10.5005/jp-journals-10036-1040

REVIEW ARTICLE

Metabolic and Cardiovascular Comorbidities in Psoriasis: Revisited

[1]Shaurya Rohatgi, [2]KH Basavaraj

ABSTRACT

There is increasing awareness that psoriasis, as a disease, is more than 'skin deep' and associated with comorbidities that potentially increase morbidity and mortality, and lower quality of life. The consistency of association and the diversity of comorbidities reported in psoriasis warrants it to be labeled as a complex syndrome. Merely finding an association between psoriasis and comorbidities is not going to suffice until this evidence is put into clinical practice. The pathogenesis of psoriasis and its comorbidities is complex but several studies have revealed certain mechanisms and factors which are common to both. These shared pathogenic mechanisms solve the mystery to this comorbid association, especially with metabolic syndrome and cardiovascular disease. Studying these pathogenic links may reveal certain parameters which can be utilized as potential biomarkers in the presumptive screening of patients for the presence of comorbidities. These shared pathogenic mechanisms hold the key toward establishing a novel biomarker which can monitor both the disease severity and the associated comorbidity. Psoriasis patients with comorbidities also incur more healthcare costs, than those without comorbidities. Cardiovascular comorbidity in psoriasis incurs the greatest increase in healthcare resource use. Early detection of cardiovascular and other comorbid conditions in psoriasis can possibly reduce the morbidity, mortality, and economic burden associated with the disease. We attempt to review the pathogenic links between psoriasis and its metabolic and cardiovascular comorbidities.

Keywords: Psoriasis, Cardiovascular, Metabolic syndrome, Comorbidity.

How to cite this article: Rohatgi S, Basavaraj KH. Metabolic and Cardiovascular Comorbidities in Psoriasis: Revisited. MGM J Med Sci 2015;2(1):25-38.

Source of support: Nil

Conflict of interest: None

[1]Lecturer, [2]Professor

[1]Department of Dermatology, Venereology and Leprosy, MGM Medical College, Navi Mumbai, Maharashtra, India

[2]Department of Dermatology, Venereology and Leprosy, JSS Medical College, Mysore, Karnataka, India

Corresponding Author: Shaurya Rohatgi, Lecturer, Department of Dermatology, Venereology and Leprosy, MGM Medical College, Navi Mumbai-410210, Maharashtra, India, Phone: 0918424020499, e-mail: shaurya023@gmail.com

What is Known?

- Literature is flooded with studies on the association of psoriasis with metabolic and cardiovascular comorbidities.
- Common pathogenic links between psoriasis and its comorbidities have been reported in individual studies.

What is New?

- Comprehensive review of the pathogenic mechanisms shared between psoriasis and its comorbidities.
- Few factors, such as C-reactive protein, have the potential of being used as a biomarker in psoriasis for associated metabolic and cardiovascular comorbidity.

INTRODUCTION

Comorbidity is most often defined in relation to a specific index condition[1] as in the seminal definition of Feinstein: 'any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study'.[2] Unlike syndromes, in which a disease manifests itself in different ways generally at the same time, comorbidities are secondary manifestations of a disease that can occur at different times and in one or more organs. Although being secondary conditions, comorbidities can sometimes have an even greater social health impact than primary conditions.[3]

Psoriasis is a common, chronic skin disease, affecting approximately 2% of the population.[4] There is increasing awareness that psoriasis as a disease is more than 'skin deep' and associated with comorbidities that potentially increase morbidity and mortality, and lower quality of life.[5] Evidence continues to accumulate to support the association of psoriasis with established comorbidities that increase the risk of cardiovascular disease (CVD), including components of metabolic syndrome (MS), such as hypertension (HTN), diabetes, dyslipidemia and obesity.[6,7] Increased mortality in the psoriatic population has also recently been reported.[8,9]

The literature is flooded with studies on the association of psoriasis with metabolic and cardiovascular comorbidities. However, the conflicting results of these studies, the importance of performing screening tests in patients and the search for a potential biomarker in psoriasis makes it one of the most interesting fields of study in psoriasis.

METABOLIC SYNDROME

Metabolic syndrome is a cluster of risk factors, including central obesity, atherogenic dyslipidemia, HTN and glucose intolerance. National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)[10] defines MS as the presence of at least 3 of the following conditions (Table 1).

Opie[11] has reviewed the pathogenesis of MS (Fig. 1). Obesity and abdominal obesity, in particular, is the main pathogenic factor in MS as abdominal adipose tissue functions as an endocrine organ[12] by releasing free fatty acids (FFA), angiotensin II, and adipokines. MS is also characterized by a proinflammatory state [high levels of C-reactive protein (CRP)] and a prothrombotic state [high plasma concentrations of plasminogen activator inhibitor-1 (PAI-1) and fibrinogen, another acute-phase reactant]. These states are probably interrelated and linked to the existence of high concentrations of proinflammatory cytokines, and tumor necrosis factor (TNF-α) in particular.[13] Although obesity and insulin resistance (IR) have a proinflammatory effect that is perpetuated through a positive feedback loop, the effect may be modulated by certain genetic factors [such as abdominal fat accumulation without increased body mass index (BMI) in Indians].[14]

Table 1: NCEP ATP III criteria for metabolic syndrome

Elevated waist circumference	≥102 cm in men ≥88 cm in women
Elevated TG	>150 mg/dl (1.7 mmol/l)
Reduced HDL-cholesterol	<40 mg/dl (1.03 mmol/l) in men <50 mg/dl (1.3 mmol/l) in women
Elevated blood pressure	≥130 mm Hg systolic blood pressure Or ≥85 mm Hg diastolic blood pressure
Elevated fasting glucose	≥100 mg/dl

HDL: High density lipoprotein; TG: Triglycerides

Recent studies have estimated a prevalence of 15% to 24% for MS in the general population.[16,17] The variation among different subpopulations is probably a result of cultural and ethnic differences. Many studies have shown a positive correlation between psoriasis and MS.[18-23] A large population based survey found abdominal obesity to be the most common abnormal metabolic feature.[19] Gisondi et al[20] showed that MS was associated with psoriasis independently of age and smoking habit. Moreover, this association neither correlated with the severity of psoriasis, nor the body surface area (BSA) involved.[20] A recent meta-analysis[24] also showed a higher prevalence with pooled odds ratio (OR) for MS among psoriasis patients being 2.26. However, a dose-response relationship was observed between psoriasis severity and prevalence of MS.[24]

Few studies[25-28] have found that individuals with MS are approximately two times more likely to develop CVD. MS is also a strong predictor of IR, type 2 diabetes mellitus (T2DM) and stroke.[25,26,28-31] The importance of MS is that it may confer a cardiovascular (CV) risk higher than the individual components.[25,32] If the positive impact of treatment on MS-related comorbidity is confirmed, and possibly extended to diseases, such as psoriasis, the impact on CV morbidity and mortality will be enormous in those patients, who are at greater CV risk. Thus, the complicating factor of MS in psoriasis patients may influence treatment. A multidisciplinary approach to treatment (i.e. co-management with primary care physicians, endocrinologists and nutritionists) may result in desirable outcomes for both the comorbid condition and the psoriasis itself.[33]

OBESITY

The association between psoriasis and obesity was first reported by Lindegard[34] in 1986. Multiple studies have demonstrated that patients with psoriasis are

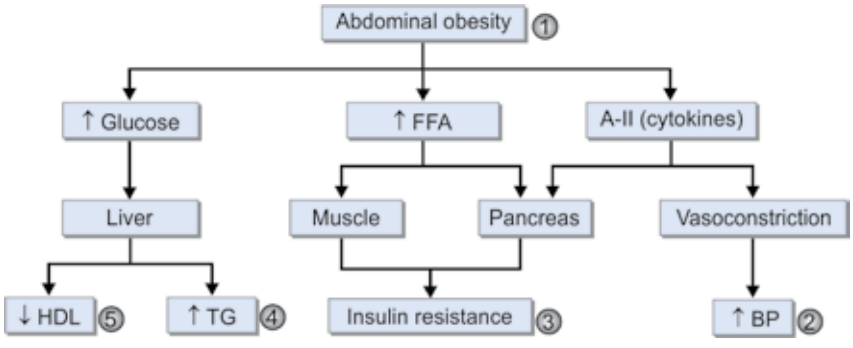

Fig. 1: Pathogenesis of metabolic syndrome (modified with permission from Opie LH)[15]: (1) Increased blood-free fatty acids (FFAs) inhibit muscle glucose uptake and, in combination with angiotensin II, has a harmful effect on the pancreas, ultimately contributing to insulin resistance, (2) angiotensin II (A-II) and cytokines cause hypertension (↑ BP) by acting as a vasoconstrictor, (3) TNF-α and other cytokines decrease the efficacy of insulin, (4,5) increased FFA and glucose stimulate the increased production of triglycerides by the liver, and this, in turn, reduces circulating levels of HDL

more frequently overweight (BMI > 25 kg/m^2 and >30 kg/m^2) or obese (BMI > 30 kg/m^2).[7,35-40] Some authors suggested that obesity may also occur prior to the onset of psoriasis and be risk factor for development of the disease.[39-42] Wolk et al[42] reported that for each unit increment in BMI, there was a statistically significant 9% increased risk for psoriasis onset and 7% higher risk for increased PASI. Obesity compared with normal body weight was associated with a two-fold increased risk for psoriasis onset.[42] Nevertheless, the distinct possibility remains that psoriasis and obesity are not reciprocally or unidirectionally causal, and instead may derive from a common underlying pathophysiology.[6]

Intra-abdominal fat is capable of secreting multiple bioactive proteins or adipocytokines, such as interleukin (IL)-6, TNF-α, adiponectin and PAI-1, levels of which are raised in visceral adiposity. They induce IR, increase endothelial adhesion molecules, promote the hepatic release of both fibrinogen and CRP, and augment the procoagulant effects on platelets, all sequelae that promote atherosclerosis. Elevated PAI-1 results in impaired fibrinolysis and uninhibited clotting.[43-45] Psoriasis and obesity share similar mediators of inflammation, such as TNF-α and IL-6. The engines of adipocytic and psoriatic inflammation—the adipocyte and macrophage respectively—both are derived from a common mesothelial origin. Importantly, psoriasis, like obesity, is associated with high systemic and local (skin and joint) levels of TNF-α. This suggests that obesity may potentiate some of the TNF-α and IL-6-driven inflammation seen in psoriasis, additionally leading to impaired glucose regulation, dyslipidaemia, endothelial dysfunction, HTN and a heightening of the inherent CV risk of cutaneous psoriatic inflammation.[6,46-48]

Weight loss is advisable in all patients who are overweight or obese, as this is the most important factor in improving MS and reducing its impact on CV morbid-mortality, in combination with smoking cessation.[49] For example, diet-associated weight loss has been shown to improve the response of obese patients with moderate-to-severe chronic plaque psoriasis to low-dose cyclosporine therapy, and there are several reports of psoriasis improvement following jejunoileal and gastric by-pass surgery.[50-52]

HYPERTENSION

Even though HTN is a constituent of MS, some studies did not demonstrate an association between psoriasis and HTN,[20,40,53-55] whereas others[7,21,22,35,41,56-59] found a strong association, with odds ratio as high as 3.[22] Some of these studies may have overestimated the association due to a Berksonian bias,[60] whereas others might have underestimated it due to over-matching.[57] It is possible that patients with psoriasis and MS are more likely to be hospitalized because of their comorbidities, hence the strong association.[57] Cohen et al[57] eliminated this bias by using a community-based database and still found a significant association. Moreover, HTN was associated with psoriasis, even after controlling for age, sex, smoking status, obesity, T2DM, NSAIDS and Cox-2 inhibitors use.[57]

This association may be attributed to angiotensin II, a product of angiotensin-converting enzyme (ACE) that regulates vascular tone and stimulates the release of proinflammatory cytokines.[61] Elevated plasma renin activity has been reported in patients with psoriasis.[62-64] Bonifati et al[65] reported that endothelin-1 (produced by keratinocytes as an autocrine growth factor) levels were increased in both sera and lesional skin of patients with psoriasis and also correlated with psoriasis severity.[65] Endothelin-1 is a potent vasoconstrictor and may contribute to HTN in psoriasis patients. Oxidative stress, which is present in patients with psoriasis, may play a role in HTN by destructive effects of reactive oxygen species (ROS), damaging endothelium dependent vasodilatation.[66]

LIPID ABNORMALITIES IN PSORIASIS

It is likely that psoriasis may predispose individuals to dyslipidemia[22] and this association is demonstrably stronger for severe psoriasis.[22,67] However, there is conflicting information about how lipid profiles might be affected by psoriasis. The serum lipid results are considerably dependent on group matching (age, gender, and ethnic and cultural factors). In most studies, a statistically significant elevated level of total cholesterol (TC), low-density lipoprotein (LDL) cholesterol and/or TG was demonstrated in psoriatic patients.[20,67-80] There was also a decrease in serum HDL.[67,77-79,81,82] Only a few studies found no differences in lipid serum levels between psoriasis patients and controls.[70,83-87] It is also unknown whether the observed lipid changes are primary or secondary to the chronic inflammatory process or its treatment.[70,88]

Pietrzak et al[89] have reviewed the lipid disturbances in psoriasis. In addition to dyslipidemia, psoriasis also affects other aspects of lipid metabolism, such as skin surface and epidermal lipids, apolipoproteins, oxidative stress, peroxisome proliferator-activated receptors and liver X receptors (Table 2).

The inverse relationship between the level of HDL and the development of atherosclerosis has triggered a renewed interest in HDL-C.[115] Reverse cholesterol transport (RCT), i.e. transport of cholesterol produced

Table 2: Lipid disturbances in psoriasis

Lipids	*Abnormality in psoriasis patients*	*Reference*
Skin surface and epidermal lipids	Alterations in ceramide content and abnormal lipid structures.	Motta et al,[90] Ghadially et al[91]
	Total lipids, phospholipids, triacylglycerol and cholesterol were found to increase both in blood and epidermis.	Khyshiktuev et al,[92] Ansidei et al[93]
	Increased levels of free and total cholesterol as well as phospholipids in the epidermis correlated to severity of psoriasis.	Fortinskaia et al,[94] Khyshiktuyev et al[95]
	Stratum corneum showed widened intracellular spaces, lack of resistant intercellular junctions, impaired intracellular adhesion, causing abnormal cholesterol homeostasis.	Maxfield et al,[96] Orfanos[97]
	Increased amount of total phospholipids in epidermis, whereas decreased amount of phosphatidylserine and increase of phosphatidylinositol in lesions and in lesion-free epidermis.	Tsambaos et al[98]
	12 to 23.5 times greater loss of lipids with scales per day.	Tekin et al,[70] Ponec et al[99]
ApoA, ApoB, ApoC3, ApoE	Elevated levels of ApoA1 (role concerning atherosclerosis controversial) and ApoB (increases risk of atherosclerosis).	Mallbris et al,[100] Rocha-Pereira et al[67]
	Elevated levels of ApoC3 (development of hypertriglyceridemia) and Apo E (regulation of TG and LDL).	Tam et al,[101] Pietrzak et al,[102] Seishima et al[103]
	ApoA1 sequestration in the inflamed tissues might lead to reduced HDL-C serum levels and thus increase the risk of CVD.	Oliveiro et al[104]
	Downregulation of ApoE expression in skin and normalization of ApoE levels precedes clinical improvement.	Karpouzis et al[105]
ROSs –$HO^{\bullet}$, $ROO^{\bullet}$, $O_2^{\bullet-}$, H_2O_2, $NO^{\bullet}$, HOCl	Increased production of ROSs overwhelming the antioxidant capacity of the body. Early and active lesions show intraepidermal penetration of activated PMNL which leads to ROS production provided by NADPH oxidase and proteolytic enzymes.	Rashmi et al[106]
Lipid peroxidation products—LHP, MDA, ox-LDL, TBA	Significantly higher lipid peroxidation markers in severe or active disease (PASI > 3) and reduced total antioxidant status.	Rocha-Pereira et al,[67] Kural et al[78]
	Increased concentrations of MDA and ox-LDL in lesions (initiates inflammation, influences the adhesion of oxidant status of endothelial cells) is important in the development of early atherogenesis.	Kural et al,[78] Rashmi et al,[106] Tekin et al,[70] Hadas et al[107]
	Higher circulating levels of TBA and AuAb-ox-LDL. AuAb-ox-LDL levels reflect the *in vivo* oxidation of LDL which is important in diseases, such as myocardial infarct, atherosclerosis, DM and psoriasis.	Rocha-Pereira et al,[67] Coimbra et al,[79] Orem et al,[77] Kural et al,[78] Rashmi et al[106]
tHcy	Hyperhomocysteinemia (endothelial injury, platelet activation, oxidative modification of LDL, and endothelial-leukocyte interactions resulting in atherothrombosis) and also its positive relationship with increased levels of AuAb-ox-LDL may play an important role in development of atherothrombotic complications.	Thambyrajah et al,[108] Kural et al[109]
PPAR and LXR	Increased expression of PPARβ/δ (mediates keratinocyte proliferation via NF-κB, induces endothelial cell proliferation and angiogenesis) and decreased expression of PPARα (modulates inflammatory response by inhibiting cytokine secretion, maturation, migration and T-cell-stimulatory activity of Langerhans cell, induces antioxidant enzymes, which would reduce the oxidative stress) and PPARγ (supposedly downregulates inflammation) in lesional skin.	Westergaard et al,[110] Plager et al,[111] Schmuth et al[112]
	MS may trigger the expression of PPARβ/δ, which in turn contributes to a nonterminated regenerative skin phenotype. This disease mechanism would be expected to be aggravated by acute inflammation, or stress via the induction of PPARβ/δ by TNFα and stress-activated kinase.	Tan et al[113]
	Significantly lower PPARγ levels with the lowest levels in patients with MS.	Hegazy et al[114]

Apolipoproteins (Apo); Reactive oxygen species (ROSs); Hydroxyl radical ($HO^{\bullet}$); Peroxyl radicals ($ROO^{\bullet}$); Superoxide anion ($O_2^{\bullet-}$); Hydrogen peroxide (H_2O_2); Nitrogen oxide ($NO^{\bullet}$); and Hypochlorous acid (HOCl); Lipid hydroperoxide (LHP); Malondialdehyde (MDA); Oxidized low-density lipoprotein (ox-LDL); Autoantibody-ox-LDL (AuAb-ox-LDL); Thiobarbituric acid (TBA); Total homocysteine (tHcy); Peroxisome proliferator-activated receptor (PPAR); Liver X receptor (LXR)

or accumulated in the peripheral tissues to the liver or other steroidogenic tissues is the basis for the antioxidant, anti-inflammatory, antithrombotic and fibrinolytic action of HDL.[115] Systemic inflammation has been shown to be associated with inflammatory modulation of HDL which loses capacity to perform RCT and 'efflux' cholesterol from the arterial wall. Mehta et al[116] reported that patients with psoriasis demonstrated significantly reduced HDL efflux capacity, a finding which persists after adjustment for traditional lipid levels and BMI. An abnormal

lipoprotein particle composition has also been suggested which may be atherogenic in nature. This abnormal lipoprotein particle composition and HDL efflux capacity in psoriasis may provide a link between psoriasis and CVD.[116] Holzer et al[117] reported that impaired cholesterol efflux capacity of HDL was a result of compositional alterations in psoriatic HDL, which finally reflects a shift to a proinflammatory profile in psoriasis patients.

The lipid disturbances are recognised as a very important part in the pathogenesis of psoriasis and also have a great impact on comorbidity observed in psoriatic patients, especially on CVD. These lipid disturbances are also connected with immunological abnormalities; hence psoriasis could be classified as an immunometabolic disease.[89]

DIABETES MELLITUS

Gibson et al,[118] in 1956, reported the association between T2DM and psoriasis for the first time. Since then, numerous studies have reported a higher risk, with a relative risk between 1.27 and 2.48.[7,22,23,35,69,119-131]

A cross-sectional design or retrospective nature is sometimes affected by selection or information bias. Moreover, these results can only reflect the relationship between psoriasis and diabetes prevalence in certain population at best rather than diabetes incidence.[128] However, Li et al[128] analyzed the data from three large cohort studies and found an elevated risk of incident T2DM among younger individuals with psoriasis and individuals with type 1 psoriasis. Obesity and MS had been proposed as an explanation for this increased risk.[132] Considering these metabolic consequences of adiposity in the development of psoriasis[41] and diabetes, BMI remains an important, possibly intermediate, pathway affecting this association. On the contrary, an association independent from BMI has been reported.[128,129,131] A possible explanation for this association is the presence of chronic inflammation that occurs due to persistent secretion of TNF-α and other proinflammatory cytokines (Table 3), which precipitates both psoriasis and diabetes.[130,133,134]

Low-grade inflammation has been shown to precede and predict the development of IR and diabetes[156,157] and elevated CRP levels are predictive of diabetes.[133,158] Specifically, inflammatory cytokines, such as IL-6 and TNF-α, have been associated with IR and T2DM. In addition, leptin and adiponection may be involved in psoriasis and T2DM, suggesting the role of adipocytokines in linking the two diseases.[150] Therefore, inflammation could be a biologically plausible mechanism underlying this association.

Table 3: Pathogenic mechanism shared between psoriasis and diabetes mellitus

Factor	*Mechanism*	*Reference*
TNF-α	Acts on adipocytes and muscle cells to induce insulin signalling defects and inhibits tyrosine kinase activity of insulin receptor.	Gustafson et al[135]
	Activates PPAR-δ (modulates adipogenesis and glucose metabolism).	Wakkee et al[136]
	Suppresses adiponectin secretion from adipocytes.	Romanowska et al[137]
IL-6	Implicated in insulin resistance and its complications.	Bastard et al[138,139]
	Elevated plasma levels in psoriasis linked to risk for T2DM independent of obesity and IR.	Wannamethee et al[140]
Leptin	Hyperleptinemia seen in psoriasis, and also associated with higher risk of developing MS.	Chen et al[141]
	Body weight loss significantly decreases leptin levels and improve insulin sensitivity and may reduce likelihood of developing MS.	Ballantyne et al[142] Hamminga et al[143]
	Although leptin improves insulin sensitivity, in common human obesity, high circulating-leptin levels suggest leptin resistance.	Minokoshi et al[144] Bjorbaek et al[145]
	Leptin-signalling pathway activates suppressor of cytokine signaling-3, which might inhibit insulin signalling.	Howard et al[146]
	Leptin: adiponectin ratio is a reliable measure of IR in nondiabetic white adults.	Finucane et al[147]
Adiponectin	Enhances insulin sensitivity through activation of adenosine monophosphate protein kinase.	Yamauchi et al[148]
	Decreased levels in psoriasis.	Shibata et al[149] Takahashi et al[150]
	Low levels associated with higher risk for developing T2DM. Levels decreased in obesity and diabetes, which negatively correlates with BMI.	Lindsay et al[151] Snehalatha et al[152] Ouchi et al[153]
IGF-II	Increased in skin and blood of psoriasis patients (promotes atherosclerosis and linked to diabetes and hyperlipidemia).	Yoo et al,[154] Zaina et al[155]

Type 2 diabetes mellitus (T2DM); Insulin-like growth factor-II (IGF-II); Interleukin (IL); Peroxisome proliferator-activated receptor (PPAR); Tumor necrosis factor (TNF); Metabolic syndrome (MS); Insulin resistance (IR)

CARDIOVASCULAR MORBIDITY AND MORTALITY

Cardiovascular disease is an important cause of morbidity and mortality in psoriatics. Almost 30 years ago, McDonald and Calabresi,[159] were the first to identify this risk in hospitalized patients of severe psoriasis. A significantly increased risk of MI has been found in psoriasis.[9,160-165] Moreover, this risk was more pronounced for young patients, and for those affected by more severe psoriasis.[160,162-166] A significant association between coronary artery disease (CAD) risk and psoriasis has also been seen,[9,22,163,167-170] the risk being higher in severe psoriasis.[22,161] Studying the association between psoriasis and stroke has given ambiguous results. Nevertheless, some studies have shown a positive association.[9,161,163,165,167,171] Gelfand et al[171] reported a 44% increase in the risk of stroke in psoriasis patients whereas; Kimball et al[161] estimated that the 10-year risk of cerebrovascular disease in psoriasis was increased by 12%. A significant association between peripheral vascular disease (PVD) risk and psoriasis was also reported[9,161,167] and prevalence of PVD rose with disease severity.[161]

Mehta et al[172] found that patients with severe psoriasis have a clinically significant 57% increased risk of CV death beyond the risk of death associated with traditional CV risk factors. The risk of CV mortality was not explained by major cardiac risk factors identified in routine medical practice, suggesting that severe psoriasis may be an independent risk factor for CV death. Moreover, the relative risk of CV death was highest in younger individuals suggesting a process of accelerated CVD in younger severe psoriasis patients. When patients with highest risk for CV death (i.e. those with history of MI, stroke or transient ischaemic attack, or atherosclerotic disease) were excluded, there was still a 56% increase in CV death. The results also persisted when examining the risk based on different treatments that theoretically could increase (e.g. cyclosporine, oral retinoids) or decrease (e.g. methotrexate) the risk of CVD,[172,173] suggesting that the increased CV mortality is not due to treatment effect.[172]

Studies indicate that psoriasis is associated with enhanced atherosclerosis and risk of CVD, and inflammation is a pivotal link between psoriasis and atherosclerosis.[174,175] In fact, atherosclerosis has a number of common

Table 4: Pathogenic mechanisms shared between psoriasis and atherosclerosis

Factor	*Mechanism*	*Reference*
Immune response	Th1 cell mediated immune compromise.	Biedermann et al,[182] Gudjonsson et al,[179] Hansson[183]
VCAM-1, ICAM-1,	Pattern of T cell activation and expression of adhesion molecules are common in both.	Hansson,[183] Schön et al,[184] Blankenberg et al[185]
L-selectin	Adhesion molecules are found in atherosclerotic plaques and also upregulated in psoriasis.	Blankenberg et al,[185] de Boer et al,[186] Cabrijan et al[187]
IFNγ	Important mediator of inflammation and can stimulate the expression of MHC class II molecules and ICAM-1.	Krueger et al,[47] Ranjbaran et al[188]
IL-8	Promotes neutrophil chemotaxis into epidermis by producing a chemotactic gradient in psoriasis. It influences adhesive properties of neutrophils (increased expression of surface adhesive molecules, thus improving intercellular interactions with endothelial cells, which in turn contributes to an increase in the passing of neutrophils through the walls of vessels, thus promoting atherosclerosis. It also stimulates the activity of granulocytes in the inflammation process of both conditions.	Krueger et al[47]
IL-6, CRP	IL-6 enables T lymphocytes to escape from regulatory T cell suppression and Th17 participation in inflammation. It not only mediates T cell activation and stimulates proliferation of keratinocytes but also mediates the acute phase response. CRP is released in response to increased levels of cytokines, such as IL-6 and TNF-α, and patients with elevated levels of CRP have increased risk for adverse CV outcome. Levels of IL-6 and CRP are raised in psoriatic patients and seem to correlate with psoriasis severity.	Goodman et al,[189] Grossman et al,[190] Koenig et al[191] Gisondi et al,[192] Coimbra et al[193]
VEGF	Angiogenesis is common to both and VEGF (potent proangiogenic factor) is upregulated in both.	Canavese et al,[194] Inoue et al,[195] Herrmann et al[196]
Th17 cells	Mediators of Th17 cells appear to become important overtime in psoriasis. Likewise, Th17 cell response has important role in CVD.	Ghoreschi et al,[197] Chen et al[198]
IL-12	IL-17 cells mediate IL-12 which has an important role in pathogenesis of psoriasis. IL-12 is also thought to be the link between inflammation and Th1-type cytokine production in coronary atherosclerosis.	Ranjbaran et al,[188] Federman et al[199]

Vascular cell adhesion molecule (VCAM); Intercellular cell adhesion molecule (ICAM); Vascular endothelial growth factor (VEGF); Interleukin (IL); Interferon (IFN); Major histocompatibility complex (MHC); Cardiovascular disease (CVD)

pathogenic features with psoriasis (Table 4), which was recently reviewed by Ghazizadeh et al.[176]

Immunological activities and pro-inflammatory cytokines play a prominent role in both diseases. Histologically, psoriasis and atherosclerosis show common features of infiltrating T-cells, monocytes, macrophages, neutrophils, dendritic cells (DCs) and mast cells.[177,178] The cytokine network in psoriasis and atherosclerosis is mainly characterized by T-helper 1 (Th1) type cytokines, such as IFNγ, IL-2 and TNF-α.[179-181] In these lesions, the major cytokine producers are DCs, $CD4^+$ and $CD8^+$ T-cells as well as keratinocytes. IFNγ and TNF-α induce keratinocytes to produce IL-6, IL-7, IL-8, IL-12, IL-15, IL-18. TNF-α in addition to several other cytokines, chemokines and growth factors may be the link between psoriasis and enhanced CVD.[176]

Psoriasis is considered to be a prototypical Th-1, 17 inflammatory disease, and Th-1 cellular secreted factors (e.g. ICAM-1, TNF-α) are indeed involved in the pathogenesis of atherosclerosis and MI.[179,182,183,200] Another important point to note is that patients with psoriasis have elevated hs-CRP[201] which has been independently associated as a marker for increased risk of CV events.[202-204]

This increase in CVD and mortality is important for clinicians to recognize so that counseling and appropriate screening for CVD and its risk factors in patients with severe psoriasis can be implemented.[205,206]

CONCLUSION

Besides affecting a patient physically, psoriasis has a detrimental socioeconomic impact on a patient's life. In fact, this economic burden can be labeled as comorbidity in itself.[207] Patients with psoriasis who have comorbidities commonly associated with their disease incur more healthcare costs, driven largely by greater utilization of medical services, than those without comorbidities.[208] Kimbal et al[208] reported that psoriasis patients with comorbidities had twice as many hospitalizations as those without comorbidities in a 6-month period with CVD incurring the greatest increase in healthcare resource use.[208] Psoriasis along with its comorbidities is associated with lesser work productivity and a greater number of missed work days, incurring substantial indirect costs and adding to the financial burden of the disease.[207]

Crown et al[209] suggested that the incremental costs of comorbidities may be caused by either an exacerbating effect of psoriasis on these comorbidities or a greater severity of psoriasis in patients who had comorbidities. Early identification and treatment of these comorbid conditions may have a positive impact on the economic burden, both for the patient and the healthcare system as a whole.

The trend in scientific literature and meeting presentations has been to 'upgrade' psoriasis from a cutaneous to a systemic disease. Merely, finding an association between psoriasis and comorbidities is not going to suffice until this evidence is put into clinical practice. Further research work should be directed toward establishing a novel biomarker which can monitor both the disease severity and the associated comorbidity. Psoriasis represents over expression or under expression of certain proteins that may serve as markers for the disease,[106] some of which are common both to psoriasis and its comorbidities. Hence, it is possible that the role of such a biomarker could also be extended to detect and monitor these comorbidities.

C-reactive protein is an acute phase reactant and a marker of inflammation that reflects the inflammatory load of the body. What makes CRP a novel biomarker? It has a relatively long half-life of 18 hours and has no relationship to fasting state or diurnal patterns which makes it a relatively stable serum protein compared to other markers. Assays for CRP are sensitive, reproducible, internationally standardized, relatively inexpensive, and widely available.[210,211] C-reactive protein is unique to psoriasis because it has been positively correlated with most of its metabolic and CVS comorbidities. Metabolic syndrome is characterized by a proinflammatory state as indicated by high levels of CRP.[13] Raised CRP levels predict the development of IR and diabetes.[156,157] At least 24 prospective studies have shown a consistent and robust relationship between levels of CRP, particularly hs-CRP and the risk of future CV events.[210] Studies have consistently shown higher levels of CRP (even hs-CRP) in psoriasis patients.[201,212] Authors have suggested the use of CRP as markers of the disease as the levels correlate with disease severity and response to treatment.[213,214] Further studies are required to validate its use as a biomarker for psoriasis and its comorbidities in clinical practice.

REFERENCES

1. Van den Akker M, Buntinx F, Metsemakers JF, Roos S, Knottnerus JA. Multimorbidity in general practice: prevalence, incidence, and determinants of co-occurring chronic and recurrent diseases. J Clin Epidemiol 1998;51(5):367-375.
2. Feinstein AR. Pre-therapeutic classification of co-morbidity in chronic disease. J Chronic Dis 1970;2(7):455-468.
3. Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M. Defining comorbidity: Implications for understanding health and health services. Ann Fam Med 2009;7(4):357-363.
4. Christophers E. Psoriasis—epidemiology and clinical spectrum. Clin Exp Dermatol 2001;26(4):314-320.

5. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008;58(5):826-850.
6. Sterry W, Strober BE, Menter A. Obesity in psoriasis: the metabolic, clinical and therapeutic implications. Report of an interdisciplinary conference and review. Br J Dermatol 2007;157(4):649-655.
7. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol 2006;55(5): 829-835.
8. Gelfand JM, Troxel AB, Lewis JD, Kurd SK, Shin DB, Wang X, et al. The risk of mortality in patients with psoriasis: results from a population-based study. Arch Dermatol 2007;143(12): 1493-1499.
9. Kaye JA, Li L, Jick SS. Incidence of risk factors for myocardial infarction and other vascular diseases in patients with psoriasis. Br J Dermatol 2008;159(4):895-902.
10. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106(25):3143-3421.
11. Opie LH. Metabolic syndrome. Circulation 2007;115(5): e32-35.
12. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 2004;89(6):2548-2556.
13. Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. Circulation 2005;111(11):1448-1454.
14. Puig-Sanz L. Psoriasis, a systemic disease. Actas Dermosifiliogr 2007;98(6):396-402.
15. Opie LH. The metabolic syndrome—does it exist? In: Diabetes at the limits II. Opie LH, Kasuga M, Yellon DM, editors. Cape Town: University of Cape Town Press; 2007. p. 95-100.
16. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the Third National Health and Nutrition Examination Survey. JAMA 2002;287(3): 356-359.
17. Hu G, Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, Pyorala K. DECODE Study Group. Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. Arch Intern Med 2004;164(10):1066-1076.
18. Rosa DJ, Machado RF, Matias FA, Cedrim SD, Noronha FL, Gaburri D, et al. Influence of severity of the cutaneous manifestations and age on the prevalence of several cardiovascular risk factors in patients with psoriasis. J Eur Acad Dermatol Venereol 2012;26(3):348-353.
19. Love TJ, Qureshi AA, Karlson EW, Gelfand JM, Choi HK. Prevalence of the metabolic syndrome in psoriasis: results from the National Health and Nutrition Examination Survey, 2003-2006. Arch Dermatol 2011;147(4):419-424.
20. Gisondi P, Tessari G, Conti A, Piaserico S, Schianchi S, Peserico A, et al. Prevalence of metabolic syndrome in patients with psoriasis: a hospital-based case-control study. Br J Dermatol 2007;157(1):68-73.
21. Augustin M, Reich K, Glaeske G, Schaefer I, Radtke M. Co-morbidity and age-related prevalence of psoriasis: analysis of health insurance data in Germany. Acta Derm Venereol 2010;90(2):147-151.
22. Sommer DM, Jenisch S, Suchan M, Christophers E, Weichenthal M. Increased prevalence of the metabolic syndrome in patients with moderate to severe psoriasis. Arch Dermatol Res 2006;298(7):321-328.
23. Cohen AD, Gilutz H, Henkin Y, Zahger D, Shapiro J, Bonneh DY, et al. Psoriasis and the metabolic syndrome. Acta Derm Venereol 2007;87(8):506-509.
24. Armstrong AW, Harskamp CT, Armstrong EJ. Psoriasis and metabolic syndrome: A systematic review and meta-analysis of observational studies. J Am Acad Dermatol 2013;68(4): 654-662.
25. McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, East HE, et al. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. Diabetes Care 2005;28(2):385-390.
26. Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation 2005;112(20): 3066-3072.
27. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005;365(9468):1415-1428.
28. Wannamethee SG, Shaper AG, Lennon L, Morris RW. Metabolic syndrome vs. Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. Arch Intern Med 2005;165(22):2644-2650.
29. Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP. Prospective analysis of the insulin-resistance syndrome (syndrome X). Diabetes 1992;41(6):715-722.
30. Laaksonen DE, Lakka HM, Niskanen LK, Kaplan GA, Salonen JT, Lakka TA. Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. Am J Epidemiol 2002;156(11): 1070-1077.
31. Lorenzo C, Okoloise M, Williams K, Stern MP, Haffner SM. The metabolic syndrome as predictor of type 2 diabetes: the San Antonio heart study. Diabetes Care 2003;26(11):3153-3159.
32. Alexander CM, Landsman PB, Teutsch SM, Haffner SM. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. Diabetes 2003;52(5):1210-1214.
33. Saraceno R, Ruzzetti M, De Martino MU, Di Renzo L, Cianci R, De Lorenzo A, et al. Does metabolic syndrome influence psoriasis? Eur Rev Med Pharmacol Sci 2008;12(5):339-341.
34. Lindegard B. Diseases associated with psoriasis in a general population of 159,200 middle-aged, urban, native Swedes. Dermatologica 1986;172(6):298-304.
35. Henseler T, Christophers E. Disease concomitance in psoriasis. J Am Acad Dermatol 1995;32(6):982-986.
36. Krueger G, Papp K, Stough D, Loven KH, Gulliver WP, Ellis CN, et al. A randomized, double-blind, placebo-controlled phase III study evaluating efficacy and tolerability of 2 courses of alefacept in patients with chronic plaque psoriasis. J Am Acad Dermatol 2002;47(6):821-833.

37. Mease P, Goffe B, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomized trial. Lancet 2000;356(9227):385-390.
38. Herron MD, Hinckley M, Hoffman MS, Papenfuss J, Hansen CB, Callis KP, et al. Impact of obesity and smoking on psoriasis presentation and management. Arch Dermatol 2005; 141(12):1527-1534.
39. Naldi L, Chatenoud L, Linder D, Belloni Fortina A, Peserico A, Virgili AR, et al. Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study. J Invest Dermatol 2005;125(1): 61-67.
40. Huerta C, Rivero E, Rodrıguez LA. Incidence and risk factors for psoriasis in the general population. Arch Dermatol 2007; 143(12):1559-1565.
41. Setty AR, Curhan G, Choi HK. Obesity, waist circumference, weight change, and the risk of psoriasis in women: Nurses' Health Study II. Arch Int Med 2007;167(15):1670-1675.
42. Wolk K, Mallbris L, Larsson P, Rosenblad A, Vingård E, Ståhle M. Excessive body weight and smoking associates with a high risk of onset of plaque psoriasis. Acta Derm Venereol 2009; 89(5):492-497.
43. Shirai K. Obesity as the core of the metabolic syndrome and the management of coronary heart disease. Curr Med Res Opin 2004;20(3):295-304.
44. Sattar N, McCarey D, Capell H, McInnes I. Explaining how 'highgrade' systemic inflammation accelerates vascular risk in rheumatoid arthritis. Circulation 2003;108(24):2957-2963.
45. Ronti T, Lupattelli G, Mannarino E. The endocrine function of adipose tissue: an update. Clin Endocrinol 2006;64(4): 355-365.
46. Bonifati C, Carducci M, Cordiali Fei P, Trento E, Sacerdoti G, Fazio M, et al. Correlated increases of tumour necrosis factor-a, interleukin-6 and granulocyte monocytecolony stimulating factor levels in suction blister fluids and sera of psoriatic patients—relationships with disease severity. Clin Exp Dermatol 1994;19(5):383-387.
47. Krueger JG. The immunologic basis for the treatment of psoriasis with the new biologic agents. J Am Acad Dermatol 2002;46(1):1-23.
48. Nickoloff B, Karabin G, Barker J, Griffiths CE, Sarma V, Mitra RS, et al. Cellular localization of interleukin- 8 and its inducer, tumor necrosis factor-alpha in psoriasis. Am J Pathol 1991; 138(1):129-140.
49. Gisondi P, Del Giglio M, Di Francesco V, Zamboni M, Girolomoni G. Weight loss improves the response of obese patients with moderate-to severe chronic plaque psoriasis to low-dose cyclosporine therapy: a randomized, controlled, investigator-blinded cliinical trial. Am J Clin Nut 2008;88(5): 1242-1247.
50. Higa-Sansone G, Szomstein S, Soto F, Brasecsco O, Cohen C, Rosenthal RJ. Psoriasis remission after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Obes Surg 2004;14(8): 1132-1134.
51. de Menezes Ettinger JE, Azaro E, de Souza CA, dos Santos Filho PV, Mello CA, Neves M Jr, et al. Remission of psoriasis after open gastric bypass. Obes Surg 2006;16(1):94-97.
52. Hossler EW, Maroon MS, Mowad CM. Gastric bypass surgery improves psoriasis. J Am Acad Dermatol 2011;65(1):198-200.
53. Naldi L, Peli L, Parazzini F, Carrell CF. Psoriasis Study Group of the Italian Group for Epidemiological Research in Dermatology. Family history of psoriasis, stressful life events, and recent infectious disease are risk factors for a first episode ofacute guttate psoriasis: results of a casecont. rol study. J Am Acad Dermatol 2001;44(3):433-438.
54. Inerot A, Enerback C, Enlund F, Martinsson T, Samuelsson L, Wahlström J, Swanbeck G. Collecting a set of psoriasis family material through a patient organisation; clinical characterisation and presence of additional disorders. BMC Dermatol 2005;5:10.
55. Garcia-Diez A, Ferrandiz-Foraster C, Vanaclocha Sebastian F, Liza´n Tudela L, Badia Llach X, Sellers-Fernandez G. What characterizes the severity of Psoriasis? Dermatology 2008; 216(2):137-151.
56. Lindegard B. Mortality and causes of death among psoriatics. Dermatologica 1989;179(2):91-92.
57. Cohen AD, Weitzman D, Dreiher J. Psoriasis and Hypertension: a case control study. Acta Derm Venereol 2010;90(1):23-26.
58. Bongiorno MR, Doukaki S, Rizzo D, Arico M. The prevalence of the obesity in patients with moderate to severe psoriasis in Sicily populations. J Eur Acad Dermatol Venereol 2010;24(1): 75-114.
59. Gerdes S, Zahl VA, Knopf H, Weichental M, Mrowietz U. Comedication related to comorbidities: a study in 1203 hospitalized patients with severe psoriasis. Br J Dermatol 2008;159(5):1116-1123.
60. Berkson J. Limitations of the application of four-fold table analysis to hospital data. Biometrics 1946;2(3):47-53.
61. Phillips MI, Kagiyama S. Angiotensin II as a pro-inflammatory mediator. Curr Opin Investig Drugs 2002;3(4):569-577.
62. Huskic J, Alendar F. Tissue angiotensin-converting enzyme in patients with various clinical forms of psoriasis. Bosn J Basic Med Sci 2007;7(2):103-106.
63. Ryder KW, Epinette WW, Jay SJ, Ransburg Rc, Glick MR. Serum angiotensin converting enzyme activity in patients with psoriasis. Clin Chim Acta 1985;153(2):143-146.
64. Ena P, Madeddu P, Glorioso N, Cerimele D, Rappelli A. High prevalence of cardiovascular diseases and enhanced activity of the renin-angiotensin system in psoriatic patients. Acta Cardiol 1985;40(2):199-205.
65. Bonifati C, Mussi A, Carducci M, D'auria L, Ameglio F. Endothelin-1 levels are increased in sera and lesional skin extracts of psoriatic patients and correlate with disease severity. Acta Derm Venereol 1998;78(1):22-26.
66. Sowers JR. Hypertension, angiotensin II, and oxidative stress. N Engl J Med 2002;346(25):1999-2001.
67. Rocha-Pereira P, Santos-Silva A, Rebelo I, Figueiredo A, Quintanilha A, Teixeira F. Dislipidemia and oxidative stress in mild and in severe psoriasis as a risk for cardiovascular disease. Clin Chim Acta 2001;303(1-2):33-39.
68. Pietrzak A, Jastrzebska A, Krasowska D, Chodorowskaa G, Tabarkiewiczb J, Tomasiewiczd K, et al. Serum pancreatic lipase [EC 3.1.1.3] activity, serumlipid profile and peripheral blood dendritic cell populations in normolipidemic males with psoriasis. J Mol Catal B Enzym 2006;40:144-154.
69. Mallbris L, Granath F, Hamsten A, Stahle M. Psoriasis is associated with lipid abnormalities at the onset of skin disease. J Am Acad Dermatol 2006;54(4):614-621.
70. Tekin NS, Tekin IO, Barut F, Sipahi EY. Accumulation of oxidized low-density lipoprotein in psoriatic skin and changes of plasma lipid levels in psoriatic patients. Mediators Inflamm 2007;2007:78454.
71. Cohen AD, Sherf M, Vidavsky L, Vardy DA, Shapiro J, Meyerovitch J. Association between psoriasis and the

metabolic syndrome: a cross-sectional study. Dermatology 2008;216(2):152-155.
72. Akhyani M, Ehsani AH, Robati RM, Robati AM. The lipid profile in psoriasis: a controlled study. J Eur Acad Dermatol Venereol 2007;21(10):1330-1332.
73. Javidi N, Meibodi T, Nahidi Y. Serum lipids abnormalities and psoriasis. Ind J Dermatol 2007;52(2):89-92.
74. Amin T, Saied E, Abdou SH. Atherosclerotic risk in psoriasis. J Pan-Arab League Dermatol 2005;16(2):39-45.
75. Bajaj DR, Mahesar SM, Devrajani BR, Iqbal MP. Lipid profile in patients with psoriasis presenting at Liaquat University Hospital Hyderabad. J Pak Med Assoc 2009;59(8):512-515.
76. Piskin S, Gurkok F, Ekuklu G, Senol M. Serum lipid levels in psoriasis. Yonsei Med J 2003;44(1):24-26.
77. Orem A, Cimsit G, Deger O, Orem C, Vanizor B. The significance of autoantibodies against oxidatively modified low-density lipoprotein (LDL) in patients with psoriasis. Clin Chim Acta 1999;284(1):81-88.
78. Kural BV, Orem A, Cimsit GU, Yandi YE, Calapoglu M. Evaluation of the atherogenic tendency of lipids and lipoprotein content and their relationships with oxidant-antioxidant system in patients with psoriasis. Clin Chim Acta 2003;328 (1-2):71-82.
79. Coimbra S, Oliveira H, Reis F, Belo L, Rocha S, Quintanilha A, et al. Circulating levels of adiponectin, oxidized LDL and C-reactive protein in Portuguese patients with psoriasis vulgaris, according to body mass index, severity and duration of the disease. J Dermatol Sci 2009;55(3):202-204.
80. Dreiher J, Weitzman D, Davidovici B, Shapiro J, Cohen AD. Psoriasis and dyslipidaemia: a population-based study. Acta Derm Venereol 2008;88(6):561-565.
81. Reynoso-von Drateln C, Martınez-Abundis E, Balcazar-Munoz BR, Bustos-Saldana R, Gonzalez-Ortiz M. Lipid profile, insulin secretion, and insulin sensitivity in psoriasis. J Am Acad Dermatol 2003;48(6):882-885.
82. Hadas E, Bozek A, Jarzab J. Impact of phototherapy on selected lipid profile indices in psoriatic patients allowing for intensification of the disease. Post Dermatol Alergol 2007;24(5):215-223.
83. Farshchian M, Zamanian A, Farshchian M, Monsef AR, Mahjub H. Serum lipid level in Iranian patients with psoriasis. J Eur Acad Dermatol Venereol 2007;21(6):802-805.
84. Ferretti G, Simonetti O, A. M. Offidani AM, Messini L, Cinti B, Marshiseppe I, et al. Changes of plasma lipids and erythrocyte membrane fluidity in psoriatic children. Pediatr Res 1993;33(5):506-509.
85. Toker A, Kadi M, Yildirim AK, Aksoy H, Akçay F. Serum lipid profile paraoxonase and arylesterase activities in psoriasis. Cell Biochem Funct 2009;27(3):176-180.
86. Farshchian M, Zamanian A, Monsef AR, Mahjub H. Serum lipid level in Iranian patients with psoriasis. J Eur Acad Dermatol Venereol 2007;21(6):802-805.
87. Vahlquist C, Michaelsson G, Vessby B. Serum lipoproteins in middle-aged men with psoriasis. Acta Derm Venereol 1987; 67(1):12-15.
88. Piskin S, Gurkok F, Ekuklu G, Senol M. Serum lipid levels in psoriasis. Yonsei Med J 2003;44(1):24-26.
89. Pietrzak A, Michalak-Stoma A, Chodorowska G, Szepietowski JC. Lipid Disturbances in Psoriasis: An Update. Mediators Inflamm. 2010; 2010. pii: 535612. doi: 10.1155/2010/535612.
90. Motta S, Monti M, Sesana S, Mellesi L, Ghidoni R, Caputo R. Abnormality of water barrier function in psoriasis: role of ceramide fractions. Arch Dermatol 1994;130(4):452-456.
91. Ghadially R, Reed JT, Elias PM. Stratum corneum structure and function correlates with phenotype in psoriasis. J Invest Dermatol 1996;107(4):558-564.
92. Khyshiktuev BS, Falko EV. Alterations in the parameters of lipid metabolism in different biological objects in psoriatic patients during exacerbation and remission. Vestn Dermatol Venerol 2005;6:40-43.
93. Ansidei V, Binazzi M, Cantelmi A, Gaiti A, Porcellati G. Phospholipid involvement in psoriatic epidermis. Ital J Biochem 1981;30(1):40-45.
94. Fortinskaia ES, Torkhovskaia TI, Sharapova GI, Loginova TK, Kliuchnikova ZI, Khalilov EM. Features of distribution of free and esterified cholesterol in the epidermis, biological membranes and plasma lipoproteins in psoriasis. Klin Lab Diagn 1996;4:38-43.
95. Khyshiktuyev BS, Karavayeva TM, Falko YV. Variability of quantitative changes in short-chain fatty acids in the serum and epidermis in psoriasis. Klin Lab Diagn 2008;8:22-24.
96. Maxfield FR, Tabas I. Role of cholesterol and lipid organization in disease. Nature 2005;438(7068):612-621.
97. Orfanos CE. Scanning electron microscopy in psoriasis. In: Farber EM CAJP, editor. Proceedings of the International Symposium on Psoriasis; 1971; Stanford, Calif, USA: Stanford University Press. p. 169-185.
98. Tsambaos D, Kalofoutis A, Stratigos J. Thin-layer chromatography of phospholipid components of normal and psoriatic epidermis. Br J Dermatol 1977;97(2):135-138.
99. Ponec M, Havekes L, Kempenaar J, Vermeer BJ. Cultured human skin fibroblasts and keratinocytes: differences in the regulation of cholesterol synthesis. J Invest Dermatol 1983; 81(2):125-130.
100. Mallbris L, Granath F, Hamsten A, Stahle M. Psoriasis is associated with lipid abnormalities at the onset of skin disease. J Am Acad Dermatol 2006;54(4):614-621.
101. Tam LS, Tomlinson B, Chu TT, Li M, Leung YY, Kwok LW, et al. Cardiovascular risk profile of patients with psoriatic arthritis compared to controls—the role of inflammation. Rheumatology (Oxford). 2008;47(5):718-723.
102. Pietrzak A, Kadzielewski J, Janowski K, Roliński J, Krasowska D, Chodorowska G, et al. Lipoprotein (a) in patients with psoriasis: associations with lipid profiles and disease severity. Int J Dermatol 2009;48(4):379-387.
103. Seishima M, S. Mori S, Noma A. Serum lipid and apolipoprotein levels in patients with psoriasis. Br J Dermatol. 1994; 130(6):738-742.
104. Oliveiro F, Sfriso P, Baldo G, Dayer JM, Giunco S, Scanu A, et al. Apolipoprotein A-I and cholesterol in synovial fluid of patients with rheumatoid arthritis, psoriatic arthritis and osteoarthritis. Clin Exp Rheumatol 2009;27(1):79-83.
105. Karpouzis A, Caridha R, Tripsianis G, C. Michailidis C, Martinis G, Veletza SV. Apolipoprotein e gene polymorpolymorphism in psoriasis. Arch Dermatol Research 2009;301(6): 405-410.
106. Rashmi R, Rao KSJ, Basavaraj KH. A comprehensive review of biomarkers in psoriasis. Clin Exp Dermatol 2009;34(6): 658-663.

107. Hadas E, Bozek A, Jarzab J. Impact of phototherapyon selected lipid profile indices in psoriatic patients allowing for intensification of the disease. Postepy Dermatologii i Alergologii 2007;24(5):215-223.
108. Thambyrajah J, Townend JN. Homocysteine and atherothrombosis—mechanisms for injury. Eur Heart J 2000; 21(12):967-974.
109. Kural BV, Orem A, Cimsit G, Yandi YE, Calapoglu M. Plasma homocysteine and its relationships with atherothrombotic markers in psoriatic patients. Clin Chim Acta 2003;332(1-2): 23-30.
110. Westergaard M, Henningsen J, Johansen C, Rasmussen S, Svendsen ML, Jensen UB, et al. Expression and localization of peroxisome proliferator-activated receptors and nuclear factor κB in normal and lesional psoriatic skin. J Invest Dermatol 2003;121(5):1104-1117.
111. Plager DA, Leontovich AA, Henke SA, Davis MD, McEvoy MT, Sciallis GF 2nd, et al. Early cutaneous gene transcription changes in adult atopic dermatitis and potential clinical implications. Exp Dermatol 2007;16(1):28-36.
112. Schmuth M, Jiang YJ, Dubrac S, Elias PM, Feingold KR. Peroxisome proliferator-activated receptors and liver X receptors in epidermal biology. J Lipid Res 2008;49(3):499-509.
113. Tan MH, Gordon M, Lebwohl O, George J, Lebwohl MG. Improvement of pyoderma gangrenosum and psoriasis associated with Crohn disease with anti-tumornecrosis factor α monoclonal antibody. Arch Dermatol 2001;137(7): 930-933.
114. Hegazy RA, Abdel Hay RM, Shaker O, Sayed SS, Abdel Halim DA. Psoriasis and metabolic syndrome: is peroxisome proliferator-activated receptor-γ part of the missing link? Eur J Dermatol 2012;22(5):622-628.
115. Kuliszkiewicz-Janus M, Mohamed AS, Abod N. The biology of HDL lipoprotein and its antisclerotic activity. Postepy Hig Med Dosw 2006;60:307-315.
116. Mehta NN, Li R, Krishnamoorthy P, Yu Y, Farver W, Rodrigues A, et al. Abnormal lipoprotein particles and cholesterol efflux capacity in patients with psoriasis. Atherosclerosis 2012; 224(1):218-221.
117. Holzer M, Wolf P, Curcic S, Birner-Gruenberger R, Weger W, Inzinger M, et al. Psoriasis alters HDL composition and cholesterol efflux capacity. J Lipid Res 2012;53(8):1618-1624.
118. Gibson SH, Perry HO. Diabetes and psoriasis. AMA Arch Derm 1956;74(5):487-488.
119. Shapiro J, Cohen AD, David M, Hodak E, Chodik G, Viner A, et al. The association between psoriasis, diabetes mellitus, and atherosclerosis in Israel: a case-control study. J Am Acad Dermatol 2007;56(4):629-634.
120. Binazzi M, Calandra P, Lisi P. Statistical association between psoriasis and diabetes: further results. Arch Dermatol Res 1975;254(1):43-48.
121. Brownstein MH. Psoriasis and diabetes mellitus. Arch Dermatol 1966;93(6):654-655.
122. Reeds RE, Fusaro RM Jr, Fisher I. Psoriasis vulgaris, I: a clinical survey of the association with diabetes mellitus. Arch Dermatol 1964;89:205-208.
123. Ollendorff-Curth H. Psoriasis and diabetes mellitus in Germans. Arch Klin Exp Dermatol 1966;227(1):240-247.
124. Vena GA, Altomare G, Ayala F, Berardesca E, Calzavara-Pinton P, Chimenti S, et al. Incidence of psoriasis and association with comorbidities in Italy: a 5-year observational study from a national primary care database. Eur J Dermatol 2010;20(5):593-598.
125. Pearce DJ, Morrison AE, Higgins KB, Crane MM, Balkrishnan R, Fleischer AB Jr, et al. The comorbid state of psoriasis patients in a University dermatology practice. J Dermatolog Treat 2005;16(5-6):319-323.
126. Pereira RR, Amladi ST, Varthakavi PK. A study of the prevalence of diabetes, insulin resistance, lipid abnormalities, and cardiovascular risk factors in patients with chronic plaque psoriasis. Indian J Dermatol 2011;56(5):520-526.
127. Xu XC, Feng AP. Characteristics of patients with psoriasis and Type 2 diabetes in a central China case-control study. Eur J Dermatol 2012;22(3):396-397.
128. Li W, Han J, Hu FB, Curhan GC, Qureshi AA. Psoriasis and Risk of Type 2 Diabetes among Women and Men in the United States: A Population-Based Cohort Study. J Invest Dermatol 2012;132(2):291-298.
129. Qureshi AA, Choi HK, Setty AR, Curhan GC. Psoriasis and the risk of diabetes and hypertension: a prospective study of US female nurses. Arch Dermatol 2009;145(4):379-382.
130. Cohen AD, Dreiher J, Shapiro Y, Vidavsky L, Vardy DA, Davidovici B. Psoriasis and diabetes: a population-based cross-sectional study. J Eur Acad Dermatol Venereol 2008; 22(5):585-589.
131. Ucak S, Ekmekci TR, Basat O, Koslu A, Altuntas Y. Comparison of various insulin sensitivity indices in psoriatic patients and their relationship with type of psoriasis. J Eur Acad Dermatol Venereol 2006;20(5):517-522.
132. Wakkee M, Thio HB, Prens EP, Sijbrands EJ, Neumann HA. Unfavorable cardiovascular risk profiles in untreated and treated psoriasis patients. Atherosclerosis 2007;190(1):1-9.
133. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001;286(3):327-334.
134. Hu FB, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory markers and risk of developing type 2 diabetes in women. Diabetes 2004;53(3):693-700.
135. Gustafson B, Hammarstedt A, Andersson CX, Smith U. Inflamed adipose tissue: a culprit underlying the metabolic syndrome and atherosclerosis. Arterioscler Thromb Vasc Biol 2007;27(11):2276-2283.
136. Wakkee M, Thio HB, Prens EP, Sijbrands EJ, Neumann HA. Unfavorable cardiovascular risk profiles in untreated and treated psoriasis patients. Atherosclerosis 2007;190(1):1-9.
137. Romanowska M, al Yacoub N, Seidel H, Donandt S, Gerken H, Phillip S, et al. PPAR delta enhances keratinocyte proliferation in psoriasis and induces heparin-binding EGF-like growth factor. J Invest Dermatol 2008;128(1):110-124.
138. Bastard JP, Jardel C, Bruckert E, Blondy P, Capeau J, Laville M, et al. Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. J Clin Endocrinol Metab. 2000;85(9):3338-3342.
139. Bastard JP, Maachi M, Van Nhieu JT, Jardel C, Bruckert E, Grimaldi A, et al. Adipose tissue IL-6 content correlates with resistance to insulin activation of glucose uptake both in vivo and in vitro. J Clin Endocrinol Metab. 2002;87(5):2084-2089.
140. Wannamethee SG, Lowe GD, Rumley A, Cherry L, Whincup PH, Sattar N. Adipokines and risk of type 2 diabetes in older men. Diabetes Care 2007;30(5):1200-1205.

141. Chen YJ, Wu CY, Shen JL, Chu SY, Chen CK, Chang YT, et al. Psoriasis independently associated with hyperleptinemia contributing to metabolic syndrome. Arch Dermatol 2008; 144(12):1571-1575.
142. Ballantyne GH, Gumbs A, Modlin IM. Changes in insulin resistance following bariatric surgery and the adipoinsular axis: role of the adipocytokines, leptin, adiponectin and resistin. Obes Surg 2005;15(5):692-699.
143. Hamminga EA, van der Lely AJ, Neumann HA, Thio HB. Chronic inflammation in psoriasis and obesity: implications for therapy. Med Hypotheses 2006;67(4):768-773.
144. Minokoshi Y, Kim YB, Peroni OD, Fryer LG, Müller C, Carling D, et al. Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. Nature 2002;415(6869):339-343.
145. Bjorbaek C, Kahn BB. Leptin signaling in the central nervous system and the periphery. Recent Prog Horm Res 2004;59: 305-331.
146. Howard JK, Flier JS. Attenuation of leptin and insulin signaling by SOCS proteins. Trends Endocrinol Metab 2006; 17(9):365-371.
147. Finucane FM, Luan J, Wareham NJ, Sharp SJ, O'Rahilly S, Balkau B, et al. Correlation of the leptin: adiponectin ratio with measures of insulin resistance in nondiabetic individuals. Diabetologia 2009;52(11):2345-2349.
148. Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med 2002;8(11):1288-1295.
149. Shibata S, Saeki H, Tada Y, Karakawa M, Karakawa M, Komine M, Tamaki K. Serum high molecular weight adiponectin levels are decreased in psoriasis patients. J Dermatol Sci 2009;55(1):62-63.
150. Takahashi H, Tsuji H, Takahashi I, Hashimoto Y, Ishida-Yamamoto A, Izuka H. Plasma adiponectin and leptin levels in Japanese patients with psoriasis. Br J Dermatol 2008;159(5): 1207-1208.
151. Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, Tataranni PA, et al. Adiponectin and development of type 2 diabetes in the Pima Indian population. Lancet 2002; 360(9326):57-58.
152. Snehalatha C, Mukesh B, Simon M, Viswanathan V, Haffner SM, Ramachandran A. Plasma adiponectin is an independent predictor of type 2 diabetes in Asian indians. Diabetes Care 2003;26(12):3226-3229.
153. Ouchi N, Walsh K. Adiponectin as an anti-inflammatory factor. Clin Chim Acta 2007;380(1-2):24-30.
154. Yoo H, Kim SJ, Kim Y, Lee H, Kim TY. Insulin-like growth factor-II regulates the 12-lipoxygenase gene expression and promotes cell proliferation in human keratinocytes via the extracellular regulatory kinase and phosphatidylinositol 3-kinase pathways. Int J Biochem Cell Biol 2007;39(6):1248-1259.
155. Zaina S, Nilsson J. Insulin-like growth factor II and its receptors in atherosclerosis and in conditions predisposing to atherosclerosis. Curr Opin Lipidol 2003;14(5):483-489.
156. Duncan BB, Schmidt MI, Pankow JS, Ballantyne CM, Couper D, Vigo A, et al. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. Diabetes 2003;52(7):1799-1805.
157. Garcia C, Feve B, Ferre P, Halimi S, Baizri H, Bordier L, et al. Diabetes and inflammation: fundamental aspects and clinical implications. Diabetes Metab 2010;36(5):327-338.
158. Yuan G, Zhou L, Tang J, Yang Y, Gu W, Li F, et al. Serum CRP levels are equally elevated in newly diagnosed type 2 diabetes and impaired glucose tolerance and related to adiponectin levels and insulin sensitivity. Diabetes Res Clin Pract 2006;72(3):244-250.
159. McDonald CJ, Calabresi P. Psoriasis and occlusive vascular disease. Br J Dermatol 1978;99(5):469-475.
160. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel A. Risk of myocardial infarction in patients with psoriasis. JAMA 2006;296(14):1735-1741.
161. Kimball AB, Robinson D Jr, Wu Y, Guzzo C, Yeilding N, Paramore C, et al. Cardiovascular disease and risk factors among psoriasis patients in two US healthcare databases, 2001-2002. Dermatology 2008;217(1):27-37.
162. Xiao J, Chen LH, Tu YT, Deng XH, Tao J. Prevalence of myocardial infarction in patients with psoriasis in central China. J Eur Acad Dermatol Venereol 2009;23(11):1311-1315.
163. Ahlehoff O, Gislason GH, Charlot M, Jørgensen CH, Lindhardsen J, Olesen JB, et al. Psoriasis is associated with clinically significant cardiovascular risk: a Danish nationwide cohort study. J Intern Med 2011;270(2):147-157.
164. Lin HW, Wang KH, Lin HC, Lin HC. Increased risk of acute myocardial infarction in patients with psoriasis: a 5-year population-based study in Taiwan. J Am Acad Dermatol 2011;64(3):495-501.
165. Li WQ, Han JL, Manson JE, Rimm EB, Rexrode KM, Curhan GC, et al. Psoriasis and risk of nonfatal cardiovascular disease in U.S. women: a cohort study. Br J Dermatol 2012;166(4):811-818.
166. Brauchli YB, Jick SS, Miret M, Meier CR. Psoriasis and risk of incident myocardial infarction, stroke or transient ischaemic attack: an inception cohort study with a nested case–control analysis. Br J Dermatol 2009;160(5):1048-1056.
167. Prodanovich S, Kirsner RS, Kravetz JD, Ma F, Martinez L, Federman DG. Association of psoriasis with coronary artery, cerebrovascular, and peripheral vascular diseases and mortality. Arch Dermatol 2009;145(6):700-703.
168. Augustin M, Reich K, Glaeske G, Schaefer I, Radtke M. Co-morbidity and age-related prevalence of psoriasis: analysis of health insurance data in Germany. Acta Derm Venereol 2010;90(2):147-151.
169. Kimball AB, Guerin A, Latremouille-Viau D, Yu AP, Gupta S, Bao Y, et al. Coronary heart disease and stroke risk in patients with psoriasis: retrospective analysis. Am J Med 2010;123(4): 350-357.
170. Yang YW, Keller JJ, Lin HC. Medical comorbidity associated with psoriasis in adults: a population-based study. Br J Dermatol 2011;165(5):1037-1043.
171. Gelfand JM, Dommasch ED, Shin DB, Azfar RS, Kurd SK, Wang X, et al. The risk of stroke in patients with psoriasis. J Invest Dermatol 2009;129(10):2411-2418.
172. Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. Eur Heart J 2010;31(8): 1000-1006.
173. Prodanowich S, Ma F, Taylor JR, Pezon C, Fasihi T, Kirsner RS. Methotrexate reduces incidence of vascular diseases in

veterans with psoriasis or rheumatoid arthritis. J Am Acad Dermatol 2005;52(2):262-267.

174. Alexandroff AB, Pauriah M, Camp RD, Lang CC, Struthers AD, Armstrong DJ. More than skin deep: atherosclerosis as systemic manifestation of psoriasis. Br J Dermatol 2009;161(1):1-7.
175. Abou-Raya A, Abou-Raya S. Review Inflammation: a pivotal link between autoimmune diseases and atherosclerosis. Autoimmun Rev 2006;5(5):331-337.
176. Ghazizadeh R, Shimizu H, Tosa M, Ghazizadeh M. Pathogenic mechanisms shared between psoriasis and cardiovascular disease. Int J Med Sci 2010;7(5):284-289.
177. Nickoloff BJ, Nestle FO. Recent insights into the immunopathogenesis of psoriasis provide new therapeutic opportunities. J Clin Invest 2004;113(12):1664-1675.
178. Nickoloff BJ, Qin JZ, Nestle FO. Immunopathogenesis of psoriasis. Clin Rev Allergy Immunol 2007;33(1-2):45-56.
179. Gudjonsson JE, Johnston A, Sigmundsdottir H, Valdimarsson H. Immunopathogenic mechanisms in psoriasis. Clin Experience Immunol 2004;135(1):1-8.
180. Hansson GK, Libby P. The immune response in atherosclerosis: a double-edged sword. Nat Rev Immunol 2006;6(7):508-519.
181. Nickoloff BJ, Xin H, Nestle FO, et al. The cytokine and chemokine network in psoriasis. Clin Dermatol 2007;25(6): 568-573.
182. Biedermann T, Röcken M, Carballido JM. TH1 and TH2 lymphocyte development and regulation of TH cell mediated immune responses of the skin. J Invest Dermatol 2004;9(1): 5-14.
183. Hansson GK. Immune mechanisms in atherosclerosis. Arterioscler Thromb Vasc Biol 2011;21(12):1876-1890.
184. Schön MP, Boehncke WH. Psoriasis. N Engl J Med 2005; 352(18):1899-1912.
185. Blankenberg S, Barbaux S, Tiret L. Adhesion molecules and atherosclerosis. Atherosclerosis 2003;170(2):191-203.
186. de Boer OJ, Wakelkamp IM, Pals ST, Claessen N, Bos JD, Das PK. Increased expression of adhesion receptors in both lesional and non-lesional psoriatic skin. Arch Dermatol Res 1994;286(6):304-311.
187. Cabrijan L, Batinac T, Lenkovic M, Gruber F. The distinction between lesional and non-lesional skin in psoriasis vulgaris through expression of adhesion molecules ICAM-1 and VCAM-1. Med Hypotheses 2009;72(3):327-329.
188. Ranjbaran H, Sokol SI, Gallo A, Eid RE, Iakimov AO, D'Alessio A, et al. An inflammatory pathway of IFN-gamma production in coronary atherosclerosis. J Immunol 2007;178(1):592-604.
189. Goodman WA, Levine AD, Massari JV, Sugiyama H, McCormick TS, Cooper KD. IL-6 signaling in psoriasis prevents immune suppression by regulatory T cells. J Immunol 2009;183(5):3170-3176.
190. Grossman RM, Krueger J, Yourish D, Granelli-Piperno A, Murphy DP, May LT, et al. Interleukin 6 is expressed in high levels in psoriatic skin and stimulates proliferation of cultured human keratinocytes. Proc Natl Acad Sci USA 1989; 86(16):6367-6371.
191. Koenig W, Khuseyinova N, Baumert J, Thorand B, Loewel H, Chambless L et al. Increased Concentrations of C-Reactive Protein and IL-6 but not IL-18 Are independently associated with incident coronary events in middle-aged men and women. Arterioscler Thromb Vasc Biol 2006;26(12): 2745-2751.
192. Gisondi P, Girolomoni G. Psoriasis and atherothrombotic diseases: Disease-specific and non-disease-specific risk factors. Semin Thromb Hemost 2009;35(3):313-324.
193. Coimbra S, Oliveria H, Reis F, Belo L, Rocha S, Quintanilha A. C-reactive protein and leucocyte activation in psoriasis vulgaris according to severity and therapy. J Eur Acad Dermatol Venereol 2010;24(7):789-796.
194. Canavese M, Altruda F, Ruzicka T, Schauber J. Vascular endothelial growth factor (VEGF) in the pathogenesis of psoriasis—a possible target for novel therapies? J Dermatol Sci 2010;58(3):171-176.
195. Inoue M, Itoh H, Ueda M, Naruko T, Kojima A, Komatsu R, et al. Vascular endothelial growth factor (VEGF) expression in human coronary atherosclerotic lesions: possible pathophysiological significance of VEGF in progression of atherosclerosis. Circulation 1998;98(20):2108-2116.
196. Herrmann J, Lerman LO, Mukhopadhyay D, Napoli C, Lerman A. Angiogenesis in atherogenesis. Arterioscler Thromb Vasc Biol 2006;26(9):1948-1957.
197. Ghoreschi K, Weigert C, Röcken M. Immunopathogenesis and role of T cells in psoriasis. Clinics in Dermatology 2007; 25(6):574-580.
198. Chen S, Crother TR, Arditi M. Emerging role of IL-17 in atherosclerosis. J Innate Immun 2010;2(4):325-333.
199. Federman DG, Shelling M, Prodanovich S, Gunderson CG, Kirsner RS. Psoriasis: an opportunity to identify cardiovascular risk. Br J Dermatol 2009;160(1):1-7.
200. O'Malley T, Ludlam CA, Riemermsa RA, Fox KA. Early increase in levels of soluble inter-cellular adhesion molecule-1 (sICAM-1); potential risk factor for the acute coronary syndromes. Eur Heart J 2001;22(14):1226-1234.
201. Chodorowska G, Wojnowska D, Juszkiewicz-Borowiec M. C-reactive protein and alpha2-macroglobulin plasma activity in medium-severe and severe psoriasis. J Eur Acad Dermatol Venereol 2004;18(2):180-183.
202. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002;347(20):1557-1565.
203. Ridker PM, Hennekens CH, Buring JE, Rifai N. C–reactive protein and other markers of imflammation in the prediction of of cardiovascular disease in women. N Engl J Med 2000; 342(12):836-843.
204. Ray KK, Cannon CP, Cairns R, Morrow DA, Ridker PM, Braunwald E. Prognostic utility of apoB/AI, total cholesterol/ HDL, non-HDL cholesterol, or hs-CRP as predictors of clinical risk in patients receiving statin therapy after acute coronary syndromes: results from PROVE IT-TIMI 22. Arterioscler Thromb Vasc Biol 2009;29(3):424-430.
205. Kimball AB, Gladman D, Gelfand JM, Gordon K, Horn EJ, Korman NJ, et al. National Psoriasis Foundation clinical consensus on psoriasis comorbidities and recommendations for screening. J Am Acad Dermatol 2008;58(6):1031-1042.
206. Friedewald VE, Cather JC, Gelfand JM, Gordon KB, Gibbons GH, Grundy SM, et al. AJC editor's consensus: psoriasis and coronary artery disease. Am J Cardiol 2008;102(12):1631-1643.
207. Schmitt J, Ford DE. Understanding the relationship between objective disease severity, psoriatic symptoms, illness-related stress, health-related quality of life and depressive symptoms

in patients with psoriasis—a structural equations modeling approach. Gen Hosp Psychiatr 2007;29(2):134-140.
208. Kimball AB, Guerin A, Tsaneva M, Yu AP, Wu EQ, Gupta SR, et al. Economic burden of comorbidities in patients with psoriasis is substantial. J Eur Acad Dermatol Venereol 2011; 25(2):157-163.
209. Crown WH, Bresnahan BW, Orsini LS, Kennedy S, Leonardi C. The burden of illness associated with psoriasis: cost of treatment with systemic therapy and phototherapy in the US. Curr Med Res Opin 2004;20(12):1929-1936.
210. Scirica BM, Morrow DA. Is C-reactive protein an innocent bystander or proatherogenic culprit? Circulation 2006; 113(17):2128-2151.
211. Ledue TB, Rifai N. Preanalytic and analytic sources of variations in C-reactive protein measurement: implications for cardiovascular disease risk assessment. Clin Chem Acta 2003;49(8):1258-1271.
212. Kanelleas A, Liapi C, Katoulis A, Stavropoulos P, Avgerinou G, Georgala S, et al. The role of inflammatory markers in assessing disease severity and response to treatment in patients with psoriasis treated with etanercept. Clin Exp Dermatol 2011;36(8):845-850.
213. Rocha-Pereira P, Santos-Silva A, Rebelo I, Figueiredo A, Quintanilha A, Teixeira F. The inflammatory response in mild and in severe psoriasis. Br J Dermatol 2004;150(5):917-928.
214. Coimbra S, Oliveira H, Reis F, et al. Circulating adipokine levels in Portuguese patients with psoriasis vulgaris according to body mass index, severity and therapy. J Eur Acad Dermatol Venereol 2010;24(12):1386-1394.