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Cardiovascular and Metabolic Comorbidities of Psoriasis

Ayman Elgendy[1]*, Eslam Alshawadfy[2], Abdelaziz Altaweel[1] and Ahmed Elsaidi[2]

[1]Department of Dermatology, Benha University, Egypt
[2]Department of Dermatology Research, National Research Centre, Al bohouth St, Dokki, Cairo, Egypt

Abstract

Once considered to be solely a cutaneous disease, there is now robust evidence that psoriasis is associated with systemic inflammation and a significantly increased risk of cardio vascular disease (CVD). Moderate to severe psoriasis is associated with a higher incidence of cardiovascular risk factors such as diabetes mellitus, obesity, smoking, and the metabolic syndrome. It is now well established that patients with severe psoriasis have an excess mortality compared with the general population.

Keywords: Cutaneous; Psoriasis; Myocardial; Cardio vascular disease

Introduction

Once considered to be solely a cutaneous disease, there is now robust evidence that psoriasis is associated with systemic inflammation and a significantly increased risk of cardio vascular disease (CVD). Moderate to severe psoriasis is associated with a higher incidence of cardiovascular risk factors such as diabetes mellitus, obesity, smoking, and the metabolic syndrome [1,2]. It is now well established that patients with severe psoriasis have an excess mortality compared with the general population [1].

It has yet to be established whether these comorbidities occur as a direct result of the systemic inflammation associated with psoriasis, as a consequence of genetically determined selection, or whether other factors are involved [3]. Some reports have emphasized that psoriasis may be an independent risk factor for myocardial infarction (MI), especially in young individuals with severe psoriasis [2,4,5]. Therefore, dermatologists should be vigilant to any risk factors that might aggravate the psoriasis patient's condition and result in the development of CVD and other disorders. As the intensity of the skin changes indicates not only the severity of psoriasis, but also that of other systemic pathologies, symptoms detected in a psoriasis patient may suggest major changes of multigenic nature. According to Mallbris, et al. [4] psoriasis patients with severe and longstanding skin lesions suffer increased morbidity and mortality from CVD-related events [4,2].

Cardiovascular Risk in Patients with Psoriasis

Although the association of psoriasis with cardiovascular disease was first described more than 20 years ago, the significance of the association between psoriasis and cardiovascular disease has only become apparent over the past decade. A population-based cohort study using the UK general practice research database (GPRD) showed that patients with psoriasis had an increased adjusted relative risk for myocardial infarction, after controlling for other cardiovascular risk factors. The relative risk increased with increasing psoriasis severity, with a 3-fold increase in the risk of myocardial infarction for male patients with psoriasis at the age of 30 years [2].

This increased risk was observed in all age groups, although it decreased with age. Patients with psoriasis at the age of 60 years still had an increased risk of cardiovascular disease even when the data were controlled for traditional cardiovascular risk factors. This finding suggests that psoriasis may be an independent risk factor for premature cardiovascular disease. Other studies have corroborated the correlation between the risk of cardiovascular morbidity and psoriasis severity, as well as demonstrating an increased risk of peripheral vascular disease, stroke, and overall mortality in psoriasis patients [1,2,4,5].

Another study using the GPRD showed that the incidence of risk factors for cardiovascular disease, including incident diabetes, hypertension, obesity, and hyperlipidemia, were increased compared with the general population after a first recorded diagnosis of psoriasis [5]. Armsrong, et al. provided epidemiologic evidence for an increased risk of microvascular and macro vascular complications among patients having both diabetes and psoriasis compared with patients having diabetes only, without psoriasis [6]. The results from epidemiology studies have prompted smaller studies to try to address whether psoriasis is causal rather than associated with cardiovascular disease. One study showed evidence of increased arterial stiffness, independent of other cardiovascular risk factors, and this stiffness worsened with duration of disease [7]. Another study showed increased risk of coronary artery calcification in patients with psoriasis compared with healthy controls [8].

Epicardial fat thickness, measured by transthoracic echocardiography, is another risk factor for atherosclerosis. In a small case-control study, epicardial fat thickness was significantly higher in patients with psoriasis compared with controls, independently of other cardio metabolic risk factors [9]. One study demonstrated that prevalence of psoriasis was twofold higher in patients with CAD than in control patients without CAD. This is may be attributed to the high prevalence of obesity among patients with CVD which may increase the risk for psoriasis [10].

Pathogenetic mechanisms of CVD in psoriasis patients appear to be of a complex nature and remain unclear. The development of atherosclerosis and its increased prevalence may be partially explained by the presence of atherosclerotic risk factors, e.g., diabetes, hypertension, obesity, and hyperlipidemia as well as by the chronic inflammatory processes that are commonly observed in psoriasis (Figure 1) [11] Both of these pathological conditions involve genetic, immunological, and environmental factors, which may modify the clinical expression of psoriasis and atherosclerosis substantially [10,12]

***Corresponding author:** Ayman Elgendy, Department of Dermatology, Benha University, Egypt, Tel: 966507364687; E-mail: aymanelgendy91@yahoo.com

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Various inflammatory diseases, such as RA, ankylosing spondylitis, psoriatic arthritis, and systemic lupus erythematosus, have been linked with atherosclerotic processes [12]. Therefore, psoriasis is also likely to be an independent risk factor for CVD occurrence, although further, especially prospective, studies are needed to prove this hypothesis [11]. Contrary to this concept, Parisi, et al. demonstrated that psoriasis was not associated with the short-to-medium term (over 3-5 years) risk of major CV events after adjusting for known cardiovascular disease risk factors and did not consider psoriasis independent cardiovascular risk factor [13].

The pathological characteristics that determine the development of CVD in psoriasis patients and the pathological events that initiate the process are yet to be determined. Recently, Boehncke, et al. [14] proposed the concept of the "psoriatic march", which denotes a causal link between psoriasis and CVD. According to these researchers, systemic inflammation may bring about insulin resistance, which, in turn, invokes endothelial cell dysfunction, leading to atherosclerosis, which may eventually result in MI or stroke [13].

Cardiovascular Risk Factors and Psoriasis

Hypertension

Several studies have reported a strong association between hypertension and moderate to severe psoriasis. In a large meta-analysis examining the prevalence of hypertension in patients with psoriasis, the odds ratio (OR) for hypertension in patients with mild psoriasis was 1.30 (95% confidence interval [CI], 1.15-1.47) and 1.49 (95% CI, 1.20-1.86) in those with severe psoriasis compared with healthy controls. In a subgroup analysis, patients with psoriatic arthritis also had an increased prevalence of hypertension with an OR of 2.07 (95% CI, 1.41-3.04) [15].

Diabetes mellitus

Psoriasis is associated with an increased prevalence and incidence of type II diabetes mellitus. A recent meta-analysis and systematic review concluded that the prevalence of diabetes was increased in patients with psoriasis with an OR of 1.53 (95% CI, 1.06-1.24) for mild disease and 1.97 (95% CI, 1.48-2.62) for severe disease. The incidence of diabetes in all patients with psoriasis had an OR of 1.27 (95% CI, 1.16-1.4) [16].

TNF-α plays an important role in both psoriasis and diabetes. It acts on adipocytes and muscle cells to induce insulin signaling defects by several ways, such as by impairing insulin signaling through inhibition of the tyrosine kinase activity of the insulin receptor; by activating peroxisome proliferator-activated receptor-d that promotes epidermal proliferation and modulates adipogenesis and glucose metabolism; and by suppressing adiponectin secretion from adipocytes, which is an important anti-inflammatory molecule that also functions in regulating insulin sensitivity [17,18].

Obesity

Although it has been well established that patients with psoriasis are more likely to be obese, it is unclear whether obesity antedates or occurs after the development of psoriasis [3,19,20]. A prospective study in 78,626 women followed for 14 years showed a biological gradient between increasing body mass index (BMI) and the risk of incident psoriasis, suggesting that obesity precedes the development of the disease [19]. Another study showed that patients with newly diagnosed psoriasis become obese at the onset of disease, compared with healthy controls [21]. In contrast, a large cross-sectional study using a self-reported questionnaire showed that patients became overweight after the onset of psoriasis and concluded that obesity was a consequence of psoriasis rather than a risk factor for development of the disease [20]. It has been shown more recently in a large international study that children and adolescents with psoriasis are more obese than age and sex-matched controls, with a tendency toward central adiposity [22,23].

Dyslipidemia

There is substantial evidence of dyslipidemia in patients with psoriasis [24]. A study from the Nurses' Health Study II showed that hypercholesterolemia is associated with an increased risk of incident psoriasis, particularly in those who had a diagnosis of hypercholesterolemia for greater than 7 years [25]. Lipid lowering agents were not shown to decrease the incidence of psoriasis. Important differences have also been observed in lipoprotein composition and particle size, and cholesterol efflux mechanisms in patients with psoriasis. Patients with psoriasis have lower levels of protective high-density lipoprotein (HDL), with an increased proportion of more atherogenic small low-density lipoprotein (LDL) and VLDL particles, similar to that observed in diabetic patients [26,27]. It has been shown that abnormal HDL particle size is associated with aortic vascular inflammation in patients with psoriasis after correction for other cardiovascular risk factors [28]. Compositional alterations of HDL in patients with psoriasis result in impaired ability to promote cholesterol efflux from macrophages, and this worsens with increasing psoriasis severity [29]. Note that successful treatment of psoriasis results in recovery of HDL particle size and cholesterol efflux capacity [30].

Psoriasis and metabolic syndrome

Patients with moderate to severe psoriasis have an increased prevalence of the metabolic syndrome in a constellation of comorbidities that includes visceral obesity, insulin resistance, dyslipidemia, and hypertension (Table 1) [31-34].

This association increases with increasing disease severity. In addition, the increased risk of individual components of the metabolic syndrome also shows a dose-response relationship with psoriasis severity, independently of other metabolic syndrome components [34]. Also, children with psoriasis have a significantly higher risk of developing the metabolic syndrome, with 30% of children meeting the criteria in one small study [35].

Patient has at least 3 of the following conditions:
• Fasting glucose greater than or equal to100 mg/dL (or receiving drug therapy for hyperglycemia)
• Blood pressure greater than or equal to 130/ 85 mm Hg (or receiving drug therapy for hypertension)
• Triglycerides greater than or equal to150 mg/dL (or receiving drug therapy for hypertriglyceridemia)
• High-density lipoprotein C (HDL-C) less than 40 mg/dL in men or less than 50 mg/dL in women (or receiving drug therapy for reduced HDL-C)
• Waist circumference greater than or equal to102 cm (40 inches) in men or greater than or equal to 88 cm (35 inches) in women; if Asian American, greater than or equal to 90 cm (35 inches) in men or greater than or equal to 80 cm (32 inches) in women. (Adapted from Gnjndy SM, Brewer HB, Cleeman ii, et al, American Heart Association. Definition of metabolic syndrome: report of the National Heart. Lung, and Blood Institute/American Heart Association conference on scientifk issues related to definition. Circu-lation 2004;109:435; with permission).

Table 1: National Heart Lung and Blood Institute and the American Heart Association (AHA) guidelines for diagnosis of the metabolic syndrome.

Cigarette smoking and excessive alcohol use in patients with psoriasis

The frequencies of smoking and excess alcohol consumption, which are independent risk factors for the development of cardiovascular disease are increased in patients with psoriasis [17,29,34-37]. However, it remains unclear whether these lifestyle factors influence the development of psoriasis or occur as a result of disease-related psychological distress. A recent meta-analysis showed an association between psoriasis and both current or former smoking and suggesting that smoking is an independent risk factor for the development of psoriasis [38]. Recent evidence has shown that cigarette smoke increases the percentage of circulating T helper 17 (Th17) cells in the peripheral blood of patients with psoriasis compared with nonsmokers [39].

Excess alcohol intake has been reported in up to 30% of patients with psoriasis and is likely associated with psychological distress [37]. Excess alcohol intake can lead to a wide spectrum of cardiovascular complications, including alcoholic cardiomyopathy, atrial fibrillation, sudden death, and hemorrhagic stroke [40]. Alcohol-related diseases accounted for a significant proportion of excess mortality in a population of Finnish patients with psoriasis [36].

Other associated comorbid conditions in patients with psoriasis

Obstructive sleep apnea and chronic obstructive pulmonary disease are associated with excessive cardiovascular disease and are more common in patients with moderate to severe psoriasis [41]. Patients with psoriasis have also been shown to have increased levels of homocysteine, which is an independent risk factor for cardiovascular disease [42]. Moderate to severe psoriasis is associated with increased levels of depression, which is another independent risk factor for cardiovascular disease [43,44]. In summary, there seems to be an excess of lifestyle factors and medical conditions in patients with psoriasis that predispose to premature cardiovascular disease.

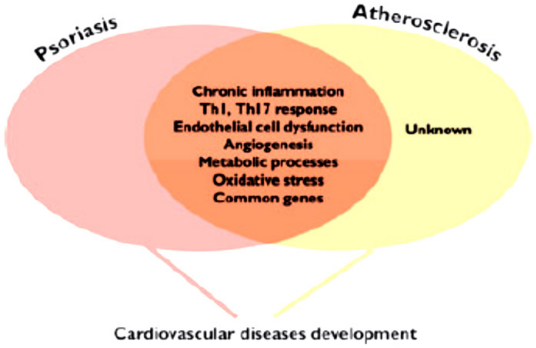

Figure 1: Pathogenetic mechanisms in psoriasis and atherosclerosis with the potential to trigger cardiovascular disease [11].

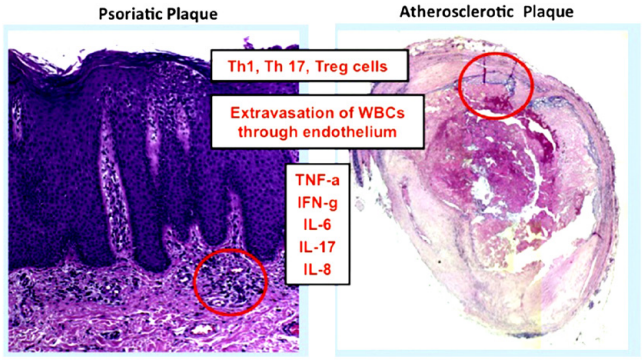

Figure 2: Comparison of the inflammatory nature of a psoriasis lesion and an atherosclerotic plaque. IFN-g, Interferon gamma; IL, Interleukin; TNF-a, Tumor necrosis factor-alpha; Treg, T regulatory cell; WBC, White blood cell [50].

Pathomechanisms Underlying the Association of Psoriasis with Cardiometabolic Comorbidites and Cardiovascular Risk

Multiple hypotheses have been suggested regarding the pathomechanisms underlying the association between psoriasis and cardio metabolic comorbidities. Although it is possible that patients with psoriasis are genetically predisposed to develop obesity, diabetes, and premature atherosclerosis, genome-wide association scans of patients with psoriasis have not shown an increased inheritance of genes associated with metabolic comorbidities [3]. Common inflammatory pathways are likely involved in the pathophysiology of psoriasis and cardiovascular inflammation, both of which are associated with a chronic proinflammatory, proangiogenic, and prothrombotic state [45-48]. The proinflammatory cytokine profile of psoriasis lesions is remarkably similar to that of atherosclerotic lesions, with a similar inflammatory cell infiltrate of T cells, macrophages, and monocytes observed in both conditions (Figure 2) [46,49,50].

Psoriasis plaques and unstable atherosclerotic plaques both have an increased frequency of activated T cells with both Th1 and Th17 patterns of cytokine production [46,49-51]. Th17 cells and their inflammatory mediators, including interleukin (IL)-17, IL-6, and IL-8, are also increased in the blood of patients with unstable coronary artery disease [52-60]. Increased expression of known cardiovascular biomarkers, such as monocyte chemoattractant protein-1 (MCP-1) and macrophage-derived chemokine has been observed in the lesional skin and serum of patients with psoriasis compared with healthy controls, suggesting shared inflammatory pathways linking psoriasis and cardio metabolic disease [61]. Although there is significant evidence that systemic inflammation drives the increased cardiovascular risk in patients with psoriasis, it is unclear whether psoriatic inflammation primarily contributes to the development of cardio metabolic comorbidities, or whether preexisting metabolic dysfunction causes immunologic dysregulation that then leads to the development of psoriasis [50].

It has been suggested that systemic inflammation caused by psoriasis affects the function of other cells and tissues driving the metabolic dysregulation, dyslipidemia, obesity, and increase in cardiovascular risk observed in patients with psoriasis [46,49]. Release of skin-derived cytokines and inflammatory mediators from psoriasis lesions into the circulation and upregulation of cell adhesion molecules may result in compartmental shifts in inflammatory cells between lesional psoriatic skin, the peripheral circulation, and atheromatous plaques of the coronary vasculature [50].

Adipocytokines

Recent studies have revealed that adipose tissue, especially visceral adipose tissue, functions as not only an energy store, but also as an endocrine organ contributing to the regulation of body functions such as glucose, lipid-and insulin-dependent metabolism, vascular tonus, coagulation and inflammation (Figure 3) [46,18].

Various cytokines involved in these process such as adiponectin,

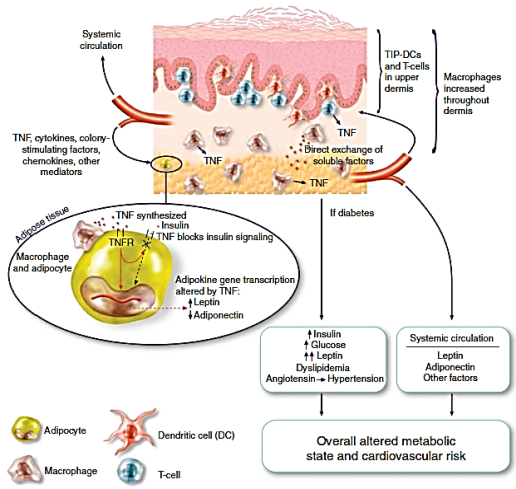

Figure 3: ''Psoriasis and obesity''. This diagram depicts inflammation in the epidermis and dermis associated with psoriasis vulgaris and likely inflammatory molecules that would be produced in adipose tissue of obese individuals. The model proposes that soluble factors could enter the systemic circulation from either dermal or adipose tissue beds and, in addition, there could be direct exchange (diffusion) of factors between dermal and adipose sites. The steps involved in blockade of insulin signaling and alteration of the production of adipokines by tumor necrosis factor (TNF) are shown. DC, Dendritic cell; TNFR, Tumor necrosis factor receptor [62].

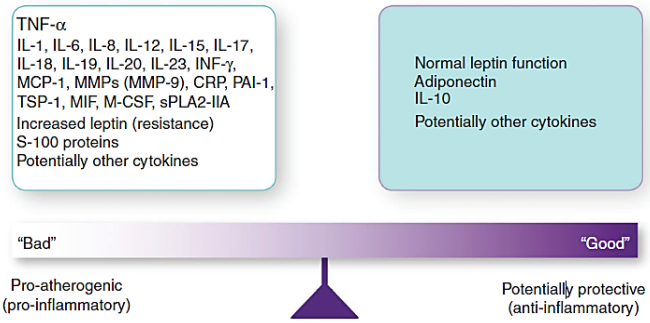

Figure 4: Potentially protective (anti-inflammatory) ''good'' and pro-atherogenic (proinflammatory) ''bad'' mediators of inflammation: modification of the Fisman model for cardiovascular risk (Fisman et al. 2003). CRP, C-reactive protein; MCP-1, Monocyte-chemoattractant protein 1; M-CSF, Macrophage colony-stimulating factor; MMP, Matrix metalloproteinase; PAI-1, Plasminogen activator inhibitor-1; sPLA2-IIA, Secretory phospholipase A2 group IIA; TNF-a, Tumor necrosis factor a.

leptin, IL-6, TNF-α and PAI-1 are produced in the adipose tissue [46,18]. Inflammation associated molecules that affect cardiovascular risk can be classified into good (anti-inflammatory) and bad (pro-inflammatory) cytokines (Figure 4) [46].

Adiponectin is an adipocyte-specific secretary protein abundantly present in circulation. A negative correlation between BMI and plasma adiponectin levels has been reported [62]. Plasma levels of adiponectin are decreased in obesity, insulin resistance and type 2 DM [63-65] and hypoadiponectinemia is assumed to be closely associated with metabolic syndrome [66,67]. *In vitro* studies disclosed that adiponectin is suppressed by other adipokines, TNF-α and IL6 [68,69]. Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist in monocytes and macrophages, while inhibiting the IL-6 level. A recent study indicates that adiponectin inhibits TNF-α production and TNF-α inhibits adiponectin production, thus antagonizing each other's function [70]. Adiponectin also inhibits the biological activity of TNF-α. Inhibition of NF-kB by adiponectin might explain at least part of these effects [71]. In endothelial cells, adiponectin down regulates the expression of adhesion molecules, ICAM-1 and vascular cell adhesion molecule 1, thus contrasting the effect of TNF-α.

Thus, adiponectin is considered to have overall beneficial effects. Plasma levels of adiponectin are decreased in obesity, insulin resistance, and type 2 diabetes. Low levels of adiponectin are a strong independent predictor of elevated diabetes risk in several populations [72,73]. Although its association with incident vascular risk remains unclear [74] Hypoadiponectinemia is assumed to be closely associated with the metabolic syndrome [75]. Plasma adiponectin levels in psoriasis are decreased compared with healthy controls. It is assumed that aberrant secretion of adipocytokines induces metabolic syndrome which is a strong predictor of cardiovascular diseases As regards its interaction with inflammation, although earlier studies on anti-TNF-α therapy have suggested increased serum adiponectin level with the improvement of RA much larger controlled trials have not confirmed this. This suggests that the links between adiponectin, psoriasis and CVD are perhaps much more complex than originally determined and more studies are required [46,71].

Leptin

Leptin is another adipocyte-specific secretory protein which acts primarily through a specific receptor in the hypothalamus [76]. It decreases appetite and increases energy expenditure [77] reflected in body fat mass [78]. The leptin receptor is also expressed in various tissues including adipocytes, endothelial cells, monocytes, and keratinocytes of injured skin [79]. Elevation of leptin levels is known to affect arterial intima-media thickness [80] and leptin is assumed to be an independent predictor of CVD and coronary heart disease [81,82].

Johnston et al. [83] showed a positive correlation between BMI and waist circumference with serum leptin levels. However, there exists no significant difference of leptin levels between psoriatics and matched healthy controls. Contrary to the results of Johnston, et al. [83]. Others demonstrated the increased leptin levels in psoriatics compared with other skin disease patients and matched healthy controls [84]. *In vitro* study disclosed that leptin increases keratinocyte proliferation, protects T lymphocytes from apoptosis and increasing the proliferation of naive T cells but reducing the proliferation of memory T cells. Leptin modulates T-cell derived cytokine production and increases expression of the activation markers CD25 and CD71 in CD4 and CD8 T cells. This is accompanied by increased secretion of TNFα and IL-6 from keratinocytes, and TNF-α IL-6, IL-17, IL-22 and IFN-γ from T lymphocytes [85]. In monocytes, leptin increases the expression of various activation markers and upregulates phagocytosis and cytokine production. In endothelial cells, leptin upregulates the expression of adhesion molecules and induces oxidative stress In light of the above activities, leptin has been implicated in the pathogenesis of immune-mediated inflammatory diseases (IMIDs) such as type 1 diabetes, Rheumatoid Arthritis (RA), inflammatory bowel disease, and psoriasis. It has been hypothesized that high levels of leptin in obese patients may contribute to psoriasis by releasing proinflammatory mediators [85].

TNF-α

TNF-α plays multiple roles in inflammation, metabolism and endothelial cell function regulation. Serum TNF-α level increases with increasing BMI, induces insulin resistance, and causes endothelial cells to produce adhesion molecules with the subsequent adherence of monocytes. TNF-α also induces an increase in Free Fatty Acids (FFA)

which further increases insulin resistance. These processes play an important role in the early stages of atherosclerosis. IL-6 likewise may induce insulin resistance, increase endothelial adhesion molecules, promote the hepatic release of both fibrinogen and C-reactive protein (CRP), and augment the procoagulant effects on platelets, all sequelae that promote atherosclerosis. TNF-α also increases the levels of plasminogen activator inhibitor Type 1 (PAI-1). PAI-1 inhibits the activity of tissue-type plasminogen activator, an anticlotting factor. Therefore, elevated PAI-1 results in impaired fibrinolysis and uninhibited clotting [18,75,86]. TNF-α and its receptors have been shown to exert a toxic effect on cardiomyocytes. This explains increased TNF-α levels in cardiac insufficiency as well as supraventricular arrhythmia [87,88].

Microparticles

Microparticle formation has recently been shown to contribute to accelerated atherogenesis in patients with psoriasis and other inflammatory conditions [89-91]. Microparticles are membrane vesicles containing nucleic acids and inflammatory mediators, such as IL-1, cluster of differentiation 40 (CD40) ligand, and intercellular adhesion molecule 1 (ICAM-1), which are released following cell activation or apoptosis and contribute to vascular inflammation, thrombosis, and angiogenesis [92]. Leukocyte-derived microparticles contribute to atherosclerotic plaque rupture and subsequent cardiovascular events, and have been shown to be predictive of cardiovascular outcomes. Studies have shown significantly higher microparticle concentrations in the blood of patients with psoriasis, even after adjusting for cardiovascular risk factors [91-93].

Hypercoagulability

Upregulation of platelets and coagulation factors may produce a hypercoagulable state contributing to an increase in thromboembolic events in psoriasis [45]. There is increased activation of platelets in patients with psoriasis compared with healthy controls, with increased levels of beta-thromboglobulin and platelet factor 4, increased platelet volume, and hyperaggregability, all of which normalize with resolution of disease [89,90]. There is an increase in platelet expression of p-selectin and increased release of platelet-derived microparticles in patients with psoriasis, which correlate with disease severity [86,91].

Management of Cardiovascular Risk

Education and primary prevention

Until alternative evidence is available, the presence of severe psoriasis should be considered an independent cardiovascular risk factor. It is the responsibility of physicians and dermatologists to counsel patients with psoriasis regarding the increased risk of cardio metabolic conditions and the need for lifestyle modifications, including smoking cessation, weight reduction, and regular screening for diabetes and hypertension [92,93]. Patients with moderate to severe psoriasis should have annual monitoring of blood pressure, BMI, waist circumference, lipid profile, fasting glucose, glycosylated hemoglobin, and smoking status.

The impact of weight reduction on the clinical course of psoriasis and treatment response needs further investigation. Weight reduction may improve psoriasis and small case series have shown a beneficial effect of gastric bypass surgery on psoriasis severity [94], several studies have suggested that weight loss may supplement the response to psoriasis therapies. [95].

Biomarkers

In recent years, much research has focused on identifying biomarkers of systemic inflammation and cardiovascular risk in patients with psoriasis. Although patients with more severe psoriasis seem to have an increased risk of cardio metabolic comorbidities, the degree of cutaneous involvement does not necessarily correlate with the level of systemic or cardiovascular inflammation. For example, patients with psoriatic arthritis may only have mild cutaneous involvement, despite significant extra cutaneous tissue inflammation and increased inflammatory markers. Validated biomarkers would provide a more reliable means of screening for increased cardiovascular risk. For example, in a recent study, increases in known cardiovascular biomarkers, including soluble ICAM-1 (sICAM-1), Soluble E (sE)-selectin, Matrix Metalloproteinase (MMP)-9, Myeloperoxidase (MPO), and total PAI-1 (tPAI-1), did not correlate significantly with Psoriasis Area and Severity Index (PASI), and it was suggested that this represented increased systemic inflammation rather than increases resulting from local cutaneous inflammation [96,50].

Because the pathomechanisms leading to increased cardiovascular risk in patients with psoriasis may differ from mechanisms in the nonpsoriatic population, it is not known whether conventional inflammatory biomarkers of atherosclerotic disease are reliable predictors of risk in patients with psoriasis. Studies have shown that conventional biomarkers of inflammation and cardiovascular disease, such as CRP, human soluble CD40 ligand (sCD40L), human matrix gla-protein, and fetuin-A, are significantly altered in patients with psoriasis after controlling for age and BMI [97]. CRP is a serum protein produced by the liver and is increased by infection and systemic inflammation [96]. Patients with immune-mediated diseases such as rheumatoid arthritis have increased levels of CRP compared with normal controls.

CRP is increased in patients with psoriatic arthritis and to a lesser extent in those with cutaneous psoriasis alone [97,98]. High-sensitivity CRP is an independent risk factor for the development of coronary artery disease and is increased in patients with psoriasis [97,98]. One study showed the neutrophil/lymphocyte ratio (NLR) to be the most reliable predictor of subclinical atherosclerosis in patients with psoriasis, as measured by the aortic velocity propagation and carotid intima media thickness, and NLR also correlated with PASI [99]. In several studies patients with psoriasis have shown significant increases in serum MPO, which is a known biomarker of cardiovascular inflammation that mediates its effects through lipid oxidation and endothelial dysfunction [100,101]. MPO is also highly expressed in psoriasis plaques. In one of these studies, serum levels of MPO correlated with coronary artery calcification, carotid plaque burden, carotid intima media thickness, and flow-mediated dilatation in patients with psoriasis but showed no association with psoriasis severity [100,101].

Careful evaluation of a patient's cardiovascular risk factor profile is needed when selecting individual therapies. When medication-related adverse effects such as hypertension and dyslipidemia occur, dermatologists should be adept at initiating antihypertensive and lipid lowering agents for the optimal management of cardiovascular risk.

Although growing evidence suggests that the aggressive management of moderate to severe psoriasis may mitigate cardiovascular risk, it is still unclear whether this is caused by the effect of individual systemic treatments on circulating immune cells, or whether clearance of cutaneous disease by any means decreases the systemic inflammatory burden [102].

Methotrexate

Methotrexate (MTX) has been the first-line systemic agent for psoriasis for more than 40 years. There is considerable evidence

to support the beneficial effect of MTX on cardiovascular risk in both the psoriasis and rheumatoid arthritis populations [103-105]. A retrospective cohort study demonstrated that MTX significantly reduced the risk of vascular disease compared with those who were not treated with MTX, particularly in those treated with low-dose MTX and concomitant folic acid [105].

Cyclosporine

Cyclosporine is a highly effective oral medication, but has an unfavorable side effect profile. In addition to nephrotoxicity, cyclosporine can adversely affect the cardiovascular risk factor profile by increasing the risk of hypertension and dyslipidemia [106]. The reported incidence of new-onset hypertension with short-course cyclosporine therapy typically ranges from 0% to 24%, and is generally reversible with dose reduction or the use of antihypertensives. The onset of hypertension did not seem to be dose related, suggesting that there may a subset of patients with increased individual sensitivity to cyclosporine [106]. Hyperlipidemia, particularly hypertriglyceridemia, develops in approximately 15% of patients with psoriasis on cyclosporine therapy [106]. If hyperlipidemia develops, a lipid-lowering diet should be introduced, followed by dose reduction of cyclosporine or commencement of a lipid lowering agent if dietary measures fail [106]. The use of cyclosporine in moderate to severe psoriasis is currently limited to short-term to medium term interventional treatment courses in order to achieve rapid disease control before transitioning to another systemic therapy with a more favorable long-term toxicity profile.

Acitretin

Acitretin is a vitamin A derivative that has been used to treat psoriasis since the early 1980s. Although less effective than other traditional systemic agents when used as a monotherapy, acitretin can play a valuable role in patients with generalized pustular psoriasis and palmoplantar disease [107]. Chronic increase of triglyceride levels may increase the risk of atherosclerosis, so monitoring of hyperlipidemia is necessary, but this should not be considered a contraindication because it is usually readily managed with dietary modification and lipid-lowering agents [108].

Tumor Necrosis Factor-Alpha Inhibitors

A large body of evidence from psoriasis and rheumatoid arthritis populations suggests that TNF-α inhibitors have a beneficial effect on cardiovascular risk. In the previously mentioned retrospective cohort study, patients receiving TNF-α inhibitors had a 50% reduction in the risk of myocardial infarction compared with those treated with topical agents, but there was no significant difference in TNF-α inhibitors use compared with traditional systemic agents or phototherapy [108]. Larger studies in patients with rheumatoid arthritis also support the cardioprotective effect of TNF-α inhibition. The effect of etanercept on inflammatory biomarkers in psoriasis has been evaluated in several studies [109,110]. In a previously mentioned study, etanercept treatment resulted in a highly significant reduction in all investigated biomarkers of cardiovascular risk including soluble vascular cell adhesion molecule-1, sICAM-1, sE-selectin, MMP-9, MPO, and tPAI-1, although these parameters did not improve in patients who had successful treatment with phototherapy [101]. Another study showed a significant decrease in CRP in patients with psoriasis and psoriatic arthritis treated with etanercept [101,109,110].

Ustekinumab

There has been considerable controversy regarding the association between the use of anti–IL-12p40 agents (Ustekinumab and Briakinumab) in patients with psoriasis and major adverse cardiovascular events (MACE) [111-113]. Ustekinumab has been approved for clinical use in psoriasis for more than 5 years, whereas Briakinumab was withdrawn from clinical trials because of concerns over cardiovascular safety. Two meta-analyses examined the association of anti–IL-12p40 inhibitors and cardiovascular events in patients with psoriasis. The first compared the excess probability of MACE in 22 randomized controlled trials (RCTs) in patients receiving active treatment of anti–IL-12p40 agents and TNF-α inhibitors. Although the apparent increase in MACE observed with patients receiving anti-IL-12p40 antibodies was not statistically significant, the findings raised questions about the cardiovascular safety of the anti-IL-12p40 agents [111]. A subsequent meta-analysis examining the rate of MACE in patients in RCTs of IL-12/23 antibodies using different statistical methods showed a significantly higher risk of MACE in patients treated with anti-IL-12p40 agents compared with placebo [114].

Note that these studies analyzed short-term use (up to 16 weeks) of anti-IL-12p40 agents in patients in clinical trials. However, a 5-year safety study conducted by the manufacturers of Ustekinumab has shown no increase or decrease in the rate of MACE over time and compares favorably with population-based rates of MACE [115].

Summary

There is strong evidence, both clinical and scientific, supporting an association between psoriasis and cardiovascular risk Reliable biomarkers of systemic inflammation or cardiovascular risk in patients with psoriasis have not yet been identified. Until further evidence is available, all patients with moderate to severe psoriasis and/or psoriatic arthritis should be considered to be at a higher risk of cardiovascular disease and managed accordingly. Further research and interventions to adequately screen for and optimally manage cardiovascular comorbidities are also warranted.

A systematic strategy needs to be implemented to ensure the cardiovascular safety of new agents under development, using appropriate imaging, assessments of endothelial function, and carefully selected biomarkers of cardiovascular risk. Further understanding of the complex pathophysiology of psoriasis and the common mechanistic pathways shared with cardiovascular disease will likely facilitate the development of more innovative approaches to reducing cardiovascular inflammation while treating the complete spectrum of psoriasis.

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