Link Between Psoriasis and other Metabolic Diseases

Amin Mohamed Amer, Somaia Gamal Mohamed, Waleed M. Albalat

Dermatology, Venereology and Andrology Department, Faculty of Medicine Zagazig University

Corresponding author: Somaia Gamal Mohamed

Email: s.gamal123@gmail.com

Abstract

Psoriasis is a serious, chronic, immune-mediated, hyperproliferative, and inflammatory skin disease of varying severity, which may induce itchy or painful lesions at different body sites and adversely impact quality of life. It is likewise associated with the presence of comorbidities, such as hypertension, obesity, diabetes mellitus, metabolic syndrome (MetS), cardiovascular diseases, and depression. The genetic, immunological and environmental factors all contribute to the pathogenesis of psoriasis. The pathological mechanism in psoriasis include cutaneous inflammation and keratinocytes hyperproliferation induced by an inflammatory cascade in dermis involving innate and adaptive immune cells. While adipose tissue may also contribute to the cutaneous inflammation by secreting adipokines and cytokines. Those could affect the activation, proliferation and differentiation of keratinocytes as well as immune cells. Recently it was outlined the proof for obesity, hypertension, diabetes mellitus, dyslipidemia, and the metabolic syndrome as comorbid diseases in psoriasis.

Key words: Psoriasis, Metabolic Diseases.

Psoriasis

Definition and Epidemiology

Psoriasis vulgaris is an inflammatory immune-mediated disease, described by sharply demarcated, erythematous, salmon pink, scaly plaques, which results from a mix of immune dysregulation and altered keratinocyte differentiation. The psoriatic phenotype reflects an altered gene expression profile and related epigenetic changes (1). It is progressively being perceived as a disease of systemic inflammation characterized by overexpression of several proinflammatory cytokines, C-reactive protein (CRP), IL-6, and perhaps adipokines (2).

It is a chronic and debilitating immune-mediated inflammatory skin disease that influences 1–3% of the overall population, around 80% of individuals with psoriasis have mild-to-moderate types of the disease. People with psoriasis typically show erythematous and scaly plaques on their skin, and extent of skin surface involvement is a key determinant of disease severity (3).
Metabolic Diseases and Psoriasis

Several epidemiological studies have confirmed that moderate to severe psoriasis is strongly associated with cardio-metabolic disorders including hypertension, obesity, type 2 diabetes, dyslipidemia, non-alcoholic fatty liver disease (NAFLD), metabolic syndrome, and chronic kidney disease (CKD). The relationship among psoriasis and comorbidities could be explained considering a common genetic background, the systemic effects of chronic inflammation, insulin resistance, and an unhealthy life-style such as heavy smoking/drinking, over-eating habit, and sedentary life, which are common in patients with psoriasis (4).

Pathogenic mechanisms linking psoriasis and metabolic diseases

The mechanisms underlying the association between psoriasis and metabolic diseases are multifactorial including both genetic and environmental factors and often overlap with metabolic abnormalities, which frequently coexist in psoriatic patients. In particular, altered transcription in genes biologically significant for psoriasis and metabolic disorders, including renin, cytotoxic T-lymphocyte antigen 4 (CTLA4) and Toll like receptor 3 (TLR3), was identified (5).

Psoriasis is a T cell–mediated inflammatory disease characterized by the expansion and activation of Th-1, Th-17 and Th-22 cells, which lead to local over-production of multiple pro-inflammatory mediators by lymphocytes and keratinocytes into the skin of psoriatic patients, including tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-1, IL-17, IL-22, IL-23, vascular endothelial growth factor (VEGF), and interferon-γ (6).

There is now evidence that these locally overproduced pro-inflammatory mediators can migrate into the systemic circulation, potentially inducing systemic insulin resistance, circulatory endothelial dysfunction, increased oxidative stress, increased angiogenesis, and hypercoagulation, all of which are common features of inflammatory conditions and cardiovascular damage (7).

Activated macrophages and T-cells infiltrate abdominal visceral adipose tissue stimulating adipocytes to release non-esterified fatty acids (NEFA) and secrete a myriad of adipokines and proinflammatory molecules, such as TNF-α, IL-6, leptin, resistin, chemerin, VEGF, procoagulant factors, which can induce a chronic low-grade inflammatory state, thus further contributing to the development of systemic insulin resistance, dysglycaemia, atherogenic dyslipidemia, vascular dysfunction, and NAFLD (7).

1 – Obesity

♦ Definition

The World Health Organization (WHO) defines obesity as an abnormal or excessive fat aggregation that may impair health. In the clinical practice, obesity is currently diagnosed by the assessment of body mass index (BMI), which is weight in kilograms divided by height in meters squared, independently from age and sex, obesity is categorized in different classes, accordingly with BMI increase. Whereas a BMI between 25 and 29.9 kg/m² defines overweight patients, those with BMI > 30 kg/m² are categorized as obese. Among them, a BMI between 30 and 34.9 kg/m² identifies a class I obesity, between 35 and 39.9 kg/m² class II, and > 40 kg/m² a class III, also known as morbid obesity (8).

The exact cause of obesity is unknown; however, there appears to be a complex relationship among biologic, psychosocial, and behavioral factors, which include genetic makeup, financial status, and
cultural influences. Obesity has been linked to microorganisms, epigenetics, increasing maternal age, lack of sleep, endocrine disruptors, and intrauterine and intergenerational effect (9).

♦ Complications of obesity

Obesity is usually associated with morbidity related to diabetes mellitus and cardiovascular diseases. However, there are numerous gastrointestinal and hepatic diseases for which obesity is the direct cause [e.g. non-alcoholic fatty liver diseases (NAFLD)] or is a significant risk factor, such as reflux esophagitis and gallstones. When obesity is a risk factor, it may interact with other mechanisms and result in earlier presentation or complicated diseases. There are increased relative risk of several gastrointestinal complications of obesity such gastroesophageal reflux disease (GERD), erosive esophagitis, erosive gastritis, gastric cancer, diarrhea, colonic polyps, cancer, liver disease, cirrhosis and hepatocellular carcinoma (10).

♦ Obesity and skin

There are various possible mechanisms connecting obesity with skin inflammation due to functional changes within adipose tissue as well as quantitative effects, such as the increased production of inflammatory cytokines from adipose tissue. Excess skin adipose tissue results in pro-inflammatory cytokine and hormone secretion. Cytokines such as tumor necrosis, The skin of obese individuals shows features of impaired barrier function, while impairment in lymphatic function may delay the clearance of inflammatory mediator (10).

♦ Obesity and psoriasis

There is an evidence for a relationship between BMI and risk of psoriasis; a conventional classification of BMI gave weak and imprecise associations, whereas the results suggested that there might be a threshold around 28 kg/m² at which the risk of psoriasis increases (11).

Obesity is associated with psoriasis risk, with the strongest association for central obesity, suggest that fat mass plays a role in disease causation. Adipose tissue, especially visceral fat, produces adipokines, which have a role in chronic inflammation. Adipokines that show pro-inflammatory activities such as leptin, visfatin, and resistin are increased in psoriasis patients, whereas the level of adiponectin, an anti-inflammatory adipokine is diminished (12).
Figure (1): Crosstalk between the skin and adipose tissue mediated by adipokines and cytokines (1).

Skin inflammation might be modulated by adipokines having pro-inflammatory (red) or anti-inflammatory effects (blue). They induce the expression of pathogenic mediators including IL-8, TNF-α, IL-17, and IL-22, and the recruitment of immune cells, such as plasmacytoid dendritic cells. Controversial evidence is related to the anti-adipogenic or pro-adipogenic role of cytokines, with the exception of TNF-α that presumably show anti-adipogenic effects. Abbreviations: IL: interleukin; mDC: myeloid dendritic cells; pDC: plasmacytoid dendritic cell, TNF-α: tumor necrosis factor alpha.

♦ Impact of obesity on the management of psoriatic patients

Obesity has several implications in the management of psoriatic patients. There is evidence that obesity diminishes the response to systemic and biologic therapies, mainly those with fixed dose regimen that obese patients are at greater risk of adverse effects and that weight loss might improve the response to therapy, several studies have compared the therapeutic efficacy of fixed versus adjusted dose biologic therapies in obese patients. Fixed dosed regimens of biologic therapies are frequently associated with a compromised efficacy in heavier patients; studies showed an evident relationship between increasing BMI and decreasing response rates in clinical trial (13).

Obesity is also a negative predictor of response in patients with psoriatic arthritis receiving TNF-alpha inhibitors. This could be justified by several reasons including that the body mass modifies the pharmacokinetic and clearance of biological drugs, and the visceral fat mass exerts pro-inflammatory effects by releasing adipokines (1).
Impact of weight loss on psoriasis and psoriatic arthritis

Weight loss in overweight or obese subjects, through decreased caloric intake, shows up to have an added beneficial impact on psoriasis or psoriatic arthritis when used in conjunction with other prescription medications. Interestingly, studies have shown that caloric restriction in obese subjects lowers the level of circulating inflammatory cytokines, this may lead to beneficial effect in psoriatic disease (1).

2- Hyperlipidemia

Definition

Hyperlipidemia is a metabolic syndrome characterized by diverse lipid profiles such hypercholesterolemia, hypertriglyceridemia and familial combined hyperlipidemia, it may have significant adverse effects on health such atherosclerosis, cardiovascular diseases, diabetes, insulin resistance and obesity. both genetic and environmental components are associated with hyperlipidemia (14).

The level of LDL is the single most important marker of atherosclerosis. Deranged LDL metabolism leads to coronary artery disease (CAD) that is often fatal, especially in patients with diabetes, increased LDL levels are found to be positively correlated with the increased cardiovascular (CV) risk. Thus, the treatment of hyperlipidemia plays a crucial role in the management of patients with CAD or those at increased risk of CAD all around the world (14).

Hyperlipidemia is classified as either primary (familial) caused by specific genetic abnormalities, or secondary (acquired) which caused by another underlying disorder. Hyperlipidemia sometimes is idiopathic, which is resulted without known cause (14).

Complications of hyperlipidemia

Hyperlipidemia is a systemic disease, which is an important risk factor resulting in atherosclerosis and cardiovascular disease. Half of the world's mortality is due to hyperlipidemia and its complications. The relevant disease-monitoring data show that the mortality caused by heart and cerebrovascular disease, stroke, cerebral infarction, hemiplegia, myocardial infarction originating from hyperlipidemia is alarming worldwide, so we need to take effective measures to detect and to treat hyperlipidemia (15).

The increased adipose tissue produces hormones and cytokines in nonphysiological quantities, which promote insulin resistance or development of the metabolic syndrome, and atherosclerosis which is defined as the pathological process comprising of accumulation of calcium. Cholesterol and lipids and development of fibrous plaques inside the lumen of medium and large arteries (15).

The pharmacotherapy and dietary approach will lead to decrease in LDL and total serum cholesterol eventually leading to decrease risk of cardiovascular morbidity and mortality and first line therapy includes dietary approach, the increment of dietary fibre in diet will lead to safe approach for reduction in cholesterol beside the role of psychological counseling (15).

Hyperlipidemia and psoriasis

Dermal and systemic inflammation are the causes of skin changes and hyperlipidemia, this
inflammation promotes atherosclerosis. Abnormalities in lipid metabolism play a critical role in the pathogenesis of psoriasis, lipid metabolism disorder is one of the cardiovascular risk factors. To date, understanding the possible mechanisms underlying the association between psoriasis and the atherosclerotic lipoprotein profile is important and may lead to the development of effective therapies (16). The concentration of lipids, lipoproteins, and apo lipoproteins has been found to be abnormal at the onset of psoriasis. Furthermore, patients with psoriasis are enriched with common genetic variants that predispose to increased risk for dyslipidemia, supporting a genetic rather than an acquired cause of the association (17).

Advanced lipid testing techniques have shown a more atherogenic lipid profile and decreased high density lipoproteins (HDL) cholesterol efflux capacity (CEC) among patients with versus without psoriasis. Increasing psoriasis severity is negatively correlated with HDL CEC in patients. HDL, CEC are also directly related to coronary artery disease burden in psoriasis patients (18).

Patients of psoriasis must be considered as a group at high risk for cardiovascular diseases. Lipid derangements correlate with the severity of disease and also act as a good prognostic sign. We propose early screening with serum lipid profile assay in psoriatic patients at the time of presentation and follow-up for assessing risk and treatment of hyperlipidemia to modify and prevent the risk of cardiovascular diseases (19).

3- Diabetes Mellitus

Definition

Insulin resistance (IR) is defined clinically as the inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and utilization in an individual as much as it does in a normal population. Under conditions of chronic inflammation as in psoriasis, high levels of pro-inflammatory cytokines induces IR leading to an increased proliferation of basal keratinocytes and, at the same time deny access to differentiation (20).

The chronic state of inflammation appears to be a central mechanism underlying the pathophysiology of insulin resistance, visceral adiposity, hypertension and dyslipidemia. All of these conditions increase the risk for the development of type 2 diabetes and cardiovascular disease (21).

The complications of diabetes mellitus have traditionally been divided into macrovascular complications such cardiovascular disease, atherosclerosis is more common in people with DM than in those without and microvascular complications (for example, complications affecting the kidney, the retina and the nervous system), complications of T2DM are very common, with half of patients with T2DM presenting with microvascular complications and 27% with macrovascular complications (22).

The number of subjects diagnosed with type 2 diabetes (T2D) is increasing, the cause of T2D is multifactorial (genes and epigenetics, insulin resistance, overweight, and physical inactivity), Previous studies indicated an association between T2D and psoriasis. Chronic inflammation contributes to both T2D and psoriasis. The association between the two diseases suggests a pathophysiologic link. In both diseases Th-1 and Th-17 cells are increased. Weight loss is an important preventive strategy for overweight persons with pre-diabetes, as it may delay the progression to DM. In addition, weight management is important for avoidance of DM related complications, since BMI even slightly above 25 puts one at a greater relative risk of a complication.
Many existing weight-loss programs, including dietary, physical activity and behavioral interventions are successful in long-term weight reduction and lead to a significant decrease in diabetes incidence (23).

- **Diabetes mellitus and psoriasis**
  
  Increased prevalence of DM has been detected in psoriatic patients. This relationship is more prominent in patients with severe psoriasis. Psoriatic patients with DM are more likely to have micro and macrovascular complications of DM, The need of insulin is higher in diabetic psoriatic patients (24).

  Genetically, psoriasis and type 2 diabetes share some genes, CDKAL1 has been linked to both, more recently, novel susceptibility genes (PTPN22, ST6GAL1, JAZF1) were identified for psoriasis and type 2 diabetes (25).

  It has been confirmed that insulin plays a key role in the differentiation of keratinocytes. Insulin resistance in human keratinocytes caused by the proinflammatory cytokine IL-1b could be responsible for the lack of differentiation and uncontrolled proliferation seen in psoriatic plaques IL-1b has long been known to be involved in the pathogenesis of psoriasis and causes insulin resistance in muscle, adipose tissue and liver cells, These possible mechanisms indicate that the low-grade inflammation present in patients with psoriasis might lead to insulin resistance, an important precursor of T2D (25).

4- **Hypertension**

- **Definition**
  
  Hypertension is defined as a sustained blood pressure more than 140/90 mmHg. Blood pressure should be measured at every routine clinical care visit, at the initial visit, blood pressure should be measured in both arms to detect and account for abnormalities such as arterial stenosis. Patients with elevated blood pressure who are not known to have hypertension should have elevated blood pressure confirmed on a separate day, within 1 month, to confirm the diagnosis of hypertension (26).

- **Hypertension complications**
  
  Hypertension is a common risk factor for cardiovascular disease (CVD) and a major global public health problem. Globally, hypertension affects approximately one in four adults and results in over ten million deaths annually (27).

  Hypertension also contributes to the pathogenesis of microvascular complications in diabetes, because blood pressure control can decrease the onset and development of microvascular complications such neuropathy, retinopathy, and nephropathy (28).

  Major consequences of being overweight or obese include higher prevalence of hypertension and a cascade of associated cardiorenal and metabolic disorders. Studies in diverse populations throughout the world have shown that the relationship between BMI and systolic and diastolic blood pressure (BP) is nearly linear, the effect of obesity on BP may also depend on how long a person has been overweight, worsening as excess adiposity is maintained during several years (28).

- **Hypertension and psoriasis**
  
  Psoriasis is associated with the occurrence of hypertension; The association has been documented to
be related to the severity of psoriasis. Psoriasis and hypertension have many common risk factors, but the association may also be due to the pro-inflammatory enzyme angiotensin-II. This enzyme causes vasoconstriction and the release of pro-inflammatory cytokines. Levels of angiotensin-converting enzyme have been found to be elevated in both psoriasis serum and psoriasis skin (17). The pathophysiologic mechanisms include several biological pathways, including over expression of endothelin1, a potent vasoconstrictor expressed in both vascular endothelium and keratinocytes increased oxidative stress and common inflammatory pathways, including key cytokines such as tumor necrosis factor and interleukin 17. CD4+ T cells are activated in hypertension and play an important role, IL-17A, produced in large part by CD4+ T cells, plays a critical role in the vascular dysfunction associated with hypertension (29).

Also, adipose tissue is a major source of angiotensinogen, the precursor of angiotensin, which plays an important role in controlling blood pressure. In addition to angiotensinogen, the secretion of resistin and leptin from adipose tissue have also been implicated in hypertension by metabolic diseases (29).

Observational studies confirmed that psoriasis increases the prevalence of hypertension by approximately 60%. Inflammatory pathways, overexpression of endothelin-1 and increased oxidative stress may predispose patients with psoriasis to develop hypertension. Further, chronic systemic inflammation and endothelial dysfunction in the pathogenesis of psoriasis may accelerate the atherosclerosis in the vessel walls, leading to increased risk for premature hypertension and cardiovascular disease, so that patients with psoriasis and hypertension are more likely to have more difficult-to-control hypertension and require more antihypertensive medications than patients with hypertension but without psoriasis (17).

References


