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Study of Chitinase- 3-Like- 1 Protein(CHI3L1) and Ghrelin Peptide in People who Suffering from Psoriasis in Babylon Province.

A Thesis

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بسم الله الرحمن الرحيم

﴿وفوق كل ذي علم عليم﴾

صدق الله العلي العظيم

(76 -يوسف)

Supervisor Certification

We certify that this thesis entitled ((**Study of Chitinase-3-like-1 protein and Ghrelin peptide in people who suffering from psoriasis in Babylon province**)) has been prepared under our supervision at the Department of Biochemistry, College of Medicine, University of Babylon, in partial requirements for the degree of master in Clinical Biochemistry.

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Dedication

To my …… mother
To my …….. father
To my brothers and sisters
To my teacher, Mr. Mohammed Reza Shirazi
To my great supervisor (Dr. Khawla and Dr. Mohammed)
To my great country
To the martyrs of the popular crowd
To my dear friends
To whom help me
And to myself
To University of Babylon, College of Medicine, Dept. of Biochemistry I appreciate what they all have done
To everyone I love.

Ahmed Hassan Sami

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رسالة

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اشراف

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List of Abbreviation

Abbreviation	Details
ADAMTSL5	A disintegrin and metalloproteinase with thrombospondin motifs-like protein 5
A2M	α2-macroglobulin
ACE	Angiotensin Converting Enzyme
AG	Acyl ghrelin
Agrp	Agouti related peptide
AMPs	Antimicrobial peptides
APC	Antigen-presenting cells
ARC	Hypothalamic arcuate nucleus
AUC	Area under the curve
BMI	Body Mass Index
CHI3L1	Chitinase-3-like-1 protein
CLPs	chitinase-like proteins
CRP	C-reactive protein
Cu	Copper
DCs	Dendritic cells
DNA	Deoxyribonucleic acid
ECM	Extracellular matrix

ELISA	Enzyme linked immunosorbent assay
ER	Endoplasmic reticulum
GH	Growth hormone
GH18	Glycoside Hydrolase Family 18
GHRL	Ghrelin
GHS-R1a	Growth hormone secretagogue receptor
GlcNAc	β(1–4)-linked N-acetyl-D-glucosamine
GOAT	Ghrelin O Acyl Transferase
GPR39	G protein-coupled receptor 39
HLA	Human leucocyte antigen
HRP	Horseradish Peroxidase
IFN-γ	Interferon gamma
Ig	Immunoglobulin
IL	Interleuken
Kb	Kilobases
KDa	Kilo Daltons
Kg	Kilograms
LC	Langerhans cells
LL-37	Cathelicidin
MØ	Macrophages
MBOAT	Membrane-bound O-acyltransferase

mCRP	Monomeric CRP
mDCs	Myeloid dendritic cells
MHC	Major histocompatibility complex
MTX	Methotrexate
nCRP	Native C- reactive protein
NK cells	Natural killer cell
NPV	Negative predictive value
Npy	Neuropeptide Y
NSAIDs	Non Steroid Anti-Inflammatory Drug
OD	Optical density
PASI	Psoriasis Area and Severity Index
PCh	Phosphocholine
pDCs	plasmacytoid dendritic cells
PPV	Positive predictive value
PsA	Psoriatic arthritis
PSORS	Psoriasis susceptibility locus
RNA	Ribonucleic acid
ROC	Receiver operating characteristic
ROS	Reactive oxygen speciese
SD	Standard deviation
SLC	solute-linked carrier families

SpA	Spondyloarthritis
SPSS	Statistical Package of Social Science
STAT	Signal Transducer and Activator of Transcription
T- reg	Regulatory T-cell
TGF- β	Transforming growth factor-beta
TGF- β	Transforming growth factor-beta
Th	T- helper
TLR9	Toll-like receptor 9
TNF-α	Tumor necrosis factor alpha
TNF-β	Tumor necrosis factor beta
UAG	Unacylated ghrelin
UV	Ultra violet
VEGF	Vascular endothelial growth factor
Zn	Zinc
ZnT	Zinc transporters
Ml	Microliter

Summary

Psoriasis is a chronic inflammatory illness characterized by the generation of well-defined raised erythematous plaques with silvery white scales on the extensor surface. Within the skin and systemically, psoriasis is characterized by keratinocyte hyperproliferation and abnormal differentiation, as well as vascular enlargement, leukocyte infiltration, and changes in cytokine production.

The aim of current study was to evaluate the level of Chitinase-3-like-1 protein among psoriatic patients and healthy control and evaluate the change in the serum level of Zinc in patients with psoriasis and compared to controls. Also evaluate the hormonal change in the serum level of Ghrelin in patients with psoriasis. This Study also evaluated the sensitivity and specificity of CHI3L1 and CRP in serum of patients with psoriasis as compared to healthy control to know who is more accurate in diagnosing psoriasis by use the ROC curve. It's also study the BMI in psoriasis patients.

This study was designed as a case-control study includes 100 individuals but in order to match between patients and control in age and gender the number was 90 individuals involved in this study, divided into three groups, sever cases group that contain 30 patients with PASI score more than 20 and moderate cases groups that contain 30 patients with PASI score from 10-20. Thirty individual apparently healthy as a control groups were involved in this study, and all of them without any skin disease or other autoimmune diseases, and identical with patients in the age, and sex. All the psoriatic subjects included in the current study were diagnosed by a dermatologist. Currents study was conducted in Dermatology Clinic in Marjan Teaching Hospital in Hilla city and

Department of Biochemistry in College of Medicine at University of Babylon from October 2021 to September 2022. All participants in this study were informed before to collecting samples and verbal agreement was obtained from each of them.

Chitinase-3-like-1 protein and Ghrelin peptide were determined using the Enzyme-linked immunosorbent assay (ELISA) technique while C-reactive protein was determine by Immunoturbidimetric Method and Zinc by spectrophotometer.

The results of current study revealed a significant increase in the serum of CHI3L1 and CRP among psoriatic patient when compare with healthy control and significant decrease of serum Zinc in psoriasis patient than healthy control, while Ghrelin level show non-significant difference between psoriasis patient and control. The body mass index(BMI) was significantly increase in psoriasis patients when compare with healthy control. Also show positive correlation between Psoriasis area and severity index(PASI) score and CRP also between BMI and CRP and between BMI and PASI score.

In conclusion, The Chitinase-3-like-1 protein and C-reactive protein increased with increase severity of psoriasis diseased so it was higher in sever psoriasis group than moderate group. Zinc are significantly higher in healthy control than psoriasis patients and ghrelin show non-significant difference between psoriasis patients and controls group. The body mass index was significantly higher in psoriasis patients than control, so that the obesity may be considered as a comorbid for psoriasis patients. There was a positive correlations between body mass index(BMI) and C-reactive protein(CRP) , also between C-reactive protein and Psoriasis area and severity index(PASI) score and between body mass index and

Psoriasis area and severity index score. The Chitinase-3-like-1 protein was more sensitive and specific marker than C-reactive protein, according to the area under the curve(AUC) in the receiver operating characteristic (ROC) curve test, so that it’s a good marker for diagnosis of psoriasis patients.

1. Introduction and Literature Review

1.1. Introduction

Psoriasis is a chronic inflammatory illness characterized by the generation of well-defined raised erythematous plaques with silvery white scales on the surface[1]. Willan'slepra is named for Robert Willan, the father of modern dermatology, who is credited with the first detailed clinical description of psoriasis[2]. Psoriasis is a Greek word that means "roughly itchy condition" (psora: "itch", sis: "action")[3].

There are two age of onset peaks: the greatest is between 20 and 30 years, while the smaller peak is between 50 and 60 years, This data suggests that there are two types of psoriasis: type I psoriasis, which appears before the age of 40 years and is associated with a positive family history of psoriasis, frequent HLA association, and more severe disease. Type II psoriasis, which appears after 40 years of age and has no HLA link and has a negative family history[4]. Within the skin and systemically, psoriasis is characterized by keratinocyte hyperproliferation and abnormal differentiation, as well as vascular enlargement, leukocyte infiltration, and changes in cytokine production[5].

Classification of psoriasis is based on a number of variable, including age of onset, severity, and anatomical site (e.g. scalp, nail, genital). There are various clinical types of psoriasis, including plaque, guttate, erythrodermic, and pustular psoriasis[6]. Chronic plaque psoriasis (also known as psoriasis vulgaris: (PV) is the most common type of psoriasis, accounting for over 90% of cases[7]. Although there is evidence of genetic predisposition, the cause of psoriasis remains unknown. External and internal factors, such as mild trauma, sunburn, infections, systemic drugs, and stress, can also trigger psoriasis [8].

Psoriasis has been linked to the major histocompatibility complex (MHC), which includes the human leukocyte antigen Cw6 (HLA-Cw6)[9]. There are two potential antigens for HLA-Cw6 recently have been discovered: LL-37, a cathelicidin-related antimicrobial peptide, and the A disintegrin and metalloproteinase with thrombospondin motifs-like protein 5 (ADAMTSL5), located on melanocytes and keratinocytes [10].

T-cell dysfunction is important in the origin of psoriasis. In particular, cytokines play a critical role in both the immunopathophysiology and the treatment of this chronic disease[11]. T cells in psoriasis lesions release Th1 / Th17 mediators, such as IFN-γ, IL2, IL17, IL23 and TNF-α. These mediators act on keratinocytes and other cells in the skin, activating them and inducing the formation of lesions. The pathogenesis of disease is mostly driven by type 1 and type 17 cytokine-producing cells, which are controlled by regulatory T cells in healthy people (Tregs). Tregs are important for immune homeostasis and help to avoid autoimmune illness by inhibiting immune responses. Tregs are impaired in their suppressive activity in psoriasis, resulting in a change in the T-helper 17/Treg balance[12].

Several epidemiological studies have found that psoriasis patients' body mass index (BMI), a commonly used indicator for obesity, is higher than healthy controls. Adipose tissue is quite metabolically active, producing a variety of systemically released, immune-modifying molecules referred to as adipocytokines. These include IL-1, IL-6, and TNF-α, which are released by resident macrophages in close proximity to adipocytes[13].

1.2. Definition

Psoriasis is an immune-mediated skin disease characterized by well-defined, erythematous, scaly plaques and chronic inflammatory skin lesions [14]. The global prevalence of psoriasis is 2 to 3 percent, with lower rates in Asia and Africa and greater rates in Scandinavian populations[15].

In Asia, near about 1% of the population is affected with psoriasis. Because of its strong link to comorbidities such as psoriatic arthritis, obesity, metabolic syndrome, chronic renal disease, stroke, and cardiovascular disease, psoriasis is also classified as a systemic inflammatory condition[16].

Increased epidermal thickness, hyperproliferation of keratinocytes due to excessive cell division in the basal layers, hyperkinetic with increased cell production of new cells 20–30 times, increased epidermal volume, increased rate of nail growth, formation of abnormal nucleated, loose scaly stratum corneum[17]. Chronic plaque, guttate, inverse, pustular, and erythrodermic psoriasis are some of the several types of psoriasis. Each of these psoriasis types, as well as the different forms within each type, can be classified into three severity levels: mild, moderate, and severe[18].

1.3. Classification

Psoriasis is a skin condition that manifests itself in a variety of ways. A person can have multiple forms at any given time. Erythema, thickening, and squamae are all common features of all of the lesions. Although it can affect any part of the body, it is most commonly found in the knees, elbows, lumbosacral region, scalp, and genital area[19].

Henseler and Christophers divided psoriasis into two types, type I and type II, based on the age at onset. Type 1 begins at or before the age of 40, while Type II develops after that age. More than 75 percent of cases are of type I disease. Those with early onset psoriasis, often known as type I psoriasis, had more relatives affected and had more severe disease than patients with type II psoriasis[4].

The most widely used tool to assess disease severity and extent is the Psoriasis Area and Severity Index (PASI).The use of the PASI score can be recommended for scientific evaluation of the clinical severity of psoriasis[20].

According to PASI score, psoriasis can be classified into three types:

A. Mild: PASI score less than 10 with absent or negligible effect on quality of life together with 65% of total population psoriatic patients that the surface area of the body was affected.

B. Moderate : PASI score between 10-20 with significant impact on quality of life together with between 25% of total population psoriatic patients that the surface area of the body was affected.

C. Sever : PASI score more than 20 with significant to debilitating impact on quality of life together with more than 10% of total population psoriatic patients that the body surface area was affected(1).

The disease spectrum, or clinical phenotypes, have been classified based on various psoriasis characteristics such as the age of onset, the degree of skin involvement, the morphologic pattern, and the predominant involvement of specific anatomic locations of the body (25). Table (1-1)[2].

Table (1-1): Classification of psoriasis.

A- Non-pustular psoriasis	**B- Pustular psoriasis**
Psoriasis vulgaris	Generalized pustular psoriasis (von Zumbusch type)
Guttate psoriasis	Impetigo herpetiformis
Erythrodermic psoriasis	Localized pustular psoriasis:- -Palmoplantar pustular psoriasis (Barber type) -Acrodermatitis continua of Hallopeau
Palmoplantar psoriasis	
Inverse psoriasis	
Psoriatic arthritis (PsA)	

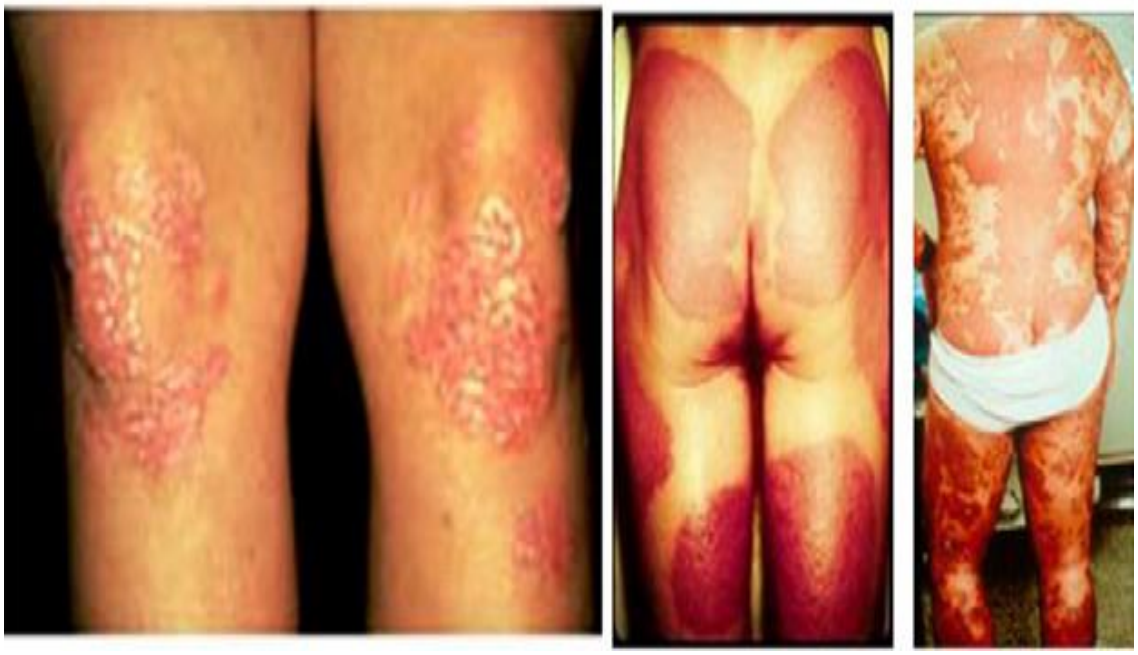
1.3.1. Non-Pustular Psoriasis

1.3.1.1. Plaque Psoriasis

This is the most common type of psoriasis, accounting for about 90% of all psoriatic patients. It is also called psoriasis vulgaris[24]. The lesions usually begin as erythematous macules or papules, spread out, and coalesce forming plaques. Dry, sharply demarcated round/oval plaques with loosely attached silvery white scales characterize the lesions (Fig. 1.1A). Psoriasis plaques can affect any part of the body but are most commonly found symmetrically on the knees and elbows (Fig.1.1A, B, C); and scalp that may be the most common site of involvement[25]. If the psoriatic plaque's surface is scraped with a blunt scalpel, Squamae like candle wax fall off as layers of white lamellae that show coherence after removal. The "wax spot phenomenon" is another name for this desquamation. A moist layer attached to the psoriatic plaque can be

revealed if the plaque is scraped further. This is the epidermis's last layer of dermal papillae, and known as the "last membrane phenomenon. Further Scraping of the plaque shows an erythematous background with bleeding foci, as well as little red pinpoints known as the "Auspitz sign"(26).

A B C



Fig(1-1): Plaque psoriasis: A. Localized plaque psoriasis. B. Stable widespread symmetrically distributed plaques. C. Unstable widespread psoriasis progressing to erythrodema[25].

1.3.1.2. Guttate Psoriasis

This type of psoriasis is commonly seen in children and young adults. The Lesions appear suddenly as small droplets or, less frequently, as squamous psoriatic papules, and generally occur after streptococcal infections. This type of psoriasis is most commonly linked to the HLA-

Cw6 gene. The trunk, proximal parts of the limbs, the face, and the scalp are the most common sites for lesions[28].

1.3.1.3 Erythrodermic psoriasis

Erythroderma is characterized by generalized erythema of the skin and frequently involves >80% to 90% of body surface area (BSA)(33).

1.3.1.4 Inverse psoriasis

Inverse psoriasis affects the skin folds and found with well-demarcated, thin erythematous plaques in flexural sites, such as the axillae, groin, neck, and inframammary folds. Inverse psoriasis lacks the classic dry scale of plaque psoriasis because these areas are moist, and as a result, may appear shiny [32].

1.3.1.5. Palmoplantar psoriasis

Usually this type of psoriasis symmetrically involves palms of the hands and soles of the feet. Erythema is not always found, but when it exists it appears as a pinkish-yellow lesion[33].

1.3.1.6. psoriatic arthritis

Psoriatic arthritis is the most common comorbidity of psoriasis. It is a heterogeneous, inflammatory musculoskeletal disease that can cause permanent damage to both peripheral and axial joints. Axial disease affects 25 % to 70 % of PsA patients. preclinical studies have shown that genes linked with axial disease, such as HLA-B27, may play a role in the overproduction of tumor necrosis factor-alpha (TNF-α) and interleukin-17 (IL-17). PsA affects about 25% to 30% of psoriasis patients[34] . PsA has a wide range of symptoms, including nail and skin abnormalities,

peripheral arthritis, enthesitis, dactylitis, and axial spondyloarthritis (SpA)(41).

1.3.2. Pustular psoriasis

1.3.2.1 Generalized pustular psoriasis (von Zumbusch type)

This is an uncommon type of psoriasis that develops as pustules. It is most commonly found in young people[33].

1.3.2.2 Impetigo herpetiformis

This kind of psoriasis, also known as generalized pustular psoriasis during pregnancy, is uncommon. It is characterized by erythematous lesions with pustules[37].

1.3.2.3 Localized pustular psoriasis

Palmoplantar pustulosis is divided into 2 types : Barber’s pustular psoriasis and acrodermatitis continua of Hallopeau.

1) Pustular psoriasis of the Barber type: It's a recurrent, chronic form that's more common in women and those who have a family history of palmoplantar pustulosis.

2) Acrodermatitis continua (Hallopeau disease): It's a slowly progressing skin condition characterised by sterile pustular eruptions on the toes and fingers, with severe cases leading to the loss of nails and distal phalange[38].

1.4. Epidemiology of psoriasis

1.4.1 Incidence and Prevalence

The worldwide prevalence is around 2%, but it varies by region. Asian and some African populations have a lower prevalence[39]. In

Asia, the prevalence of psoriasis is less than 0.5%. In Saudi Arabia, psoriasis prevalence is estimated to be 1.5% and 3.4%[40]. The incidence of psoriasis in Iraq was 1.8%[41].

1.4.2 Genetic Epidemiology

Psoriasis has a complex molecular genetic basis, with evidence of multiple genes being involved. At least nine susceptibility loci on the chromosome have been discovered (PSORS1-9). The PSORS1 gene, which is found on chromosome 6 (6p21) in the major histocompatibility complex region, appears to be associated to the majority of psoriasis cases. The most well-studied gene associated with psoriasis is HLA-Cw6, which encodes a major histocompatibility complex class I allele supporting psoriasis as a T cell–mediated reaction to an autoantigen[10].

1.5. Trigger factors of psoriasis.

1.5.1. Clinical factors

1.5.1.1. Genetics

Genetic factors play an important role in psoriasis. A study involving 8,045 twins in Norway reported that the prevalence of psoriasis in identical twins was much higher than in fraternal twins[42].

1.5.1.2. Drug

In a patient with a family history of psoriasis different drug can exacerbate pre-existing lesion or inducing new lesion. These drugs include β-blocker, lithium, anti-malarial, non-steroidal anti-inflammatory drugs (NSAID)[43].

1.5.1.3. Infection

Streptococcal infection considered as an important stimulator for guttate psoriasis[44]**.**

1.5.1.4. Obesity

There is a positive correlation between body mass index (BMI) and psoriasis especially in women that have high BMI; many studies proved that the women with higher BMI are more likely to have psoriasis[45]. The severity of psoriasis tend to increasing as the BMI increasing and these confirmed depending on a special study that applied the psoriasis area and severity index (PASI) score on a psoriatic patient after calculation the BMI[46]**.**

1.5.2. Behavioral Factors

1.5.2.1. Stress

Stress is known to be an important risk factor for developing psoriasis. In some studies, more than 60% of subjects complained of exacerbation of psoriasis following stressful events such as divorce, loss of job, loss of family member, and severe disease[47].

1.5.3. Physical Factors

1.5.3.1. Physical Trauma

Psoriasis can develop as a result of cutaneous trauma, which is known as the Koebner phenomenon, which was first described by Heinrich Koebner in 1877[48]. The prevalence of the Koebner phenomenon are approximately 11 to 75% in psoriasis. The Koebner phenomenon requires differentiation from the reverse Koebner

phenomenon, which is the disappearance of skin lesions following trauma over the existing lesions[4].

1.5.3.2. Climate

Studies have shown that psoriasis occurs more frequently in cold, dry climates compared to warm, humid climates[49].

1.6. Pathogenesis of psoriasis

Hyperproliferation of the epidermis, followed by massive dermal and epidermal inflammatory infiltration and enhanced angiogenesis inside the dermis, are the primary pathogenic alterations in psoriasis. Hyperkeratosis (stratum corneum thickening) and acanthosis (thickening of other epidermal layers) characterize psoriatic plaques, that are resulted from keratinocyte proliferation and abnormal differentiation[50].

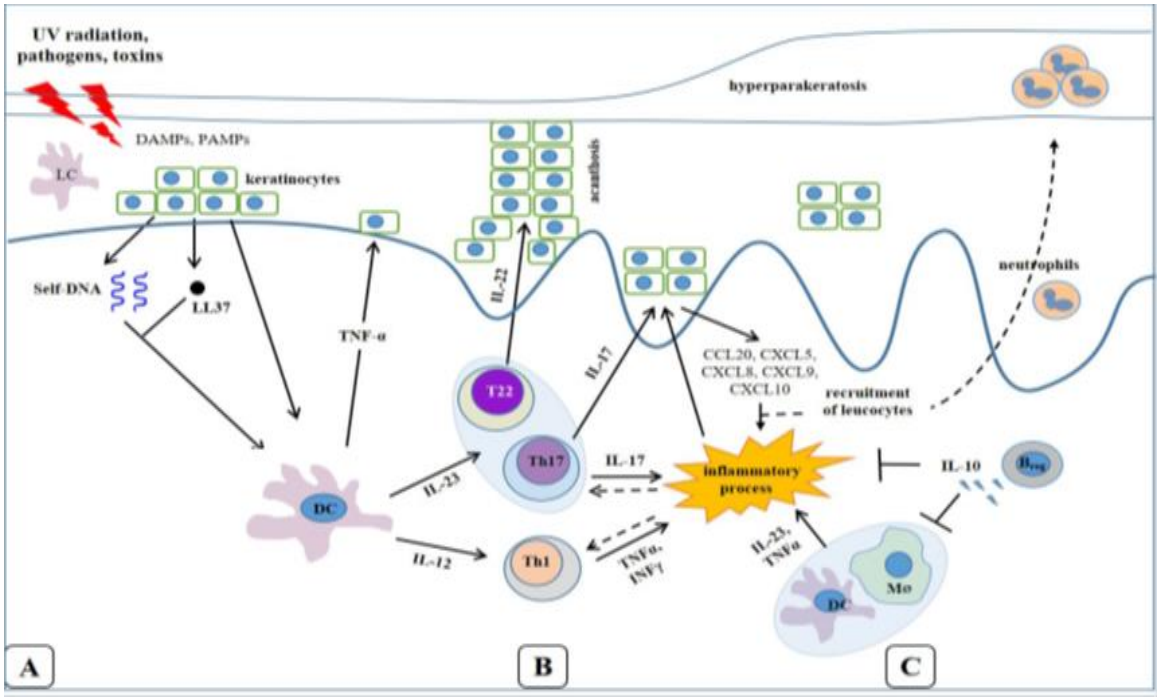
Psoriasis is a systemic inflammatory disease controlled by T cells and influenced by genetic predisposition as well as environmental factors. The infiltration of lymphocytes, macrophages, and neutrophils into the skin is characteristic of psoriatic lesions. In psoriasis there is a lot of interaction between innate immune cells (e.g. dendritic cells (DCs), macrophages, neutrophils), adaptive immune cells (B and T cells) and resident skin cells (e.g. keratinocytes, melanocytes, and endothelial cells)[51].

Professional antigen-presenting cells are dendritic cells. The recognition of antimicrobial peptides (AMPs), which are released by keratinocytes in response to injury and are overexpressed in psoriatic skin, is one of the proposed mechanisms. LL37, β -defensins, and S100 proteins are among the most investigated psoriasis-related AMPs. In psoriasis, the protein LL37, also known as cathelicidin, is thought to play

a pathogenic function. Damaged keratinocytes release it, which then combines with the self-genetic material from other damaged cells to form complexes. In plasmacytoid dendritic cells (pDCs), LL37 bound with DNA stimulates the toll-like receptor 9 (TLR9)[39].

The generation of type I IFN(IFN-α and IFN-β) by pDC is important in the generation of the psoriatic plaque. Type I IFN signaling enhances the phenotypic maturation of myeloid dendritic cells (mDCs) and has been linked to Th1 and Th17 differentiation and function includeing IFN-γ and interleukin (IL)-17 production, respectively[52]. LL37–DNA complexes stimulate pDCs via TLR9, whereas LL37 linked to RNA stimulates them via TLR7. LL37–RNA complexes also have an effect on mDCs via TLR8[53]. Activated mDCs move into draining lymph nodes and release tumor necrosis factor , interleukin (IL)-23, and interleukin (IL)-12, which are the latter two regulate Th17 and Th1 cell differentiation and proliferation, respectively [54]. Dermal DCs secrete the cytokines IL-12 and IL-23, which enhance Th1, Th17, and Th22 responses[55].

Th1 activation, which results in increased IFN-γ production, triggers the production of chemokines (CXCL9, CXCL10, and CXCL11) that help recruit more Th1 cells. Stimulations of IL-17-producing T cells, leading to IL-17 release, activates CCL20, CXCL1، CXCL2, and CXCL8/IL-8 synthesis, leading to recruitment of more IL-17-producing T cells and neutrophils into the skin. In keratinocytes, IL-17 is a strong inducer of AMP production. When Th22 cells are activated, they produce more IL-22, which can induce keratinocyte hyperplasia[56]. Keratinocytes further enhance psoriatic inflammation by producing proinflammatory cytokines, including IL-6, IL-8, IL-25, IL-36, TNF-α[6].



Fig(1-2). The Psoriasis pathogenesis. A) During exposure to microbial or mechanical injury, the damaged keratinocytes faster activation of antigen-presenting cells (APC) such as macrophages and dermal dendritic cells (DC). B) APCs including Langerhans cells (LC), DCs and potentially B cells interaction with T cells leading to their activation and proinflammatory cytokine production. C) Regulatory B cells (Breg) may modulate inflammation. To counteract inflammation, Breg release IL-10, which inhibits the activation of other leukocytes such as macrophages (MØ) and T cells[51].

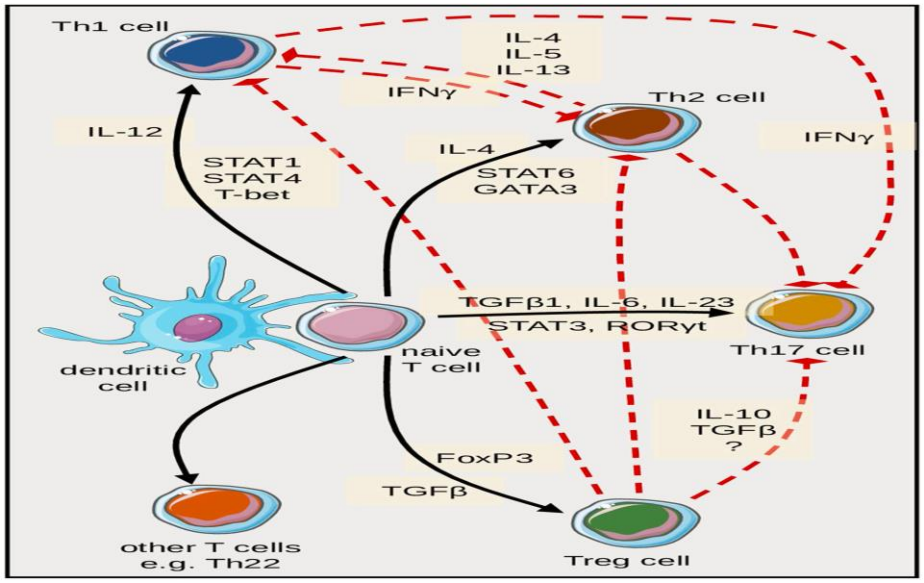


Fig (1-3): Differentiation of pathogenic T cells in psoriasis[57].

1.7. Diagnosis of psoriasis

Clinically the diagnosis is usually easy but may at times be difficult and challenging due to the psoriatic lesions may be similar to those of other inflammatory, infectious, and/or neoplastic skin diseases. Scratching or pressure can cause new lesions to form at the site of cutaneous trauma known as the Koebner phenomenon. When psoriatic scales are removed, a smooth, glossy, red membrane with small bleeding points where the thin suprapapillary epithelium is ripped away is frequently shown (Auspitz sign)[58].

There are no specific laboratory tests for diagnosing or determining the severity of psoriasis vulgaris. Only clinical manifestations guide diagnosis and allow for the selection of the appropriate treatment based on the severity of the disease. VEGF levels were shown to be higher in the serum of patients with severe psoriasis and to be related to disease severity. Increased levels of IL-17 and interferon gamma in the blood have been linked to a higher PASI score[59].

The Psoriasis Area and Severity Index is the current gold standard for assessing disease activity (PASI). This scale, developed by Fredrikson and Pettersson in 1978, is one of the most widely used instruments for assessing the severity of psoriasis. It calculates the affected body surface area and the psoriatic plaque intensity[60].

The physician divides the body into four parts (head, trunk, upper extremities, and lower extremities). Each body part is scored based on erythema, induration (thickness), and desquamation (scaling)[59]. It was calculated using online PASI calculator and on the formula {1} (given below) which relays on four parameters include Erythema (redness),

Induration (thickness), Desquamation (scaling) and Area of involvement, as in the figure (1-3). The scores from the regions are weighted and summed together to get a PASI score that ranges from 0 to 72[61].

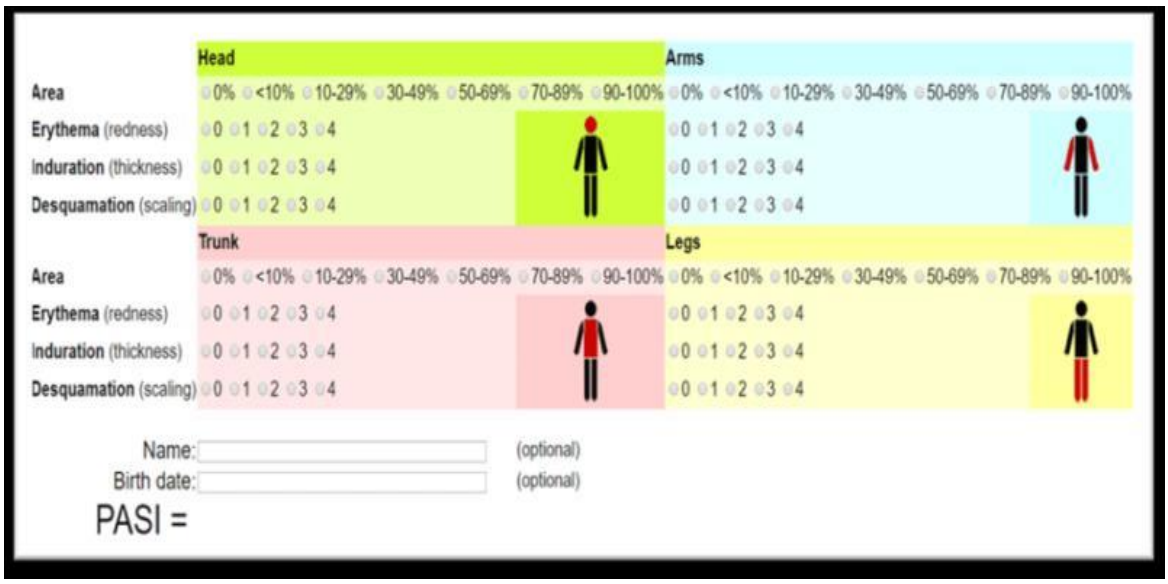


Figure (1-4) : Showing PASI score calculation[62].

PASI= 0.1(Eh+ Ih+ Dh) Ah + 0.2(Eu+ Iu+ Du) Au + 0.3 (Et+ It+ Dt) At + 0.4 (El+ Il+ Dl) Al. formula (1).

Where, E- Erythema, I- Induration, D- Desquamation, A- Area Involved, h- Head, u- Upper Limbs, t- Trunk And l-Lower Limbs.

1.8. Treatment of psoriasis

Psoriasis is a recurrent chronic illness that often demands long-term treatment. Psoriatic patients are usually divided into two groups: mild or moderate to severe psoriasis based on the clinical severity of the lesions, the percentage of body surface area affected. The PASI score has been widely used in clinical investigations, particularly those involving the development of biologic drugs. A combination of glucocorticoids, vitamin D analogues, and phototherapy can be used to treat mild to

moderate psoriasis topically. Systemic therapy is often required for moderate to severe psoriasis[63].

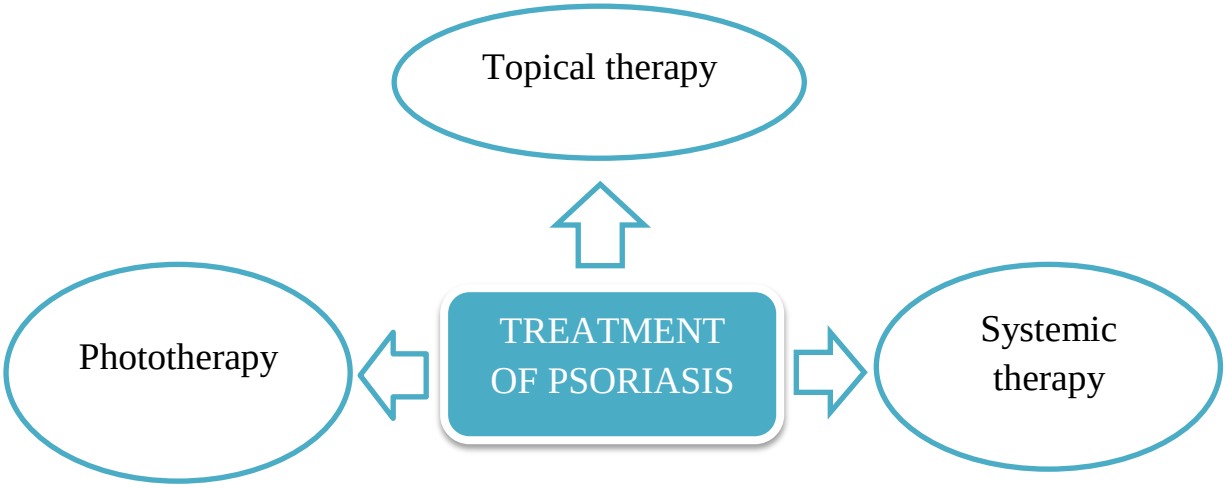


Fig (1-5): Major line of psoriasis treatment[64].

1.8.1. Topical therapy

For the treatment of mild to moderate illness, topical therapy is the gold standard. Topical therapy, which may be started at the primary care level, would assist a large number of patients [64].

1.8.1.1. Corticosteroids.

Corticosteroids which are considered the cornerstone of topical treatment, are often well tolerated and helpful for patients with mild psoriasis. Salicylic acid, a keratolytic agent, can be used in conjunction with steroid therapy to treat plaques with thicker scales[65].

1.8.1.2. Vitamin D3 analogues

Calcipotriol, a vitamin D3 analogue, is used to treat plaque psoriasis and moderately severe scalp psoriasis as a first-line topical treatment[66].

1.8.1.3. Combination products

Calcipotriol and betamethasone dipropionate in combination have been demonstrated to be more effective for psoriasis than either treatment alone [64].

1.8.1.4. Miscellaneous

Urea is a hygroscopic molecule that, because of its moisturising properties, is topically used for the treatment of skin dryness at concentrations ranging from 2% to 12%[67].

1.8.2 Phototherapy

Phototherapy is a treatment that is effective, safe, and easy to use. For the treatment of severe psoriasis, phototherapy can be coupled with biologic agents[68].

1.8.3. Systemic therapy

1.8.3.1. Methotrexate(MTX)

MTX is a folic acid analogue that inhibits DNA synthesis by inhibiting the formation of thymidine and purine. Nausea, leucopenia, and an increase in liver transaminase are the most common side effects[69].

1.8.3.2. Cyclosporine

Cyclosporine is an immunosuppressant that inhibits T cells[69].

1.8.3.3. Acitretin

Acitretin is a synthetic retinoid use to treat moderate to severe psoriasis[70].

1.8.3.4 Apremilast

Apremilast is a small-molecule phosphodiesterase 4 inhibitor that works intracellularly by preventing the breakdown of cyclic adenosine

3′,5′-monophosphate, resulting in elevated intracellular cyclic adenosine 3′,5′-monophosphate levels in phosphodiesterase 4-expressing cells. This results in reduce amounts of pro-inflammatory cytokines TNF ,IFNγ , and IL-12, and rise levels of IL-10[71].

1.8.3.5 Biologic therapy

Today's definition of biologics includes complex engineered molecules such monoclonal antibodies and receptor fusion proteins[39].

1.8.3.5.1 TNF-α inhibitors

They are known as "first-generation biologics." Etanercept, infliximab, adalimumab, and certolizumab are the four drugs currently available in this category[72].

1.8.3.5.2 IL- 23 inhibitors

Ustekinumab was the first biologic approved for psoriasis vulgaris following TNF-α inhibitors[73].

1.8.3.5.3 IL-17 inhibitors

Interleukin-17 is targeted by three human monoclonal antibodies. Secukinumab and ixekizumab inhibit IL-17A[74].

1.9. Chitinase-3-like 1 protein (CHI3L1)

The most abundant polysaccharides on Earth are chitin and cellulose, which serve as stable structural elements in most animals and plants, respectively. Chitin, like cellulose, is a simple linear homopolysaccharide made up of β(1–4)-linked N-acetyl-D-glucosamine (GlcNAc), which is synthesized by chitin synthases in chitin-producing organisms[75].

Chitinases are classified into two groups, Glycoside Hydrolase Family 18(GH18) and 19, based on their amino acid sequences, structures, and catalytic processes. GH family 18 chitinases are found in mammals, plants, viruses, bacteria, fungi, nematodes, and arthropods. Although mammals do not synthesize chitin, they do produce chitinases and chitinase-like proteins (CLPs), which lack chitinolytic enzyme activity due to mutations in their active domain[76]. Enzymatically active chitinases and enzymatically inactive chitinase-like proteins(CLPs) belong to the Glycoside Hydrolase Family 18 (GH18) proteins[77].

Chitinase 3-like 1 protein (CHI3L1, also known as YKL-40), a member of the evolutionarily conserved glycosyl hydrolase family 18, has a high affinity for chitin, which it lacks the enzymatic activity to breakdown directly. Primarily, chitinase like proteins(CLPs) are carbohydrate binding molecules, but individual proteins often differ in the complexity of sugars they bind[78]. Human YKL-40 contains a single polypeptide chain of 383 amino acids, molecular mass of 40 KDa. On the basis of its three N-terminal amino acids tyrosine (Y), lysine (K) and leucine (L) and its molecular mass of 40 KDa, the protein was named YKL-40. The gene encoding YKL-40 glycoprotein was discovered in 1997. The CHI3L1 gene is found on chromosome 1q31–1q32 in humans[79].

Chitinase-3-like-1 protein is produced by a wide range of cells, including macrophages, neutrophils, stem cells, bone cells, synoviocytes, chondrocytes, fibroblast-like cells, endothelial cells, vascular smooth muscle cells, hepatic stellate cells, mammary epithelial cells, and cancer cells. Overexpression of CHI3L1 has been seen in a number of inflammatory disorders including asthma, sepsis, diabetes, cirrhosis,

preeclampsia, rheumatoid arthritis, and coronary artery disease. At the cellular level, cytokines, growth factors, cellular and extracellular matrix (ECM) factors, medications, and stress are all effective CHI3L1 regulators. IL-6, IL-13, IL-17, IFN-α, parathyroid hormone-related proteins, and vasopressin are among the cytokines and hormones that are known to regulate the expression of CHI3L1 in various cell types[80].

The exact biological functions of CHI3L1 are unknown. However, It is suggested to play a role in physiological and pathological processes such angiogenesis, mitogenesis, and remodeling[81].

This protein has already been investigated in many inflammatory disorders, including inflammatory bowel diseases, rheumatoid arthritis, inflammatory lung diseases, osteoarthritis, viral hepatitis, cardiovascular disease, and many malignant processes. Recently, few studies have looked into the role of CHI3L1 in cutaneous psoriasis; nevertheless, the results so far have been conflicting[82].

In addition to Th2 cells, Th17 cells express CHI3L1 selectively, raising interest in its potential function in psoriasis. CHI3L1 is stored in neutrophil granules and released after the neutrophil has fully activated. Because neutrophils significantly express CHI3L1 in the epidermis, active neutrophils may be a major source of serum CHI3L1 in psoriasis[81].

Chitinase-3-like-1 protein has a chemotactic effect on vascular endothelium and smooth muscle cells during tissue injury and remodeling, inflammation, and fibrosis. It regulates the morphology of vascular endothelial cells by stimulating endothelium tubulogenesis as well as vascular smooth muscle cell migration and adhesion[79].

1.10. Ghrelin

Ghrelin is a 28-amino-acid peptide hormone that is the only known human hunger-stimulating hormone. Ghrelin is an endogenous ligand for the growth hormone secretagogue receptor (GHS-R1a), which promotes the release of growth hormone (GH) when the receptor is activated. It was discovered in 1999 during the search for an endogenous ligand for the growth hormone secretagogue receptor (GHS-R1a). It is mainly synthesized by X/A-like cells in the stomach mucosa, but it can also be found in the hypothalamus, pituitary gland, hippocampus, brain cortex, adrenal gland, intestine, pancreas, and other human tissues[83].

Mark Heiman and Matthias Tschöp discovered in 2000 that ghrelin regulates food intake, body weight, adiposity, and glucose metabolism in the brain. Ghrelin is made from preproghrelin, a 117-amino-acid precursor produced by X/A-like cells in the stomach's gastric oxyntic glands. Preproghrelin is broken into a small signal peptide, ghrelin and obestatin[84]. Obestatin was previously assumed to play a function in food intake by acting on the G protein-coupled receptor 39 (GPR39), but this was not supported by all studies[85].

Ghrelin promotes its biological action by binding to GHSR1a, a seven-transmembrane G protein-coupled receptor found in the pituitary, pancreatic islets, adrenals, thyroid gland, myocardium, hypothalamic arcuate nucleus (ARC), hippocampus[86]. GHSR1a is found in neurons in the feeding center of the hypothalamus that express neuropeptide Y (Npy) and Agouti related peptide (Agrp), two well-known neuropeptides that stimulate food intake[84]. Ghrelin is found in the blood in two major forms: acyl (octanoylated) and non-acyl, but only acyl-ghrelin can bind to the growth hormone secretagogue receptor type 1 (GSH-R1a).

Although less than 10% of ghrelin in the blood is acylated, it is necessary for its activity[87]. Ghrelin is also said to be expressed in a variety of cell types in the skin, including epidermal cells, lymphocytes, and macrophages[88]. In negative energy balance conditions such as anorexia and caloric restriction, circulating ghrelin levels are elevated, while in positive energy balance states such as obesity, circulating ghrelin levels are decreased[89].

Ghrelin, like other peptide hormones, is expressed as a larger polypeptide that undergoes multiple processing steps before being released as show in Figure (1-1)[90]. The ghrelin precursor preproghrelin (117 amino acids) contains an N-terminal secretion signal peptide which is cleaved by signal peptidase in the endoplasmic reticulum (ER) to create the 94-amino acid ghrelin precursor proghrelin[91]. Proghrelin is modified with octanoic acid by GOAT, one of three members of the membrane-bound O-acyltransferase (MBOAT) superfamily of enzymes that acylate protein substrates, in a unique hormone processing step[92].

In 2008, GOAT was discovered to be a member of the MBOAT enzyme family, which catalyzes the octanoylation of ghrelin. The mature 28-amino-acid acylated ghrelin ('ghrelin') is then released into the bloodstream after a second proteolytic cleavage[91]. Serum esterases degrade acyl ghrelin (AG) into unacylated ghrelin (UAG), which loses the ester-linked octanoyl chain and the capacity to activate the GHS-R1a receptor. While UAG does not activate GHS-R1a, there is evidence to suggest that it is still biologically active, playing a role in insulin production[83].

On chromosome 3p25–26, the ghrelin gene spans up 5 kilobases (kb) of genomic DNA[93]. The half-life of acyl-ghrelin has been

observed to range from 30 minutes in rats to 240 minutes in humans. Ghrelin is collected by its receptor and eliminated in urine as part of the clearance process[94].

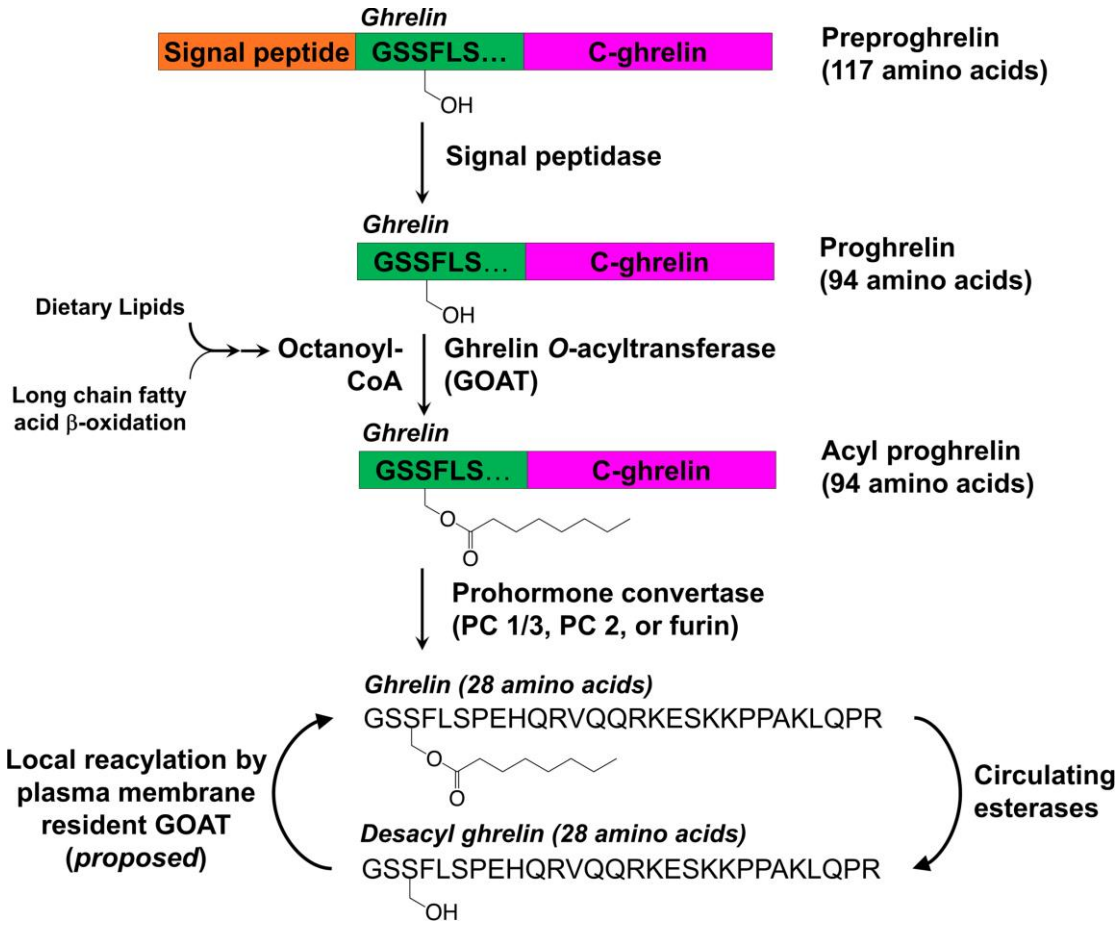


Figure (1-6): Ghrelin maturation .

Ghrelin's pleiotropic functions are mediated by the ghrelin receptor, also known as the growth hormone secretagogue receptor, which was identified in the pituitary gland and hypothalamus for the first time[87]. Ghrelin secretion is significantly inhibited by glucose. In humans, an oral glucose infusion can lower total ghrelin levels in the blood 30 minutes after ingestion. The concentration of circulating ghrelin increases before a meal and decreases after meal. Total ghrelin levels in humans rise at night and reduce after breakfast [95].

By inhibiting insulin secretion and regulating gluconeogenesis/glycogenolysis, ghrelin controls glucose hemostasis. By stimulating muscle differentiation and fusion, ghrelin inhibits muscular atrophy. Ghrelin regulates bone formation and metabolism by influencing osteoblast proliferation and differentiation. Ghrelin stimulates the secretion of growth hormone and Adrenocorticotropic hormone, increases appetite and nutrient intake, enhances gut motility and gastric acid secretion, influences energy expenditure, affects learning and memory, and contributes to the hedonic aspects of food[96].

Ghrelin has anti-inflammatory effects resulting from the downregulation of proinflammatory cytokines include interleukin 1 beta (IL-1β) and TNF-α[97].

1.11. C-reactive protein(CRP)

C-reactive protein (CRP) is a polypeptide and acute phase reactant produced mostly by hepatocytes in response to cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α during inflammation[98]. CRP is synthesized as a homopentameric protein known as native CRP (nCRP), which can irreversibly dissociate into five monomers known as monomeric CRP at locations of inflammation and infection (mCRP). CRP is produced primarily by hepatocytes in the liver, but it is also produced by smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes[99].

Tillett and Francis at Rockefeller University discovered CRP in 1930. Researchers discovered a substance in the blood of individuals with acute pneumococcal pneumonia that reacted with the bacteria cell wall C-polysaccharide[100]. The reaction with Pneumococcus capsular (C)-polysaccharide give it its name[99]. In the presence of calcium, CRP

binds to polysaccharides on microorganisms, such as phosphocholine (PCh), and activates C1q, that stimulates the classical complement pathway of innate immunity. CRP is an appropriate marker since it has a long half-life, its levels are constant throughout time without demonstrating circadian variability, and it does not require fasting blood samples. Serum CRP increases six to eight hours after IL-6 stimulation, with a half-life of 20 to 24 hours[101].

CRP is first synthesized as monomers, then assembled into a pentamer in the source cell's endoplasmic reticulum. The pentameric protein is retained in the endoplasmic reticulum of hepatocytes by binding to two carboxylesterases. CRP is released slowly from the endoplasmic reticulum while it is in a resting (non-inflammatory) condition, but when inflammatory cytokine levels rise, CRP's binding to carboxylesterases reduces, and CRP is secreted rapidly[102].

The pentameric protein, termed native CRP (nCRP), is characterized by a discoid configuration of five identical non-covalently bound subunits, each 206 amino acids long with a molecular mass of about 23 kDa[103]. The nCRP isoform induces phagocytosis and promotes apoptosis by activating the classical complement system. On the other hand, The monomeric C-Reactive protein(mCRP), stimulates chemotaxis and the recruitment of circulating leukocytes to regions of inflammation, as well as delaying apoptosis[99]. The human CRP gene is found on the long arm of chromosome 1q23.2[100].

Although its exact function in vivo is unknown, it is thought to be involved in the opsonisation of infectious pathogens and damaged cells[104]. The first line of defense against pathogens is C-reactive proteins(CRPs). Despite structural differences, CRP has similar

functional properties to immunoglobulin (Ig) molecules, such as the ability to stimulate agglutination, complement fixation, bacterial capsular swelling, phagocytosis, and the precipitation of polycationic and polyanionic substances. CRP is involved in the clearance of bacteria, as well as the death and alteration of cells, and it may also have more complex immunomodulatory functions [105].

Higher levels of CRP have been shown to increase blood pressure via lowering nitric oxide production by endothelial cells, which can lead to vasoconstriction. Because vasoconstriction reduces blood supply to different regions of the body, including joints, it causes hypoxia and impaired joint function, which can lead to arthritis in psoriasis patients. In psoriasis and other illnesses, C-reactive protein (CRP) has been suggested as an inflammatory biomarker[106]. High doses of CRP are associated with the induction of IL-10, whereas low doses of CRP may activate complement or induce proinflammatory cytokines[100].

1.12. Zinc

Minerals are essential for the normal growth and maintenance of the body. If the daily requirement is more than 100 mg, they are called major elements or macrominerals. If the requirement of certain minerals is less than 100 mg/day, they are known as minor elements or microminerals or trace elements[107]. Zinc, an essential trace element, is important for the development and maintenance of all tissues, including the skin. The human body has a total of 2–3 grams of zinc. Each day, gastrointestinal system loses about 2–4 mg of zinc, and kidneys lose about 0.5 mg. Additionally, the zinc is lost physiologically through the skin and hair[108].

Zinc is absorbed in the small intestine by the zinc transporter ZIP4 and then released to the bloodstream by zinc transporters like ZnT-1. A large portion of the absorbed zinc is bound to albumin, then transported to the liver and eventually deposited in the muscles and bones (80–85%), as well as the skin and liver (8–11%)[109].

Free zinc is rare in serum since it is predominantly associated with proteins including albumin, α2-macroglobulin (A2M), and transferrin. Albumin has a low affinity for zinc, whereas A2M has a medium affinity and transferrin has a high affinity. Subcellularly, zinc is distributed in 50 percent inside zinc-storing vesicles termed zincosomes, 30–40 percent inside the nucleus, and the remainder between the cytoplasm and other organelles[110].

Two zinc transporter families (solute-linked carrier families, SLC) regulate zinc homeostasis: the zinc transporters ZnT, which are encoded by the genes SLC30A1 to SLC30A10, and the Zrt-and Irt-like protein transporters ZIP, which are encoded by the genes SLC39A1 to SLC39A14[108]. Zinc is transported in opposite directions via ZnT and ZIP. ZnT mediates zinc transport from the cytosol to extracellular or other intracellular compartments, whereas ZIP increases zinc levels in the cytosol. Small cytosolic proteins known as metallothioneins play a significant role in cytosolic zinc homeostasis, in addition to the zinc transporters ZnT and ZIP. These proteins maintain zinc levels under control by binding and releasing heavy metals (including zinc) as needed[111]. Requirement of zinc for adults is 10 mg/day; children 10 mg/day; in pregnancy and lactation 15-20 mg/day. Since iron inhibits absorption of zinc, when iron is supplemented, zinc is also given to prevent any deficiency[107].

Zinc is a cofactor for more than 1,000 enzymatic reactions and more than 2,000 transcription factors, making it essential for the development, differentiation, and cell growth of many tissues. Zinc regulates DNA and RNA polymerases, thymidine kinase, and ribonuclease, all of which are necessary for maintaining healthy reproductive function, immunological state, and wound repair. It keeps macrophage and neutrophil functions, as well as natural killer cell and complement activity, going on. It suppresses keratinocyte integrin expression and modulates TNF-alpha and IL-6 production and inhibits the formation of inflammatory mediators such as nitric oxide[112].

Zinc also contains antioxidant properties, which have been demonstrated to be helpful in avoiding UV-induced damage and lowering the risk of cancer[113]. Zinc containing protein, Gusten, in saliva is important for taste sensation. Insulin when stored in the beta cells of pancreas contains zinc, which stabilizes the hormone molecule. But the insulin released into the blood does not contain zinc[107].

Zinc is involved in the differentiation, anti-inflammatory, and wound healing processes of epidermal keratinocytes[114]. Zinc deficiency has been linked to a variety of immune system problems such as abnormalities in the balance between Th1 and Th2 immune responses, as well as between regulatory and proinflammatory T cells, and impairment of T and B lymphocyte maturation and function. Zinc deficiency promotes Th17 immune responses while lowering the activity of NK cells. Zinc deficiency is also important for innate immunity[115].

Aims of study:

The aims of the study was to evaluate:

- The role of CHI3L1 in patients with psoriasis.
- The change in the level of serum Zinc in psoriasis patient and compared to the healthy control.
- The hormonal change in the level of serum Ghrelin in patient with psoriasis.
- The sensitivity and specificity of CHI3L1 and CRP in the serum of psoriasis patients as compare to the healthy control.
- The BMI in psoriasis patients.

2. Materials and Methods

2.1. Materials

2.1.1. Chemicals and Kits

All the chemicals and kits that were used in the present study are listed in Table(2-1).

Table(2-1): Chemicals and kits that were used in the study.

No	Chemicals Substance	Origin
1	Human Chitinase-3-like 1 Protein , CHI3L1 ELISA Kit	Bioassay Technology Laboratory (China)
2	Human Ghrelin ELISA Kit	Bioassay Technology Laboratory (China)
3	C-Reactive Protein (CRP)Kit (Immunoturbidimetric Method)	Zybio (china)
4	Zinc kit (spectrophotometer Method)	Centronic GmbH (Germany)

2.1.2. Instruments and Equipment.

All the instruments and equipment that were used in the work are listed in Table (2-2).

Table (2-2): The Instruments and Equipments Used.

No	Instruments and Equipments	Origin
1	Deep Freeze	GFL (Germany)
2	Centrifuge	Hettich (Germany)
3	ELISA Reader	Biotek (USA)
4	ELISA Washer	Biotek (USA)
5	Distiller	GFL (Germany)
6	Spectrophotometer	CECIL (England)
7	Blue and yellow tips	JRL (Lebanon)
8	Incubator	Fisher Cient (Germany)
9	Water bath	Grant (Germany)
10	Micropipettes (5-50µl), (2-20µl),(20-200µl) , (100-1000µl)	Slamed (Germany)
11	Multichannel micropipette(0-250 µl)	Slamed (Germany)
12	Printer	Epson (Indonesia)
13	Gel tube	AFCO (Jordan)
14	Plain tube	China
15	Eppendorf tube (1.5ml)	China
16	Alcohol 70%	China
17	Filter papers	China
18	Disposable syringes (5 ml)	Universal (china)
19	cylinder flask	Schoot (Germany)
20	Tourniquet	China
21	Cooling box	China
22	Zybio analyzer	China

2.2. Methods

2.2.1. Date and Place of the Study

The study was approved on patients be present at Merjan Teaching Hospital in Babylon province in Hilla city. All samples were collected from the 1st of October 2021 to the 1st of September 2022. The practical side of the study was performed at the laboratory of the clinical biochemistry department in the college of the Medicine / University of Babylon.

2.2.2. Study Design and Sample Size

The current study was designed as a case-control study. The following simple formula (sample size formula) (Daniel, 1999) was used to determine sample size as following[116].

$$n= \frac{Z^2 P(1-P)}{d^2}$$

Where n= sample size

Z= Z statistic for the level of confidence interval 95% which = 1.96.

P= Prevalence of psoriasis which is 2% in the world.

d= precision (in proportion of one; if 5%, d = 0.05).

$n= (1.96)^2 *0.02*0.98 / 0,05^2$

n=30

2.2.3. Study population

This study was designed as a case-control study includes 100 individuals but in order to match between patients and control in age and gender the number was 90 individuals involved in this study, the age of them were more than 18 years. These subjects were divided into three groups, the first group includes 30 patients with severe psoriasis and the second group included 30 patients with moderate psoriasis and the third group include 30 healthy individuals. All individuals were assessed for status of obesity by measuring the body mass index (BMI) and determine the severity of psoriasis by measure the psoriasis area and severity index (PASI) score.

2.2.4. Ethical approval

All participants in this study were informed before to collecting samples and verbal agreement was obtained from each of them.

2.2.5. Collection of Data.

The inclusion and exclusion criteria for current study were as follows:

Inclusion criteria :

- Psoriasis Patients with age more than 18 years.
- The durations of psoriasis was more than one year.

Exclusion criteria :

- Pregnancy and lactating women.
- Patient less than 18 years of age.
- Patients with other autoimmune and inflammatory diseases.
- Patients taken systemic treatment at the last month.

2.2.6. Patients groups.

Sixty patients were involved in this study, divided into two groups, group 1 (PASI score more than 20) that contained 30 patients and group 2

(PASI score between 10-20) that contained 30 patients. All psoriasis patients in both groups were diagnosed and classified by the dermatologist in the Department of Dermatology in Merjan Teaching Hospital in Hilla city by calculating the PASI score for all patients. To diminish subjectivity, PASI score was evaluated by the same dermatologist. A PASI Score below 10 defined psoriasis as mild, between 10 and 20 as moderate and above 20, as severe psoriasis[117].

Full patients history regarding name, age, sex, phone number, duration of disease, comorbidities of disease, PASI score, weight, height, body mass index(BMI). All these information were collected in a questionnaire sheet from involved subjects according to the patient's interview.

2.2.7. Control groups

Thirty individuals apparently healthy as a control subjects were involved in this study, and all of them without any skin disease or other autoimmune diseases, and identical with patients in the age, and sex.

2.2.8. Physical Examination

Physical examination was applied on both patients and control groups such as body weight, height, and body mass index (BMI) in the nutrition department of Merjan teaching hospital. Body mass index was calculated for all subjects that involved in this study by using the specific formula which required the presence of body weight in (Kg) and body height in (m^2). Body Mass Index (BMI) is a simple weight-for-height index that is commonly used to classify people as underweight, overweight, or obese. It is measured by dividing the weight in kilograms by the square of the height in meters (kg/m^2)[118]. BMI categories are underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9),

obesity class I (30.0–34.9), obesity class II (35.0–35.9), and obesity class III (≥40.0)[119].

2.2.9. Clinical Examinations

Psoriasis Area and Severity Index (PASI) is currently the preferred method for evaluation of disease severity according to the surface area involvement and the grade of redness, induration, and scaliness of the skin lesions [120]. In current study, we classified psoriasis patients as moderate and sever group according to the PASI score. The severe case measured by dermatologist in marjan hospital by using PASI score, show in the fig (2-1).

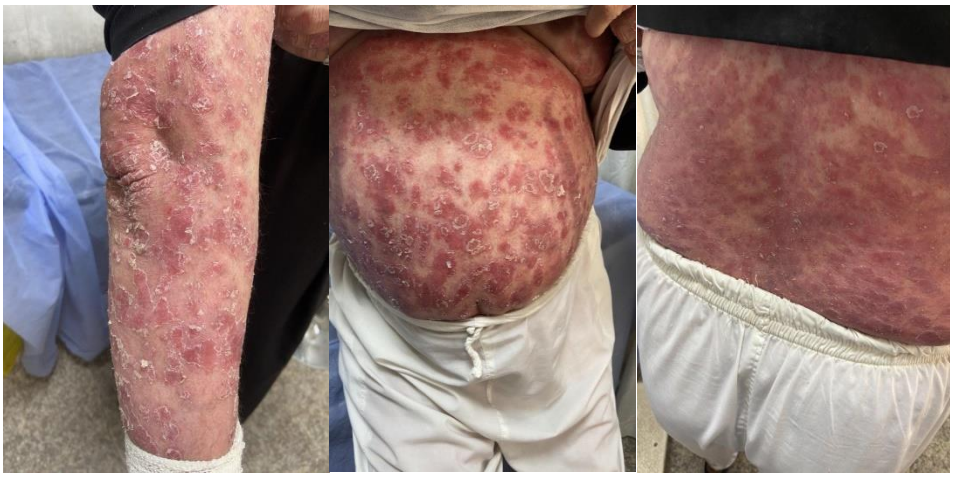


Fig (2-1): Severe case measured by PASI score.

2.2.10. Blood Collection

In the current study, the blood sample was collected from patients admitted to the room of blood collection in Merjan Teaching Hospital after diagnosis by the specialist dermatologist. Venous blood was collected from patients arm by using syringe (5ml) and tourniquet after sterilization patient's arm vein area by using 70% alcohol. Collected blood then transferred from these syringe to the gel tube when labeled with a label containing patient's name, date of collection and time.

According to the kit instruction, after waiting for the blood in gel tube for 20 minute at room temperature and then separated in centrifuge on 3000 xg, for 5 minutes to obtaining patients serum, then the serum is stored at -40°C until analysis of (Chitinase-3-like protein 1,Ghrelin peptide ,C- reactive protein, Serum Zinc).

2.2.11. Biochemical Measurements.

2.2.11.1 Quantitative Determination of Human Chitinase-3-like Protein 1

Chitinase-3-like Protein 1 was measured by enzyme linked immunosorbent assay(ELISA) kit.

ELISA instrument used for analyzed serum CHI3L1 show in the fig (2-2).

Fig (2-2): ELISA instrument.

2.2.11.1.1 Principle

The Sandwich-ELISA technique was used in this ELISA kit. The plate has been precoated with Human CHI3L1 antibody. CHI3L1 present in the sample was added and binds to antibodies coated on the wells.

After removing any unbound substances, a biotinylated human CHI3L1 antibody was added to wells and binds to CHI3L1 in the sample.

After washing, Streptavidin- Horseradish Peroxidase (HRP) was added to wells and binds to the biotinylated CHI3L1 antibody. After incubation, unbound Streptavidin-HRP was washed away during a washing step. Substrate solution was added to wells and color develops in proportion to the amount of human CHI3L1 bound. The color development was stopped and the intensity of the color was measured at 450 nm[121].

2.2.11.1.2. Component of kit

Table (2-3): Components of ELISA kits.

Components	**Quantity (96T)**
Standard solution (480ng/ml)	0.5ml x1
Pre-coated ELISA plate	12 * 8 well strips x1
Standard diluent	3ml x1
Streptavidin-HRP	6ml x1
Stop solution	6ml x1
Substrate solution A	6ml x1
Substrate solution B	6ml x1
Wash buffer Concentrate (25x)	20ml x1
Biotinylated Human CHI3L1 antibody	1ml x1
User instruction	1
Plate sealer	2 pics

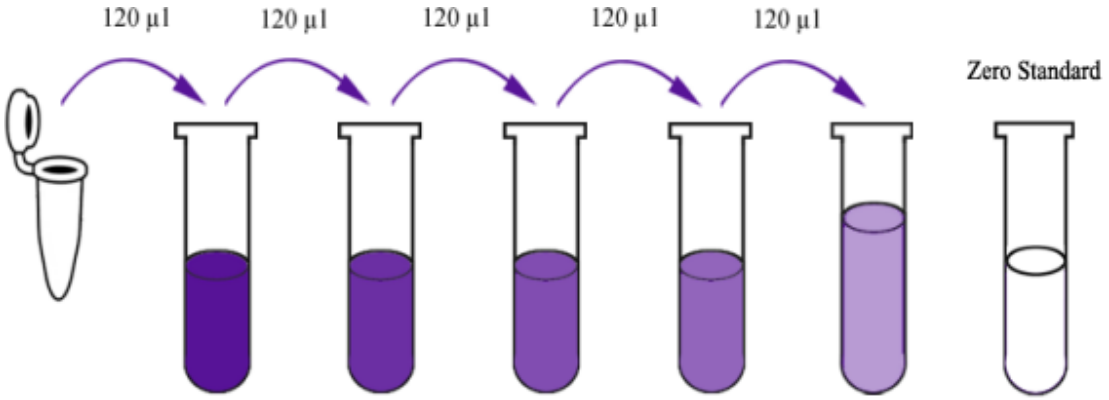
2.2.11.1.3 Preparation of Reagents

- All reagents should be brought to room temperature before use.

- The original density of standard sample was diluted as the following table (2-4):

Table (2-4) : standard diluted.

240 ng/ml	Standard No.5	120ul Original standard + 120ul Standard diluent
120 ng/ml	Standard No.4	120ul Standard No.5 + 120ul Standard diluent
60 ng/ml	Standard No.3	120ul Standard No.4 + 120ul Standard diluent
30 ng/ml	Standard No.2	120ul Standard No.3 + 120ul Standard diluent
15 ng/ml	Standard No.1	120ul Standard No.2 + 120ul Standard diluent



Standard concentration	Standard No.5	Standard No.4	Standard No.3	Standard No.2	Standard No.1
480ng/ml	240ng/ml	120ng/ml	60ng/ml	30ng/ml	15ng/ml

- 20 ml of wash buffer concentrate 25x was diluted into deionized or distilled water to yield 500 ml of 1x Wash Buffer. If crystals have formed in the concentrate, mix gently until the crystals have completely dissolved.

2.2.11.1.4 Procedure

1. Before use, all reagent put to room temperature. The assay was performed at room temperature .

2. The number of stripes that necessary for test were identified. The strips that used place inside the frames. The strips that were not used must be kept at 2 to 8°c .

3. A volume of 50µl of standard was added to well standard.

4. A volume of 40µl from sample was added and then added 10µl of human CHI3L1 antibody to sample well, then 50µl of Streptavidin-HRP to both sample and standard wells then Mix well.

5. The over plate covered with sealer and incubated for 60 min at 37 °c .

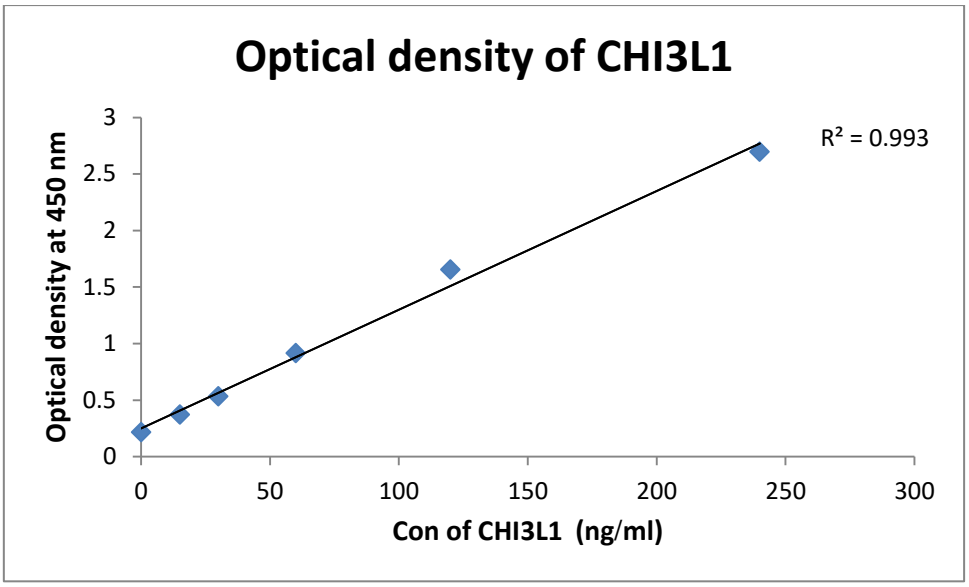
6. The coating eliminated and cleaned the plate 5 times over with a wash buffer. For each wash, soak wells for 30 sec. to 1 min., with at least 0.35 ml wash buffer. Aspire for automatic washing of all wells, by washing with wash buffer 5 times, filling wells with wash buffer. The plate was blotted into paper towels or other absorbing material .

7. A volume of 50µl substrate solution A added and then 50µl substrate solution B for each wells. The coated plate incubated with new sealer for 10 min. at 37°c in dark media .

8. To each well 50µl of stop solution was added, and the color change from the blue to yellow immediately .

9. The optical density (OD value) of each well identified directly after applying the stop solution by utilize a microplate reader set at 450 nm within 10 min.

2.2.11.1.5 Calculation of Result



Fig(2-3): Standard curve of Chitinase-3-like-1 protein.

2.2.11.2 Quantitative determination of Human Ghrelin (also known as GHRL)

Human Ghrelin level was measured by enzyme linked immunosorbent assay kit.

2.2.11.2.1 Principle

The Sandwich-ELISA technique is used in this ELISA kit. The plate has been precoated with human GHRL antibody. GHRL present in the sample was added and binds to antibodies coated on the wells. After removing any unbound substances, a biotinylated human GHRL antibody was added to wells and binds to GHRL in the sample. After washing, Streptavidin- Horseradish Peroxidase (HRP) was added to wells and binds to the biotinylated GHRL antibody. After incubation unbound

Streptavidin-HRP was washed away during a washing step. Substrate solution was added to wells and color develops in proportion to the amount of human GHRL bound. The color development was stopped and the intensity of the color was measured at 450 nm[122].

2.2.11.2.2 Component of kit

Table (2-5) component of ELISA kit.

Components	Quantity (96T)
Standard Solution (12.8ng/ml)	0.5ml x1
Pre-coated ELISA Plate	12 * 8 well strips x1
Standard Diluent	3ml x1
Streptavidin-HRP	6ml x1
Stop Solution	6ml x1
Substrate Solution A	6ml x1
Substrate Solution B	6ml x1
Wash Buffer Concentrate (25x)	20ml x1
Biotinylated Human GHRL Antibody	1ml x1
User Instruction	1
Plate Sealer	2 pics
Zipper bag	1 pic

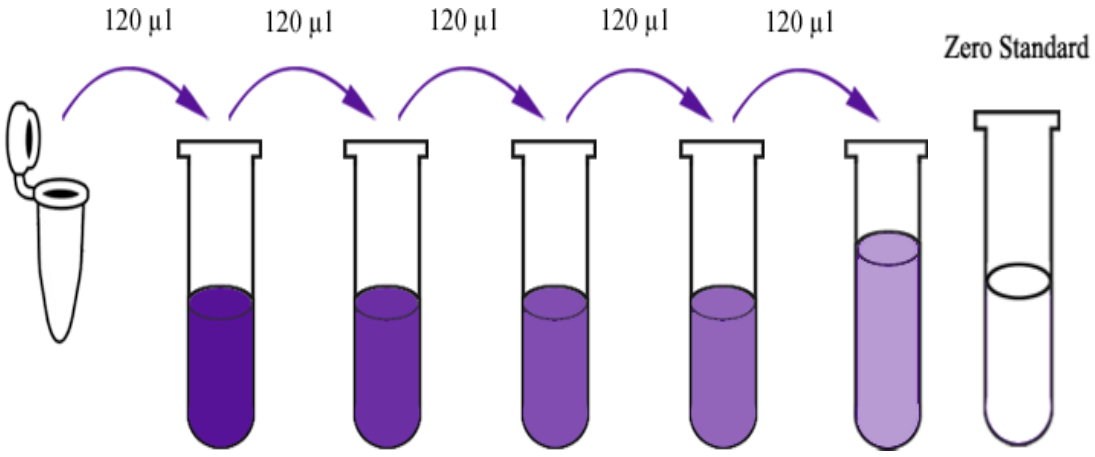
2.2.11.2.3. Preparation of reagent

A-All reagents should be brought to room temperature before use.

B-The original density of standard sample was diluted as the following table (2-6):

Table (2-6):Standard diluent.

6.4ng/ml	Standard No.5	120µl Original Standard + 120µl Standard Diluent
3.2ng/ml	Standard No.4	120µl Standard No.5 + 120µl Standard Diluent
1.6ng/ml	Standard No.3	120µl Standard No.4 + 120µl Standard Diluent
0.8ng/ml	Standard No.2	120µl Standard No.3 + 120µl Standard Diluent
0.4ng/ml	Standard No.1	120µl Standard No.2 + 120µl Standard Diluent



Standard Concentration	Standard No.5	Standard No.4	Standard No.3	Standard No.2	Standard No.1
12.8ng/ml	6.4ng/ml	3.2ng/ml	1.6ng/ml	0.8ng/ml	0.4ng/ml

C- 20 ml of wash buffer concentrate 25x was diluted into deionized or distilled water to yield 500 ml of 1x wash buffer. If crystals have formed in the concentrate, mix gently until the crystals have completely dissolved.

2.2.11.2.4. Procedure

1. Before use, all reagent put to room temperature. The assay is performed at room temperature.

2. The number of stripes that necessary for test were identified. The strips that used place inside the frames. The strips that were not used must be kept at 2 to 8°c.

3. A volume of 50µl of standard was added to well standard.

4. A volume of 40µl from sample were added and then added 10µl of GHRL antibody to sample well, then 50µl of Streptavidin-HRP to both sample and standard wells then Mix well.

5. The over plate covered with sealer and incubated for 60 min at 37 °c.

6. The coating eliminated and cleaned the plate 5 times over with a wash buffer. For each wash, soak wells for 30 sec. to 1 min., with at least 0.35 ml wash buffer. Aspire for automatic washing of all wells, by washing with wash buffer 5 times, filling wells with wash buffer. The plate was blotted into paper towels or other absorbing material.

7. A volume of 50µl substrate solution A added and then 50µl substrate solution B for each wells. The coated plate incubated with new sealer for 10 min. at 37°c in dark media.

8. To each well 50µl of stop solution was added, and the color change from the blue to yellow immediately.

9. The optical density (OD value) of each well identified directly after applying the stop solution by utilize a microplate reader set at 450 nm within 10 min.

2.2.11.2.5 Calculation of Result

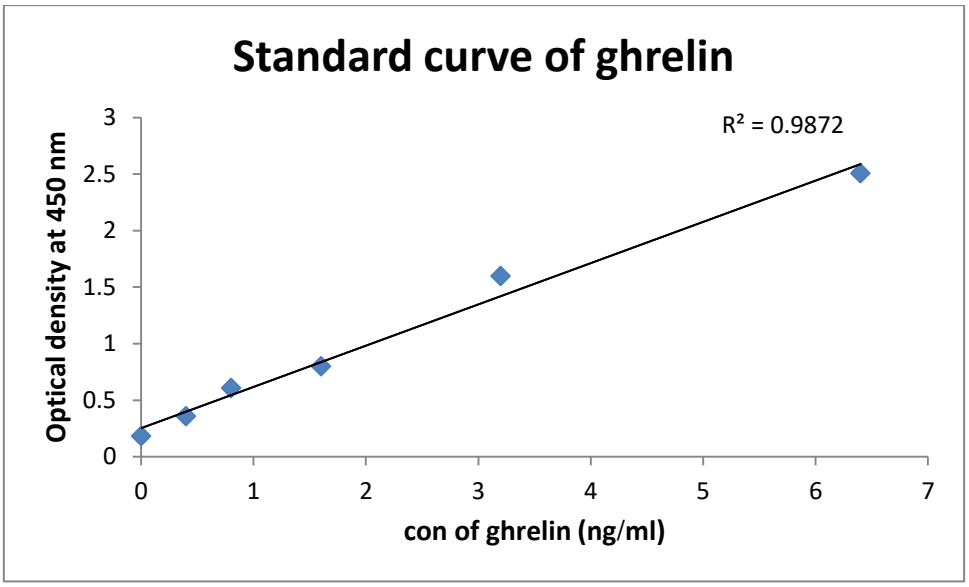


Fig (2-4): Standard curve of Ghrelin.

2.2.11.3. Quantitative determination of C-Reactive Protein (CRP) in serum (Immunoturbidimetric Method)

2.2.11.3.1 Principle

C-reactive protein and its corresponding antibody sensitized latex particles met in solution, agglutination reaction occurred, and a certain turbidity was produced in the linear range of 0.2 - 320mg/L. The turbidity was proportional to the content of antigen in the presence of a certain amount of antibodies. The change of turbidity was detected by scattering turbidimetry. The content of C- reactive protein in the sample was detected by comparing with the curve equation fitted by the same calibrator[123].

2.2.11.3.2 Procedure

1. Mouse anti-human C-reactive protein sensitivity latex(R2) were taken and transferred from the refrigerator or other low-temperature equipment and placed on the matching analyzer.

3. The vial of R1were placed on the analyzer as instructed.

4. The sampling probe were putted under liquid level. And the result was obtain automatically when clicked the measure button.

5. The instrument used for analyzed CRP was zybio analyzer china as show in the fig (2-5).

Fig (2-5): Zybio analyzer for CRP[123].

2.2.11.4. Colorimetric test for quantitative measurement of Zinc in serum.

2.2.11.4.1 Principle

Zinc forms with 2-(5-Brom-2-pyridylazo)-5-(N-propyl-N-sulfo-propylamino)-phenol a red chelate complex. The increase of absorbance can be measured and is proportional to the concentration of total zink in the sample.

2.2.11.4.2 Procedure

The can tube was Mixed and incubated for 5 minutes at 37°C and measured the absorbance of the sample and of the standard against the reagent blank by using spectrophotometer at wavelength 560 nm. The instrument used for analyzed serum Zn was spectrophotometer (CECIL (England**)** show in the fig (2-6).

- Calculation the result through this equations :

$$\text{Concentration (µg/dl)} = \frac{\text{absorbtion of sample}}{\text{absorbtion of standard}} \times 200 \text{ (µg/dl)}.$$

Table (2-7): Procedure of Zinc

	Standard	**Sample**
Reagent	1000 µl	1000µl
Serum	_	50 µl
Standard	50 µl	_

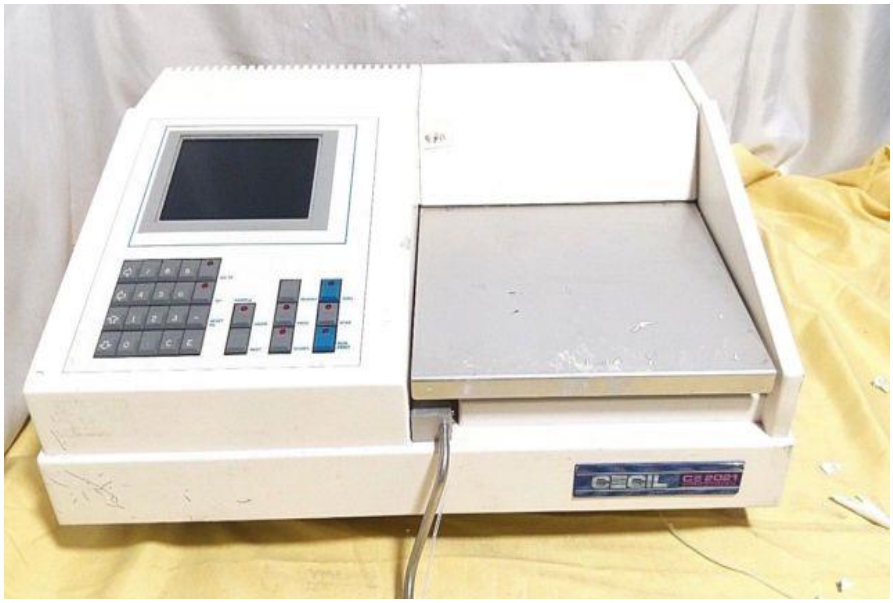


Fig (2-6): CECIL spectrophotometer.

2.2.12. Statistical Analysis.

The statistical analysis was carried out using Statistical Package of Social Science (SPSS) version 21. Continuous variables were given as (Mean ± SD) while categorical variables were provided as frequencies and percentages. One-way Anova test was used to compare means between three groups and the correlation test (Pearson test) was performed to find the association between variables. *P* value less than or equal to 0.05 was considered to be statistically significant.

Receiver operating characteristic(ROC) curve was used to evaluate the diagnostic value of chitinase-3-like-1 protein and C- reactive protein in psoriasis patients. The sensitivity and specificity of biochemical parameter and calculate the optimal cutoff according to "Youden Index" by select the point that is closest to the top-left corner of the ROC curve giving equal weight to sensitivity and specificity when picking a cut-off point is a typical practice. This idea is often referred to as the Youden Index[124].

The area under the curve (AUC) provides a useful tool to compare different biomarkers as Table (2-8). Positive predictive value, negative predictive value were calculated by cross-tabulation.

Table (2-8) List of AUC ranges and their classification levels[125].

AUC Range	Classification Level
0.90 - 1.00	Excellent
0.80 - 0.90	Good
0.70 - 0.80	Fair
0.60 - 0.70	Poor
0.50 - 0.60	Failure

3. Results and Discussion.

3.1. General Characteristic of Study.

3.1.1. Age in patients and control.

The age of patients with severe psoriasis group ranged from (18-68) years with mean ± SD (42.4 ± 15.22) year and the moderate psoriasis group ranged from (19-65) years with mean ± SD (38.2 ±13.38) years and the age of healthy control group ranged from (18-68) years with mean ± SD (41.6 ± 15.67) years. Table (3-1).

The result of current study showed no significant difference(P value >0.05) between the age of these groups. This was in agreement with a previous study done in Iraq for psoriatic patients in 2017[1].

Table (3-1): Age distribution in patients and control.

Variable	Study Group	No	Mean ± SD	P-value
Age	Severe	30	42.4 ± 15.22	0.516
	Moderate	30	38.2 ± 13.38	
	Control	30	41.6± 15.67	

P value ≤ 0.05 was significant.

P value > 0.05 was non- significant.

3.1.2. Sex distribution in psoriasis patients and control.

The severe psoriasis patients was included in current study and classified according to the sex into 21 (70%) males and 9 (30%) females. The moderate psoriasis patients then were 21(70%) males and 9(30%) females. Healthy controls also were classified depending on sex into 21(70%) healthy males and 9(30%) healthy females. Figure 3-1.

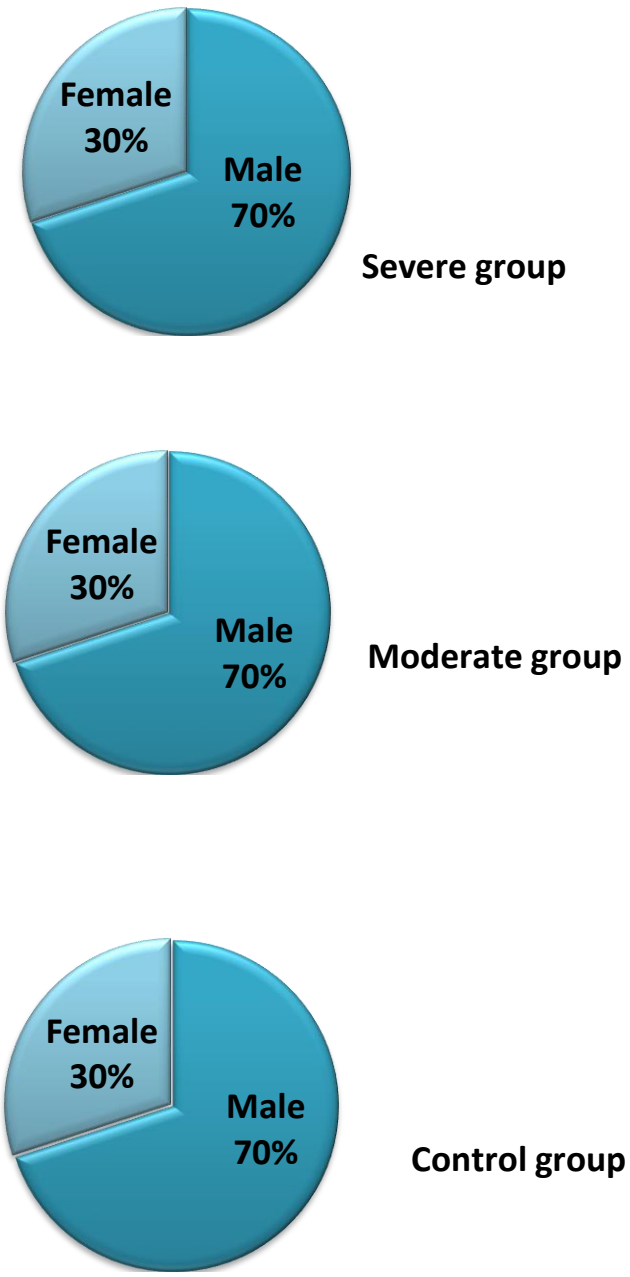


Fig (3-1): Distribution of sex among psoriatic and control Groups.

3.1.3. Body Mass Index (BMI) of Participants.

The results of the present study revealed a significant higher level (p value ≤ 0.05) in the BMI among severe psoriatic patients group when compared with healthy control group and also significantly higher among moderate psoriatic patients when compared with healthy control group. Table (3-2).

Table (3-2): The Body Mass Index (kg /m2) of Participants

Subject	Study group	No	Mean ± SD	P value
BMI(kg/m²)	Severe group	30	30.1 ± 6.96	**≤ 0.001**
	Control group	30	23.1 ± 1.70	
	Moderate group	30	27.7 ± 6.08	**0.001**
	Control group	30	23.1 ± 1.70	

P value > 0.05 was non- significant.

P value ≤ 0.05 was significant.

Obesity is frequently subdivided into categories: obesity class I (30.0–34.9), obesity class II (35.0–35.9), and obesity class III (≥40.0)[119]. In current study the significant higher BMI may be attributed to the development of obesity in psoriasis patients that is particularly due to that the Th17 cells which produce IL-17 play a key role in the development of obesity as a comorbidity in psoriasis patients. Immune dysregulation, represented by increased expression of IL-17 and the cell subsets that generating IL-17 and decreased expression of regulatory T-cells (T-regs) and associated cytokines (such as IL-10) is a driving complex reaction leading to the development and progression of

obesity in psoriasis[126]. Another study showed that IL-17 controls adipogenesis and glucose metabolism[127].

On other hand, keratinocytes in psoriasis patients contribute to psoriasis inflammation by secreting proinflammatory cytokines such as IL-6 and tumor necrosis factor-α (TNF-α)[6].

Physiologically, TNF-α promotes adipocyte leptin synthesis, induces lipolysis, and inhibits both lipogenesis and anabolic insulin-like growth factor 1 production[128]. As a result, TNF-α is considered to be an anti-obesity cytokine, that limits body mass increase. Thereby, the increased TNF-α levels in obese people are supposed to play a protective function. On the contrary, the TNF-α secreted by keratinocyte in psoriasis patients may also contribute to obesity by counteracting insulin receptor activity and inhibiting glucose transporter-4, with a consequent enhancement of insulin levels that stimulate the hunger center, which lead to an increase in food and therefore an increase in body mass of psoriasis patients. the potential TNF-α contribution to insulin resistance[71].

Some studies have suggested that psoriasis predisposes patients to the development of obesity related to stress and reduced physical activity[129].

The results of current study was agreement with study conducted by (Zachariae *et al*.2020)[130], which report that cutaneous Psoriasis patients are at higher risk of developing obesity.

3.2. Biochemical Parameters

3.2.1. Serum Human Chitinase-3-like-1 protein among Psoriatic and Control group

Results of the present study revealed that there was a significant higher level ($P< 0.05$) in serum concentration of human Chitinase-3-like-1 protein (CHI3L1) among the severe psoriatic patient when compared with control group. The results also revealed a significant higher serum concentration of human CHI3L1 among moderate psoriatic patient when compared with control group. Table (3-3).

Table (3-3): Comparison of mean serum CHI3L1(ng/ml) level in patients and control groups.

Parameter	Study group	No	Mean ± SD	P value
CHI3L1(ng/ml)	Severe group	30	68.57 ± 25.17	**≤ 0.001**
	Control group	30	43.99 ± 8.34	
	Moderate group	30	63.59 ± 22.60	**≤ 0.001**
	Control group	30	43.99 ± 8.34	

P value > 0.05 was non-significant

P value ≤ 0.05 was significant

The exact biological roles of CHI3L1 are unknown. It was suggested to play an active role in the physiological and pathological processes such as angiogenesis, mitogenesis and remodeling[131].

Furthermore, CHI3L1 was present to play a role in the up regulation of VEGF expression and enhanced angiogenesis. Therefore both CHI3L1 and vascular endothelial growth factor (VEGF) may synergistically promote endothelial cell angiogenesis[132]. Besides, it has

been revealed that CHI3L1 was also an adhesion and migration factor which was involved in migration of cells and remodeling of tissues, leading to angiogenesis in the course of the endothelial dysfunctions.

The elevation of CHI3L1 can be attributed to the Immunohistochemistry on bone marrow cells revealed that neutrophil precursors begin to synthesize CHI3L1 at the myelocyte-metamyelocyte stage, the stage of maturation at which other specific granule proteins are produced. CHI3L1 is kept in neutrophil granules and released after the neutrophil has been fully activated[133].

The results of current study were in agreement with a previous study done by Imai *et al*.[134] and El-gamal *et al*.[81] which reported that the CHI3L1 involvement in the psoriasis pathogenesis manifested by its rise in the serum of psoriatic patients in comparison to the control group. In addition, Jensen *et al*.[135] and Ahmed *et al*.[136] reported that serum CHI3L1 was found to be greater in psoriatic patients than in controls.

The result of this study disagreed with the study of Ataseven and Kesli[137], who observed that there was no statistically significant difference in CHI3L1 serum concentrations between psoriatic patients and the control group.

3.2.2 Serum Human Ghrelin peptide among Psoriatic patient and Control group

The results of this study revealed that there was a difference (but statistically non-significant) in the level of Ghrelin in severe psoriatic patients group in comparison with healthy control group, it was higher in severe group than healthy control. Then was also non-significant difference in the moderate psoriasis patients group when compared with

healthy control group but higher level of Ghrelin in moderate group than control group. Table (3-4).

Table (3-4): Comparison of mean serum Ghrelin (ng/ml) level in patients and control groups.

Parameter	Study group	No	Mean ± SD	P value
Ghrelin(ng/ml)	Severe group	30	1.54 ± 0.33	0.582
	Control group	30	1.49 ± 0.36	
	Moderate group	30	1.65 ± 0.29	0.074
	Control group	30	1.49 ± 0.36	

P value > 0.05 was non-significant

P value ≤ 0.05 was significant

In this work the non-significant elevation of serum ghrelin in psoriasis patients may be contributed to strong inhibitory effects of ghrelin on the mRNA and protein expression levels of proinflammatory cytokines, such as IL-6 and TNF-α, which are important in the pathogenesis of psoriasis[138].

Other reason for increase serum ghrelin in psoriasis patients is possibly related to a compensatory effect against inflammation in the disease or increased insulin resistance in psoriatic patients or a relatively high BMI in psoriatic patients[139].

In addition, TNF-α, IL-6 are suppressed by ghrelin, whereas IL-10, an anti-inflammatory cytokine, is enhanced by ghrelin so that may lead to elevation of ghrelin in psoriasis patients[140].

The current study result was in agreement with a previous study done by Ozdemir¨ *et al*. 2012[139], reported that the ghrelin level was

higher in psoriasis patients than in controls, but the difference was not statistically significant, and show that an increment of ghrelin in psoriasis patients might lead to increase appetite and stimulate food ingestion, and so it may contribute to obesity development in psoriatic patients[139]

The result of current study disagreed with *Ucak et al.* 2014[141], which reported a significant higher level in the serum ghrelin of psoriatic patients than healthy control.

3.2.3. Serum C- reactive protein among psoriatic patient and control group

Results of the current study revealed that there was a significant higher level (P< 0.05) in serum concentration of C-reactive protein (CRP) among the severe psoriatic patients when compared with control group. The result also revealed a significant higher level in the serum concentration of human CRP among the moderate psoriatic patients when compared to the control group. Table (3-5).

Table (3-5): Comparison of mean serum C-reactive protein (mg/L) level in psoriasis patients and control groups.

Parameter	Study group	No	Mean ± SD	P value
C-reactive protein(mg/L)	Severe group	30	13.33 ± 4.84	**≤ 0.001**
	Control group	30	9.54 ± 2.18	
	Moderate group	30	11.35 ± 2.83	**0.04**
	Control group	30	9.54 ± 2.18	

P value > 0.05 was non-significant P value ≤ 0.05 was significant

CRP is synthesized by the liver in response to many cytokines especially IL-1, IL-6 and TNF-α, which play an important functions in the pathogenesis of many diseases[142].

The elevation in the mean serum level of CRP in the psoriasis patients may be attributed to increase in some immunological mediators and proinflammatory cytokines such as TNF-α and IL-6 that lead to the formation of psoriatic lesions or atherosclerotic plaques which induce releasing of CRP[143].

The other reason for CRP elevation may be due to that the CRP itself, beyond serving as a biomarker, may be an active inflammatory protein with a role in endothelial cell dysfunction and vascular remodeling[144].

Among 28 studies comparing the CRP values in psoriatic patients with those of controls, 24 found a statistically significant increase of serum CRP in psoriasis patients than healthy control, similar to our study[120].

3.2.4. Serum zinc among Psoriatic patients and Control group

The Result of the current study reveal that there was a significant(P value < 0.05) difference in serum concentration of zinc among severe psoriatic patients when compared with control group. Serum zinc concentration was much higher in control group when compared to severe psoriatic group. Serum zinc concentration reveled non-significant decrease among moderate psoriasis patients in comparison with control group. Table (3-6).

Table (3-6): Comparison of zinc(mg/L) level in psoriasis patients and control groups.

Parameter	Study group	No	Mean ± SD	P value
Zinc (mg/L)	Severe group	30	96.05 ± 28.75	**0.002**
	Control group	30	125.01 ± 39.92	
	Moderate group	30	111.99 ± 32.46	0.171
	Control group	30	125.01 ± 39.92	

P value < 0.05 was significant

P value ≥ 0.05 was non-significant

Psoriasis is an immune-mediated skin disease characterized by the production of reactive oxygen species(ROS) due to the overexpression of pro inflammatory cytokines. Lipid peroxidation and decrease of natural antioxidants are involved in stimulation the toxic effects of free oxygen species. Zinc is important cofactor and modulator of many critical biological roles in skin disorders such as psoriasis[145].

The lower serum Zn level in current study may lead to involvement of Zn in the normal keratinization processes of animal skin and the roles of Zn in skin disease have been widely investigated. It is reported that Zn element is present in all cells and indispensable for the normal functions of cells, tissues, and organs of the body[146]. Also Zn are the integral part of many metalloenzymes, especially Cu/Zn superoxide dismutase which has antioxidant and anti-inflammatory properties, so that this may lead to decrease level in psoriasis patients. Through enzyme systems, Zn is involved in the destruction of free radicals[147].

Many other factors may be contributed to the decrease of serum Zn level in psoriasis patients included First, Zn is a trace element that is found in around 300 metalloenzymes, which are required for carbohydrate, lipid, and nucleic acid metabolism, as well as the oxidative

stress that contributes to psoriasis pathogenesis. Secondly, Psoriasis' antimicrobial activity is inhibited by zinc, which is an important mediator in the skin's natural defense. Thirdly, Keratinocytes in psoriasis lesions recruit a large quantity of Zn to participate in nucleotide synthesis and replication, resulting in over-proliferation, all these reason lead to depletion of Zinc[148].

Among 19 studies comparing the Zinc levels in psoriatic patients with those of controls, seven studies found a significantly decreased serum Zn levels in psoriasis patients when compared with the healthy controls, similar to our finding[148].

Some studies indicated that the serum Zn status may be related to the severity of psoriasis, for instance it is reported that psoriatic patients with more than 10% body surface area had significantly lower serum Zn levels than those with less body surface area involvement[149].

3.3. Correlations between BMI, Chitinase-3-like-1 protein, Ghrelin, CRP, Zinc, PASI score in psoriatic patient and control group, shown in table (3-7).

Table (3-7) : Correlations between biochemical markers.

		BMI	Ghrelin	Zinc	PASI
BMI (kg/m²)	**R**	1	0.122	- 0.171	0.264
	P	----	0.252	0.106	0.042
	No	90	90	90	60
Chitinase (ng/ml)	**R**	0.251	0.283	- 0.102	0.005
	P	0.017	0.007	0.336	0.970
	No	90	90	90	60
CRP	**R**	0.265	0.054	- 0.336	0.285
	P	0.012	0.615	0.001	0.028
	No	90	90	90	60

R: correlation coefficient , P: P-value, No : number of case

A- Correlation between CRP and PASI score.

In this study the result shown statistically significant positive correlation between CRP and PASI score , *P value* = 0.028 , R(0.285). Figure (3-2).

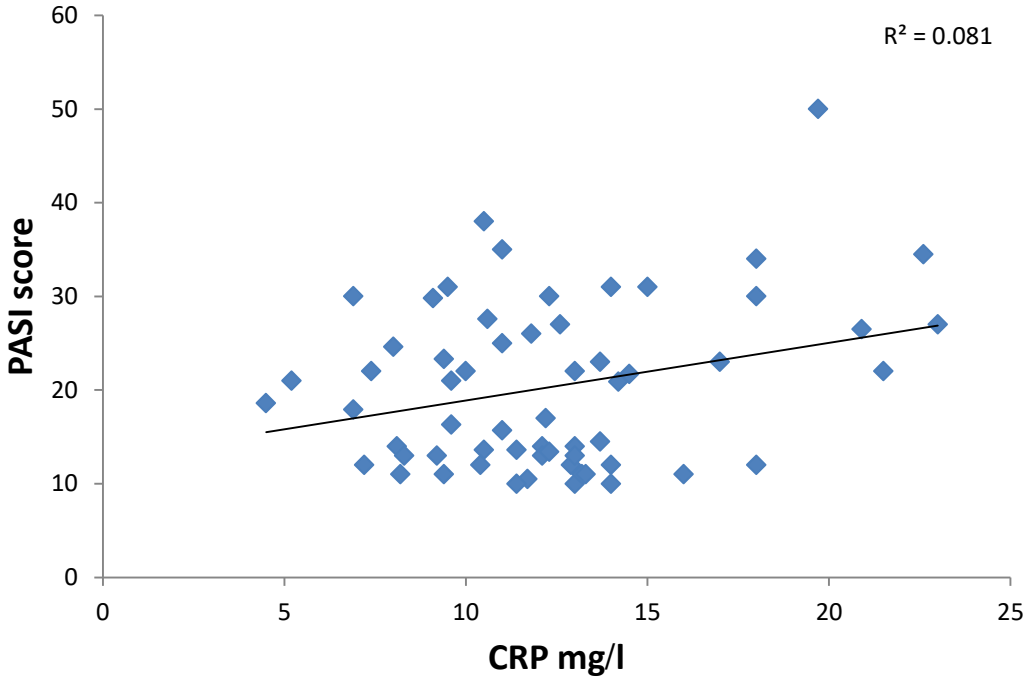


Fig (3-2):Correlation between CRP and PASI score.

B- Correlation between CRP and BMI

The result of current study showed statistically significant positive correlation between CRP with BMI *p-value* (0.012) ,R(0.265). Figure (3-3).

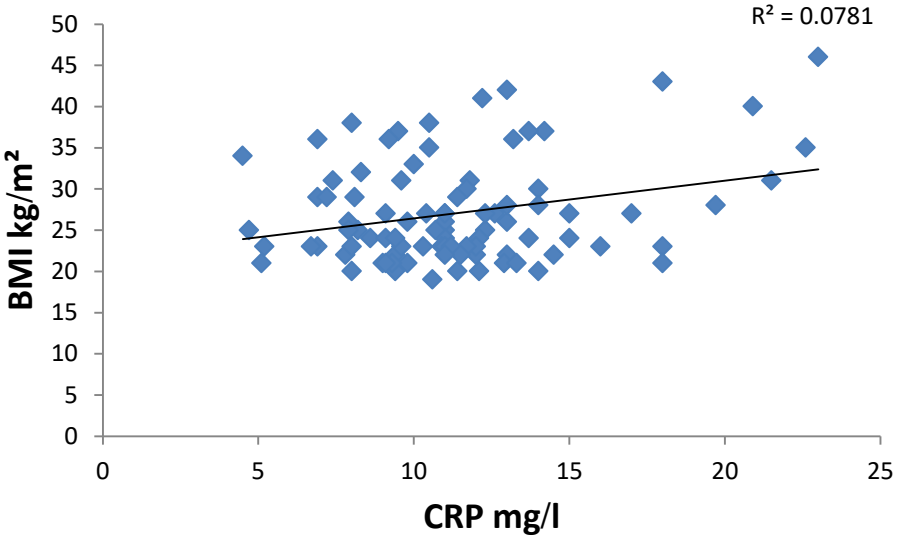


Fig (3-3): Correlation between CRP and BMI.

C- Correlation between BMI and PASI score

In current study significant positive correlation between BMI and PASI score, *p-value* (0.042) , R(0.264). Figures (3-4).

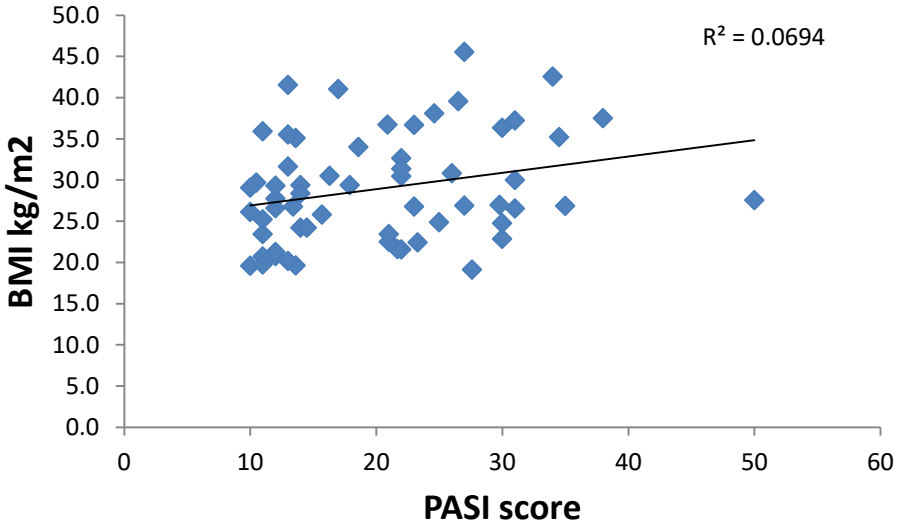


Fig (3-4): Correlation between BMI and PASI score .

In psoriasis patients Keratinocytes contribute to psoriasis inflammation by secreting proinflammatory cytokines such as IL-6 and tumor necrosis factor-α (TNF-α)[6]. As a result the TNF-α and IL-6 are immunological mediators and proinflammatory cytokines that lead to the released of CRP in psoriasis patients[143].

So that the increase of serum CRP level in psoriasis patients may lead to increase the activity of skin disease that measured by PASI score[150]. Therefore, Some studies analyzed the role of inflammatory markers such as serum CRP among psoriasis patients to evaluate the severity of the disease demonstrated an association between higher CRP levels and the severity of the psoriasis, similar to our study, as show in the fig (3-2). Due to this relation, inflammatory markers, especially CRP can be used to evaluate the severity of psoriasis[120].

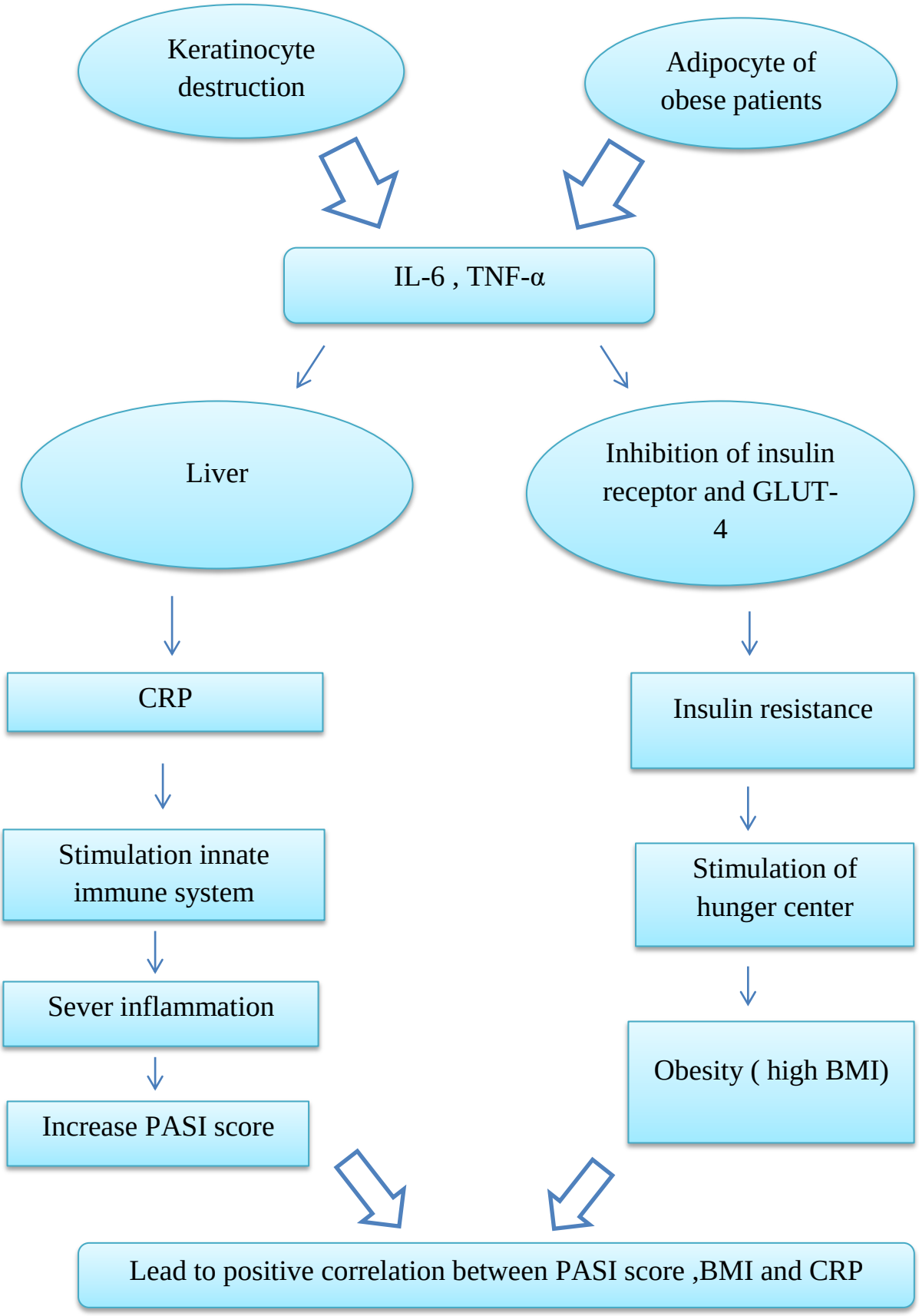
The increased adipocyte mass in overweight and obese individuals is a significant source of IL-6 and other proinflammatory cytokines[153].

The positive correlation result in current study between CRP and BMI, between BMI and PASI score may be contributed to the obesity that have been related to increased production of pro-inflammatory cytokines (TNF-α, IL-6) which are accountable for some aspects of the insulin resistance[154]. Also TNF-α and IL-6 are proinflammatory cytokines that lead to the release of CRP in psoriasis patients[143].

In addition the TNF-α may possibly have a role in obesity by blocking glucose transporter-4 and counteracting insulin receptor function, resulting in an increase in insulin levels that stimulate the hunger center[71]. Therefore, the important role of TNF-α and IL-6 in psoriasis lead to positive correlations between CRP and BMI, also between BMI and PASI score , as show in the fig (3-5).

In our study, there was numerical positive correlation between BMI and CRP values in psoriatic patients, as was also shown by Strober *et al.*[155].

A case-control study with 448 subjects found that obesity was associated with increasing PASI, similar to our study[11].



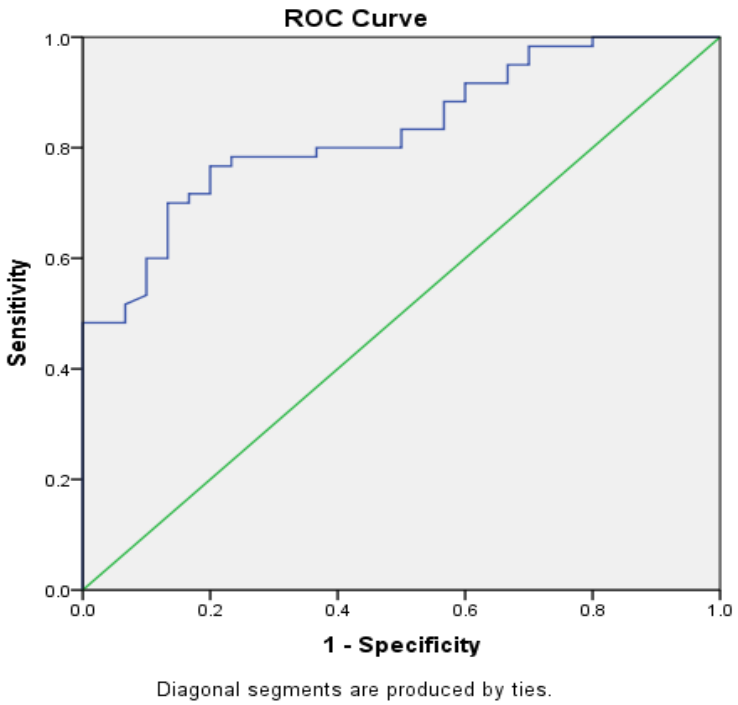
Fig(3-5): Scheme summarize correlation between PASI score, BMI,CRP.

3.4. ROC curve of biochemical parameters.

3.4.1. Roc curve of Chitinase-3-like-1 protein (CHI3L1).

Receiver operating characteristic (Roc) curve for the sensitivity and specificity of CHI3L1 (ng/ml) for diagnosis of psoriasis disease , (Cut-off point was ≤ 49.81 (ng/ml)) , AUC= 0.83 , P value ≤ 0.001 , 95% CI (0.747- 0.912), the sensitivity and the specificity was 76%, 80% respectively, positive predictive value(PPV) was 80%, negative predictive value(NPV) was 60%, as shown in figure (3-4).

For Chitinase-3-like 1 protein, our result state that good diagnostic value in the diagnosis of psoriasis patients according to the area under the curve(AUC) in ROC curve.



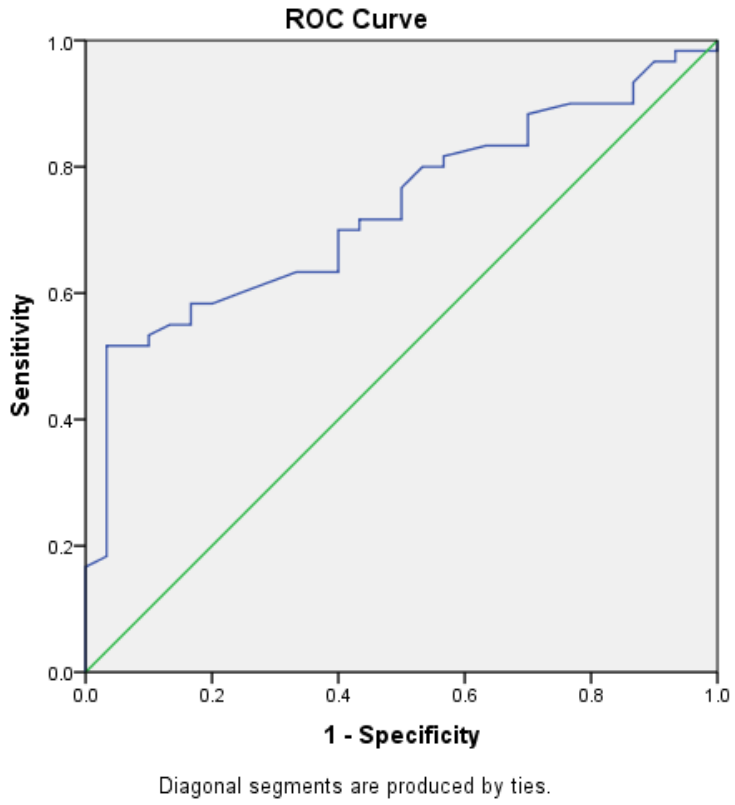
Fig(3-6): Roc curve of CHI3L1.

3.4.2. Roc curve of CRP.

Roc curve for the sensitivity and specificity of CRP (ng/ml) for diagnosis of psoriasis disease , (Cut-off point was ≤ 10.35 (ng/ml)) , AUC=0.73 , P value ≤ 0.001 , 95% CI (0.630 - 0.835), the sensitivity and the specificity was 70%, 60% respectively, positive predictive value(PPV) was 75%, negative predictive value(NPV) was 53.8 %, as shown in figure (3-5).

For C-reactive protein, our results state that fair diagnostic value in the diagnosis of psoriasis patients according to the area under the curve(AUC) in the ROC curve.

On the basis of area under the curve(AUC) that higher in CHI3L1(0.83) than in the CRP(0.73) , the CHI3L1 biomarker was more sensitive and specific than CRP in the diagnosis of psoriasis patients.



Fig(3-7): Roc curve of CRP.

Conclusions

- The biochemical parameters included in this study such as CHI3L1 and CRP are significantly higher in psoriasis patients when compare with normal healthy control and its influenced by the severity of psoriasis. The CHI3L1 and CRP increased with increase severity of psoriasis so it was higher in sever than moderate group and in moderate than healthy control groups.
- Zinc are significantly higher in healthy control than psoriasis patients, suggest that Zn supplement should be considered in psoriasis patients.
- Ghrelin show non-significant difference between psoriasis patients and controls group.
- The body mass index was significantly higher in patients than healthy control groups and increase with increase severity of psoriasis, so that obesity considered as a comorbid for psoriasis patients.
- There was a positive correlations between CRP and PASI score, CRP and BMI and between BMI and PASI score due to the important role of TNF-α and IL-6 in psoriasis diseased.
- The CHI3L1 could be considered as a biomarker of inflammation in psoriasis and is more sensitive and specific than CRP according to the ROC curve, so that it's a good biomarker for diagnosis of psoriasis patients.

Recommendations

- A future study is to be done on larger scale size to give results that are more accurate.
- Other markers of psoriasis diseases (such as TNF-α , IL-17) are needed to be measured due to it is role in development of obesity in psoriasis patients.
- Assessment of antioxidant secondary to Zinc depletions due to important in defense against skin lesion in psoriasis patients.
- Determination of the level of other biochemical components like insulin.

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الخلاصة :

الصدفية مرض التهابي مزمن يتميز بتكوين لويحات حمامية بارزة واضحة المعالم مع قشور بيضاء فضية على السطح الخارجي. داخل الجلد وعلى نحو جهازي ، تتميز الصدفية بفرط تكاثر الخلايا الكيراتينية والتمايز غير الطبيعي ، فضلاً عن تضخم الأوعية الدموية ، وتسلل الكريات البيض ، والتغيرات في إنتاج السيتوكينات.

ان الهدف من الدراسة الحالية هو مقارنة مستوى بروتين Chitinase-3-like-1 بين مرضى الصدفية ومجموعة الاصحاء. وكذلك دراسة التغير في مستوى الزنك (Zinc) في مصل الدم لدى مرضى الصدفية ومقارنتها مع مجموعة الاصحاء. وايضا دراسة التغير الهرموني في مستوى مصل جريلين (Ghrelin) في مريض الصدفية. ومن الاهداف المهمة ايضا دراسة حساسية (sensitivity) وخصوصية (specificity) ال CHI3L1 و CRP في مصل مرضى الصدفية ومعرفة من هو اكثر دقة في تشخيص مرض الصدفية باستخدام الروك كيرف (ROC curve). كذلك دراسة تأثير مؤشر كتلة الجسم (BMI) على شدة الصدفية.

صممت هذه الدراسة لتكون دراسة حالة وضبط. شارك في هذه الدراسة ٩٠ شخص ، مقسمين إلى ثلاث مجاميع (مجموعة شديدة الاصابة تحتوي على ٣٠ مريضاً ، والتي تم تصنيفها حسب الجنس إلى ٢١ (٧٠٪) من الذكور المصابين بالصدفية و ٩ (٣٠٪) من الإناث المصابات بالصدفية ومجموعة متوسطة الاصابة تحتوي على ٣٠ مريضاً و التي تصنف وفقًا للجنس إلى ٢١ (٧٠٪) ذكر مصاب بالصدفية و ٩ (٣٠٪) أنثى مصابة بالصدفية. و ايضا شارك في هذه الدراسة ٣٠ فردًا يبدو أنهم يتمتعون بصحة جيدة كمجموعة اصحاء ، والتي صنفت اعتمادًا على الجنس إلى ٢١ (٧٠٪) من الذكور الأصحاء و ٩ (٣٠٪) إناث يتمتعن بصحة جيدة وجميعهن ليس لديهن أي مرض جلدي أو أي مظهر آخر ، ومتطابقين مع المرضى في العمر والجنس. ولقد تم ابلاغ جميع المشاركين في هذه الدراسة قبل جمع العينات وتم الحصول على موافقة شفهية من كل منهم.

جميع حالات الصدفية المشمولة في الدراسة الحالية تم تشخيصها من قبل طبيب أمراض جلدية متخصص. أجريت الدراسة الحالية في عيادة الأمراض الجلدية في مستشفى مرجان التعليمي بمدينة الحلة وقسم الكيمياء الحياتية السريرية في كلية الطب بجامعة بابل من أكتوبر ٢٠٢١ إلى سبتمبر ٢٠٢٢ ، وتم تحديد بروتين إنزيم الكيتيناز ٣-شبيه-١ وببتيد جريلين(Ghrelin) باستخدام تقنية الفحص المناعي المرتبط بالانزيم (ELISA) بينما تم تحديد البروتين التفاعلي C(CRP) باستخدام طريقة القياس المناعي(Immunoturbidimetric Method) والزنك (Zinc) بواسطة مقياس الطيف الضوئي(Spectrophotometer).

أظهرت نتائج الدراسة الحالية زيادة معنوية في مصل CHI3L1 و CRP بين مرضى الصدفية مقارنة بالاشخاص الاصحاء وانخفاض معنوي في مصل الزنك في مريض الصدفية مقارنة بالشخص الطبيعي ، بينما أظهر مستوى جريلين فرقا غير معنوي بين مريض الصدفية والمجموعة الطبيعية. كان مؤشر كتلة الجسم (BMI) يزيد بشكل كبير في المرضى عن الاشخاص الاصحاء ، كما يظهر ارتباط إيجابي بين منطقة الصدفية ودرجة مؤشر الشدة

(PASI) و CRP أيضًا بين مؤشر كتلة الجسم(BMI و CRP) كذلك بين (BMI) وال (PASI).

الدراسة اظهرت ايضا زيادة كل من CHI3L1 و CRP مع زيادة شدة الصدفية لذلك كان أعلى في المجموعة الشديدة منها في المجموعة المتوسطة. يعتبر الزنك أعلى بشكل ملحوظ في الاشخاص الاصحاء من المرضى ويظهر الجريلين(Ghrelin) فرقًا غير مهم بين المرضى ومجموعة الاصحاء. كان مؤشر كتلة الجسم(BMI) أعلى بشكل ملحوظ في المرضى من مجموعة الاصحاء، لذلك هنالك احتمالية انه تعتبر السمنة مرضًا ناتجا عن مرض الصدفية حيث كان هناك ارتباط إيجابي بين مؤشر كتلة الجسم(BMI) و (CRP) ، وكذلك بين (CRP) ودرجة (PASI) وبين مؤشر كتلة الجسم (BMI) ودرجة (PASI). كان CHI3L1 أكثر حساسية وخصوصية من CRP وفقًا للمنطقة الواقعة أسفل المنحنى(AUC) في اختبار منحنى ROC ، لذلك فهو علامة جيدة لتشخيص مرضى الصدفية.