adults in iraq: Prevalence and correlates from a national survey in 2015. *International Journal of Environmental Research and Public Health*, *18*(8). https://doi.org/10.3390/ijerph18084198

Petito, A., Piazzoli, A., Altamura, M., Bellomo, A., Bernardini, F., Scarponi, L., & Porcelli, P. (2020). Psychosomatic syndromes and symptom severity in chronic psoriasis. *Clinical Neuropsychiatry*, *17*(4). https://doi.org/10.36131/cnfioritieditore20200402

Piipponen, M., Li, D., & Landén, N. X. (2020). The immune functions of keratinocytes in skin wound healing. In *International Journal of Molecular Sciences* (Vol. 21, Issue 22). https://doi.org/10.3390/ijms21228790

Płoski, R., Łuszczek, W., Kuśnierczyk, P., Nockowski, P., Cisło, M., Krajewski, P., & Malejczyk, J. (2006). A Role for KIR Gene Variants Other Than KIR2DS1 in Conferring Susceptibility to Psoriasis. *Human Immunology*, *67*(7). https://doi.org/10.1016/j.humimm.2006.04.001

Plužarić, V., Štefanić, M., Mihalj, M., Tolušić Levak, M., Muršić, I., Glavaš-Obrovac, L., Petrek, M., Balogh, P., & Tokić, S. (2020). Differential Skewing of Circulating MR1-Restricted and γδ T Cells in Human Psoriasis Vulgaris. *Frontiers in Immunology*, *11*. https://doi.org/10.3389/fimmu.2020.572924

Polese, B., Zhang, H., Thurairajah, B., & King, I. L. (2020). Innate Lymphocytes in Psoriasis. In *Frontiers in Immunology* (Vol. 11). https://doi.org/10.3389/fimmu.2020.00242

Prager, I., & Watzl, C. (2019). Mechanisms of natural killer cell-mediated cellular cytotoxicity. In *Journal of Leukocyte Biology* (Vol. 105, Issue 6). https://doi.org/10.1002/JLB.MR0718-269R

Prinz, J. C. (2003). The role of T cells in psoriasis. In *Journal of the European Academy of Dermatology and Venereology* (Vol. 17, Issue 3). https://doi.org/10.1046/j.1468-3083.2003.00720.x

Prinz, J. C. (2017). Melanocytes: Target Cells of an HLA-C*06:02–Restricted Autoimmune Response in Psoriasis. In *Journal of Investigative Dermatology* (Vol. 137, Issue 10). https://doi.org/10.1016/j.jid.2017.05.023

Psomadakis, C. E., & Han, G. (2019). New and emerging topical therapies for psoriasis and atopic dermatitis. In *Journal of Clinical and Aesthetic Dermatology* (Vol. 12, Issue 12).

Raharja, A., Mahil, S. K., & Barker, J. N. (2021). Psoriasis: A brief overview. In *Clinical Medicine, Journal of the Royal College of Physicians of London* (Vol. 21, Issue 3). https://doi.org/10.7861/CLINMED.2021-0257

Rendon, A., & Schäkel, K. (2019). Psoriasis pathogenesis and treatment. In *International Journal of Molecular Sciences* (Vol. 20, Issue 6). https://doi.org/10.3390/ijms20061475

Res, P. C. M., Piskin, G., de Boer, O. J., van der Loos, C. M., Teeling, P., Bos, J. D., & Teunissen, M. B. M. (2010). Overrepresentation of IL-17A and IL-22 Producing CD8 T Cells in Lesional Skin Suggests Their Involvement in the pathogenesis of psoriasis. *PLoS ONE*, *5*(11). https://doi.org/10.1371/journal.pone.0014108

Rivera-Díaz, R., Daudén, E., Carrascosa, J. M., Cueva, P. de la, & Puig, L. (2023). Generalized Pustular Psoriasis: A Review on Clinical Characteristics, Diagnosis, and Treatment. In *Dermatology and Therapy* (Vol. 13, Issue 3). https://doi.org/10.1007/s13555-022-00881-0

Robert, M., Miossec, P., & Hot, A. (2022). The Th17 Pathway in Vascular Inflammation: Culprit or Consort? In *Frontiers in Immunology* (Vol. 13). https://doi.org/10.3389/fimmu.2022.888763

Rønholt, K., & Iversen, L. (2017). Old and new biological therapies for psoriasis. In *International Journal of Molecular Sciences* (Vol. 18, Issue 11). https://doi.org/10.3390/ijms18112297

Roy, A., Srivastava, M., Saqib, U., Liu, D., Faisal, S. M., Sugathan, S., Bishnoi, S., & Baig, M. S. (2016). Potential therapeutic targets for inflammation in toll-like receptor 4 (TLR4)-mediated signaling pathways. In *International Immunopharmacology* (Vol. 40). https://doi.org/10.1016/j.intimp.2016.08.026

Sabri, M. A., Mohammad, A. R., Al-Saadi, K., Mohsin Ahmed, M., & Thaher Naji, A. (2015). Estimation of interlukins IL-17A and IL-23 in the psroriasis Iraqi patients. *J Sci*, *5*, 204–207.

Saczonek, A. O., Krajewska-Włodarczyk, M., Kasprowicz-Furmańczyk, M., & Placek, W. (2020). Immunological memory of psoriatic lesions. In *International Journal of Molecular Sciences* (Vol. 21, Issue 2). https://doi.org/10.3390/ijms21020625

Sakamoto, S., Putalun, W., Vimolmangkang, S., Phoolcharoen, W., Shoyama, Y., Tanaka, H., & Morimoto, S. (2018). Enzyme-linked immunosorbent assay for the quantitative/qualitative analysis of plant secondary

metabolites. In *Journal of Natural Medicines* (Vol. 72, Issue 1). https://doi.org/10.1007/s11418-017-1144-z

Samotij, D., Nedoszytko, B., Bartosińska, J., Batycka-Baran, A., Czajkowski, R., Dobrucki, I. T., Dobrucki, L. W., Górecka-Sokołowska, M., Janaszak-Jasienicka, A., Krasowska, D., Kalinowski, L., Macieja-Stawczyk, M., Nowicki, R. J., Owczarczyk-Saczonek, A., Płoska, A., Purzycka-Bohdan, D., Radulska, A., Reszka, E., Siekierzycka, A., … Reich, A. (2020). Pathogenesis of psoriasis in the "omic" era. Part I. Epidemiology, clinical manifestation, immunological and neuroendocrine disturbances. In *Postepy Dermatologii i Alergologii* (Vol. 37, Issue 2). https://doi.org/10.5114/ada.2020.94832

Santos-Sierra, S. (2021). Targeting toll-like receptor (Tlr) pathways in inflammatory arthritis: Two better than one? In *Biomolecules* (Vol. 11, Issue 9). https://doi.org/10.3390/biom11091291

Saraceno, R., Schipani, C., Mazzotta, A., Esposito, M., Di Renzo, L., De Lorenzo, A., & Chimenti, S. (2008). Effect of anti-tumor necrosis factor-α therapies on body mass index in patients with psoriasis. *Pharmacological Research*, *57*(4). https://doi.org/10.1016/j.phrs.2008.02.006

Sato, Y., Ogawa, E., & Okuyama, R. (2020). Role of innate immune cells in psoriasis. In *International Journal of Molecular Sciences* (Vol. 21, Issue 18). https://doi.org/10.3390/ijms21186604

Sauer, R. S., Hackel, D., Morschel, L., Sahlbach, H., Wang, Y., Mousa, S. A., Roewer, N., Brack, A., & Rittner, H. L. (2014). Toll like receptor (TLR)-4 as a regulator of peripheral endogenous opioid-mediated analgesia in inflammation. *Molecular Pain*, *10*(1). https://doi.org/10.1186/1744-8069-10-10

Schinocca, C., Rizzo, C., Fasano, S., Grasso, G., La Barbera, L., Ciccia, F., & Guggino, G. (2021). Role of the IL-23/IL-17 Pathway in Rheumatic Diseases: An Overview. In *Frontiers in Immunology* (Vol. 12). https://doi.org/10.3389/fimmu.2021.637829

Schmitt, H., Neurath, M. F., & Atreya, R. (2021). Role of the IL23/IL17 Pathway in Crohn's Disease. In *Frontiers in Immunology* (Vol. 12). https://doi.org/10.3389/fimmu.2021.622934

Schmitz, G., & Orsó, E. (2002). CD14 signalling in lipid rafts: New ligands and co-receptors. In *Current Opinion in Lipidology* (Vol. 13, Issue 5). https://doi.org/10.1097/00041433-200210000-00007

Schön, M. P. (2019a). Adaptive and Innate Immunity in Psoriasis and Other Inflammatory Disorders. In *Frontiers in immunology* (Vol. 10). https://doi.org/10.3389/fimmu.2019.01764

Schön, M. P. (2019b). Adaptive and Innate Immunity in Psoriasis and Other Inflammatory Disorders. In *Frontiers in immunology* (Vol. 10). https://doi.org/10.3389/fimmu.2019.01764

Schüler, R., Brand, A., Klebow, S., Wild, J., Veras, F. P., Ullmann, E., Roohani, S., Kolbinger, F., Kossmann, S., Wohn, C., Daiber, A., Münzel, T., Wenzel, P., Waisman, A., Clausen, B. E., & Karbach, S. (2019). Antagonization of IL-17A Attenuates Skin Inflammation and Vascular Dysfunction in Mouse Models of Psoriasis. *Journal of Investigative Dermatology*, *139*(3). https://doi.org/10.1016/j.jid.2018.09.021

Schwarz, P. E. H., Pinter, A., Melzer, N., Barteczek, P., & Reinhardt, M. (2019). ERAPSO: Revealing the High Burden of Obesity in German Psoriasis Patients. *Dermatology and Therapy*, *9*(3). https://doi.org/10.1007/s13555-019-0314-1

Sherlock, J. P., & Cua, D. J. (2021). Interleukin-23 in perspective. In *Rheumatology (Bulgaria)* (Vol. 60). https://doi.org/10.1093/rheumatology/keab461

Singh, S., Young, P., & Armstrong, A. W. (2017). An update on psoriasis and metabolic syndrome: A meta-analysis of observational studies. *PLoS ONE*, *12*(7). https://doi.org/10.1371/journal.pone.0181039

Smith, R. L., Hébert, H. L., Massey, J., Bowes, J., Marzo-Ortega, H., Ho, P., McHugh, N. J., Worthington, J., Barton, A., Griffiths, C. E. M., & Warren, R. B. (2016). Association of Toll-like receptor 4 (TLR4) with chronic plaque type psoriasis and psoriatic arthritis. *Archives of Dermatological Research*, *308*(3). https://doi.org/10.1007/s00403-016-1620-4

Sobhan, M., & Farshchian, M. (2017). Associations between body mass index and severity of psoriasis. *Clinical, Cosmetic and Investigational Dermatology*, *10*. https://doi.org/10.2147/CCID.S147236

Solimani, F., Meier, K., & Ghoreschi, K. (2019). Emerging Topical and Systemic JAK Inhibitors in Dermatology. In *Frontiers in Immunology* (Vol. 10). https://doi.org/10.3389/fimmu.2019.02847

Sugiura, K., Takemoto, A., Yamaguchi, M., Takahashi, H., Shoda, Y., Mitsuma, T., Tsuda, K., Nishida, E., Togawa, Y., Nakajima, K., Sakakibara, A., Kawachi, S., Shimizu, M., Ito, Y., Takeichi, T., Kono, M., Ogawa, Y., Muro, Y., Ishida-Yamamoto, A., … Akiyama, M. (2013). The majority of generalized pustular psoriasis without psoriasis vulgaris Is caused by deficiency of interleukin-36 receptor antagonist. *Journal of Investigative Dermatology*, *133*(11). https://doi.org/10.1038/jid.2013.230

Sumarac-Dumanovic, M., Stevanovic, D., Ljubic, A., Jorga, J., Simic, M., Stamenkovic-Pejkovic, D., Starcevic, V., Trajkovic, V., & Micic, D.

(2009). Increased activity of interleukin-23/interleukin-17 proinflammatory axis in obese women. *International Journal of Obesity*, *33*(1). https://doi.org/10.1038/ijo.2008.216

Sun, L., Liu, W., & Zhang, L. J. (2019). The Role of Toll-Like Receptors in Skin Host Defense, Psoriasis, and Atopic Dermatitis. In *Journal of Immunology Research* (Vol. 2019). https://doi.org/10.1155/2019/1824624

Sun, L.-D., Cheng, H., Wang, Z.-X., Zhang, A.-P., Wang, P.-G., Xu, J.-H., Zhu, Q.-X., Zhou, H.-S., Ellinghaus, E., Zhang, F.-R., Pu, X.-M., Yang, X.-Q., Zhang, J.-Z., Xu, A.-E., Wu, R.-N., Xu, L.-M., Peng, L., Helms, C. A., Ren, Y.-Q., … Zhang, X.-J. (2010). Association analyses identify six new psoriasis susceptibility loci in the Chinese population. *Nature Genetics*, *42*(11), 1005–1009. https://doi.org/10.1038/ng.690

Swanson, K. V., Deng, M., & Ting, J. P. Y. (2019). The NLRP3 inflammasome: molecular activation and regulation to therapeutics. In *Nature Reviews Immunology* (Vol. 19, Issue 8). https://doi.org/10.1038/s41577-019-0165-0

Takahashi, H., Takahashi, I., Honma, M., Ishida-Yamamoto, A., & Iizuka, H. (2010). Prevalence of metabolic syndrome in Japanese psoriasis patients. In *Journal of Dermatological Science* (Vol. 57, Issue 2). https://doi.org/10.1016/j.jdermsci.2009.11.002

Takahashi, T., & Yamasaki, K. (2020). Psoriasis and antimicrobial peptides. In *International Journal of Molecular Sciences* (Vol. 21, Issue 18). https://doi.org/10.3390/ijms21186791

Takeuchi, O., & Akira, S. (2010). Pattern Recognition Receptors and Inflammation. In *Cell* (Vol. 140, Issue 6). https://doi.org/10.1016/j.cell.2010.01.022

Tang, C., Chen, S., Qian, H., & Huang, W. (2012). Interleukin-23: As a drug target for autoimmune inflammatory diseases. In *Immunology* (Vol. 135, Issue 2). https://doi.org/10.1111/j.1365-2567.2011.03522.x

Theodorakopoulou, E., Jamieson, L., Bundy, C., Chularojanamontri, L., Middleton, L., Motta, L., Warren, R. B., & Griffiths, C. E. M. (2012). Clinical and immunological aspects of late-onset psoriasis. *British Journal of Dermatology*, *167*.

Thomas, L., Canoui-Poitrine, F., Gottenberg, J. E., Economu-Dubosc, A., Medkour, F., Chevalier, X., Bastuji-Garin, S., Le Louët, H., Farrenq, V., & Claudepierre, P. (2012). Incidence of new-onset and flare of preexisting psoriasis during rituximab therapy for rheumatoid arthritis: Data from the French AIR registry. In *Journal of Rheumatology* (Vol. 39, Issue 5). https://doi.org/10.3899/jrheum.111347

Tollefson, M. M., Crowson, C. S., McEvoy, M. T., & Maradit Kremers, H. (2010). Incidence of psoriasis in children: A population-based study. *Journal of the American Academy of Dermatology*, *62*(6). https://doi.org/10.1016/j.jaad.2009.07.029

Torti, D. C., & Feldman, S. R. (2007). Interleukin-12, interleukin-23, and psoriasis: Current prospects. In *Journal of the American Academy of Dermatology* (Vol. 57, Issue 6). https://doi.org/10.1016/j.jaad.2007.07.016

Triantafilou, K., Triantafilou, M., Lepper, P. M., Olden, R., & Dias, I. D. S. R. (2011). Location, location, location: Is membrane partitioning everything when it comes to innate immune activation? In *Mediators of Inflammation* (Vol. 2011). https://doi.org/10.1155/2011/186093

Tribó, M. J., Turroja, M., Castaño-Vinyals, G., Bulbena, A., Ros, E., Garcíamartínez, P., Tausk, F., Sagristà, M., Pujol, R. M., Ferran, M., & Gallardo, F. (2019). Patients with moderate to severe psoriasis associate with higher risk of depression and anxiety symptoms: Results of a multivariate study of 300 Spanish individuals with psoriasis. *Acta Dermato-Venereologica*, *99*(4). https://doi.org/10.2340/00015555-3114

van Acht, M. R., van den Reek, J. M., de Jong, E. M., & Seyger, M. M. (2022). The Effect of Lifestyle Changes on Disease Severity and Quality of Life in Patients with Plaque Psoriasis: A Narrative Review. *Psoriasis: Targets and Therapy*, *Volume 12*. https://doi.org/10.2147/ptt.s294189

Vaure, C., & Liu, Y. (2014). A comparative review of toll-like receptor 4 expression and functionality in different animal species. In *Frontiers in Immunology* (Vol. 5, Issue JUL). https://doi.org/10.3389/fimmu.2014.00316

Vičić, M., Peternel, S., Simonić, E., Sotošek-Tokmadžić, V., Massari, D., Brajac, I., Kaštelan, M., & Prpić-Massari, L. (2016). Cytotoxic T lymphocytes as a potential brake of keratinocyte proliferation in psoriasis. *Medical Hypotheses*, *87*. https://doi.org/10.1016/j.mehy.2015.12.004

Vijay, K. (2018). Toll-like receptors in immunity and inflammatory diseases: Past, present, and future. In *International Immunopharmacology* (Vol. 59). https://doi.org/10.1016/j.intimp.2018.03.002

Volarić, I., Vičić, M., & Prpić-Massari, L. (2019). The role of cd8+ t-cells and their cytokines in the pathogenesis of psoriasis. In *Acta Dermatovenerologica Croatica* (Vol. 27, Issue 3).

Wadachi, R., & Hargreaves, K. M. (2006). Trigeminal nociceptors express TLR-4 and CD14: A mechanism for pain due to infection. *Journal of Dental Research*, *85*(1). https://doi.org/10.1177/154405910608500108

Wang, A., & Bai, Y. P. (2020). Dendritic cells: The driver of psoriasis. In *Journal of Dermatology* (Vol. 47, Issue 2). https://doi.org/10.1111/1346-8138.15184

Yang, X. O., Pappu, B. P., Nurieva, R., Akimzhanov, A., Kang, H. S., Chung, Y., Ma, L., Shah, B., Panopoulos, A. D., Schluns, K. S., Watowich, S. S., Tian, Q., Jetten, A. M., & Dong, C. (2008). T Helper 17 Lineage Differentiation Is Programmed by Orphan Nuclear Receptors RORα and RORγ. *Immunity*, *28*(1). https://doi.org/10.1016/j.immuni.2007.11.016

Yasuda, K., Takeuchi, Y., & Hirota, K. (2019). The pathogenicity of Th17 cells in autoimmune diseases. In *Seminars in Immunopathology* (Vol. 41, Issue 3). https://doi.org/10.1007/s00281-019-00733-8

Yen, D., Cheung, J., Scheerens, H., Poulet, F., McClanahan, T., Mckenzie, B., Kleinschek, M. A., Owyang, A., Mattson, J., Blumenschein, W., Murphy, E., Sathe, M., Cua, D. J., Kastelein, R. A., & Rennick, D. (2006). IL-23 is essential for T cell-mediated colitis and promotes inflammation via IL-17 and IL-6. *Journal of Clinical Investigation*, *116*(5). https://doi.org/10.1172/JCI21404

Yip, K. H., Papadopoulos, M., Pant, H., & Tumes, D. J. (2019). The role of invariant T cells in inflammation of the skin and airways. In *Seminars in Immunopathology* (Vol. 41, Issue 3). https://doi.org/10.1007/s00281-019-00740-9

Zenewicz, L. A., & Flavell, R. A. (2011). Recent advances in IL-22 biology. In *International Immunology* (Vol. 23, Issue 3). https://doi.org/10.1093/intimm/dxr001

Zhang, G. L., Huang, F., Zhang, J. L., & Li, X. F. (2009). A clinical study of leflunomide and methotrexate therapy in psoriatic arthritis. *Zhonghua Nei Ke Za Zhi [Chinese Journal of Internal Medicine]*, *48*(7).

Zhang, X., Angkasekwinai, P., Dong, C., & Tang, H. (2011). Structure and function of interleukin-17 family cytokines. In *Protein and Cell* (Vol. 2, Issue 1). https://doi.org/10.1007/s13238-011-1006-5

Assessment Questionnaire

Name: Age : Date: Length:
Weight: Address :

Urban: Rural:

Gender Work

Family History:

Clinical Symptoms:

1.

2.

Nutrition:

Smoking:

Medical History:

Cardiovascular :

Respiratory : Shortness of breath : Asthma:

Diabetic : Renal Diseases : Hypertension :

Otitis Media: Tonsilitis:

Infectious diseases :

Blood Diarrhea:

Weight loss :

Lab tests:

1.

2.

3.

Past Surgeries:

1.

2.

Drug Chemotherapy:

1. 2. 3.

الخلاصة

تعتبر الصدفية مرضًا مناعيًا يؤثر على الجلد وله أساس وراثي ومناعي معقد. يمكن تحسين علاج الصدفية من خلال فهم أفضل لدور العلامات المناعية والعوامل الاجتماعية والديموغرافية المعنية. هدف هذه الدراسة هو فحص العلاقة بين العلامات المناعية (IL-17 و IL-23 و TLR-4 و TLR-7) وعدة متغيرات اجتماعية وديموغرافية، بما في ذلك العمر والجنس وشدة المرض وتصنيف كتلة الجسم في مرضى الصدفية.

أُجريت الدراسة الحالية على مرضى الصدفية في مستشفى إمام الحسين في محافظة كربلاء، العراق، من ديسمبر 2022 إلى أبريل 2023. تم استخدام عينات الدم للمشاركين من أفراد صحيين ومرضى الصدفية الذين تم تشخيصهم حديثًا ولم يعالجوا. تم استبعاد النساء الحوامل والذين يعانون من حالات مزمنة والذين يتلقون علاج الصدفية. تم إجراء دراسة مراقبة توضيحية باستخدام عينات مريحة لاختيار المشاركين. تم استخدام طريقة تقييم نظام PASI لتقييم أربع مناطق في الجسم، وتم استخدام طريقة الإليزا الساندويتش لتحليل العلامات المناعية.

أظهرت الدراسة أن مرضى الصدفية (5650) ٪ ((كانوا أكثر انتشارًا من السيطرة (40 44)٪((، دون وجود فرق كبير في العمر أو الجنس. كانت الإناث (5626) ٪ ((تفوق الذكور (14 35)٪ ((في كلتا المجموعتين. هناك فرق كبير في مؤشر كتلة الجسم (BMI) بين السيطرة الصحية ومرضى الصدفية، ولكن متوسط مؤشر كتلة الجسم كان مختلفًا إحصائيًا. كان لدى مرضى الصدفية نسبة أعلى من المدخنين من السكان العامين. أبقى كل من السيطرة ومرضى الصدفية على نظام غذائي صحي، مع أقل نسبة لاستخدام الأطعمة الاصطناعية. أبلغ معظم المرضى عن أعراض معتدلة، مع البقية تجربة أعراض شديدة. لم تكن فروق العمر مهمة، ولكن مرضى الصدفية الذين يعانون من أعراض شديدة هم أكبر سنا في فئات العمر المعينة. كانت لدى مرضى الصدفية الذين يعانون من أعراض شديدة قيم BMI أعلى، وكانوا أكثر عرضة للتدخين، وكانوا يعانون من مستويات أعلى من التوتر، ويتناولون الطعام الاصطناعي. وجد أن العلامات المناعية (IL-17 و IL-23 و TLR-4 و TLR-7) كانت أعلى في مرضى الصدفية مقارنة بالسيطرة الصحية، مما يشير إلى إمكانية مشاركتها في نشوء المرض.

جامعة كربلاء

كلية العلوم الطبية التطبيقية

قسم التحليلات المرضية

دراسة مستويات الانترلوكينات 17 ، 23 والمستلمات الشبيهة بالتول 4 ، 7 في مصل مرضى الصدفية

رسالة مقدمة الى

مجلس كلية العلوم التطبيقية وهي جزء من متطلبات نيل شهادة الماجستير في التحليلات

المرضية

كتبت بواسطة

عبد الله حمـــــــد عبـــود

بكالوريوس علوم الحياة/ كلية العلوم/ جامعة كربلاء 2007

بإشراف

الاستاذ الدكتور

حسن علي حسين سعدي

2023 ميلادي **1445 هجري**