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Inflammation, Atherosclerosis, and Psoriasis

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Abstract Increasing evidence supports an important role for inflammation in all phases of atherosclerosis, from initiation of the fatty streak to final culmination in acute coronary syndromes. Numerous inflammatory biomarkers including cell adhesion molecules, cytokines, chemokines, and acute-phase reactants such as fibrinogen, serum amyloid A, and C-reactive protein (CRP) have been shown to predict cardiovascular (CVD) events. Several prospective studies have shown a consistent and robust relationship between levels of high-sensitivity CRP and the risk of future CVD events. Toll-like receptors are pattern recognition receptors and members of the innate immune system that contribute to inflammation and appear to play key roles in atherosclerosis. Lipoprotein-associated phospholipase A2 may also be an independent CVD risk factor. Psoriasis has been associated with an increasing risk for atherosclerosis, including coronary artery disease and stroke. Patients with psoriasis have a 5-year shorter life expectancy, most frequently due to CVD. Psoriasis is associated with a chronic inflammatory state and with elevated levels of CRP and other inflammatory cytokines and these may play a causative role in the increased risk of psoriatic patients for CVD. Patients with psoriasis may represent an emerging risk population and patients with moderate to severe psoriasis should be screened and aggressively treated for CVD risk factors.

Keywords Psoriasis · Coronary artery disease · Inflammatory biomarkers · C-reactive protein · Toll-like receptors · Lipoprotein-associated phospholipase A_2

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Introduction

Unique among inflammatory dermatosis, psoriasis has been recently associated with coronary artery disease (CAD), type 2 diabetes, and metabolic syndrome, together the leading cause of mortality in the western world. It is possible that chronic state of systemic inflammation in psoriatic disease is a predisposing factor for atherosclerosis and CAD. In this article, we will discuss about risks of CAD in psoriatic disease and possible mechanisms which likely integrates the inflammatory cascades of both psoriasis and atherosclerosis.

Inflammation and Atherosclerosis

Mounting evidence supports a pivotal role for inflammation in all phases of atherosclerosis, from initiation of the fatty streak to final culmination in acute coronary syndromes [1–3]. The earliest event in atherogenesis appears to be endothelial cell dysfunction precipitated by various noxious insults including obesity, hypertension, metabolic syndrome,

diabetes, smoking, and dyslipidemia. Endothelial cell dysfunction manifests primarily as deficiency of nitric oxide $(NO)_2$ and an increase in endothelin 1 (ET-1), angiotensin II (Ang II), plasminogen activator inhibitor 1 (PAI-1), cellular adhesion molecules, and cytokines/chemokines.

With onset of endothelial cell dysfunction, mononuclear cells such as monocytes and T lymphocytes tether and roll along the endothelium, initially loosely; thereafter, they adhere firmly to the endothelium and transmigrate into the sub-endothelial space. The rolling and tethering of leukocytes on the endothelium is orchestrated by adhesion molecules such as selectins (E-selectin, P-selectin), cell adhesion molecules [intercellular adhesion molecule 1, vascular cell adhesion molecule 1], and integrins. Chemotaxis and entry of monocytes into the sub-endothelial space is promoted by the chemotactic cytokines (chemokines), monocyte chemoattractant protein 1, interleukin 8 (IL-8), and fractalkine. Thereafter, macrophage colony-stimulating factor (M-CSF) promotes the differentiation of monocytes into macrophages. Macrophages incorporate lipids from retained low-density lipoprotein cholesterol (LDL-C) that can undergo oxidative or enzymatic modification (Ox-LDL or E-LDL) and are taken up via the scavenger receptor (SR) pathway [CD36, SR-A, CD68, lectin-like oxidized low-density lipoprotein receptor 1 (LOX-1), SR-B1], becoming foam cells, the hallmark of the early fatty streak lesion.

After the fatty streak lesion, smooth muscle cells under the influence of Ang II and other growth factors such as PDGF migrate into the intima, proliferate, and form the fibrous cap. It is currently believed that lipid-laden macrophages, during the process of cytokine stimulation, CD40 ligation, necrosis, and apoptosis, release matrix metalloproteinases (MMPs), which cause a thinning of the endothelial layer in concert with cathepsins such as S and K. Macrophages also release cytokines, reactive oxygen species, tissue factor, and MMP. Because the lipid-laden macrophage is enriched in tissue factor, this is released from the macrophage and activates factor VII, initiating the coagulation cascade, resulting in thrombus formation and acute coronary syndromes (unstable angina and myocardial infarction).

Exciting data is emerging with respect to macrophage subtypes including the pro-inflammatory M1 phenotype (IL-1, tumor necrosis factor (TNF), MCP-I) and the anti-inflammatory M2 phenotype (IL-10, 1L-1RA, etc.). Macrophages also interact with T cells and other cells via activation of the CD40–CD40 ligand pathway, which contributes to a more atheromatous and less fibrous lesion that is prone to plaque rupture. The T cells in the plaque also appear to display heterogeneity. Subsets such as Th1 are pro-inflammatory while Treg and Th2 appear to attenuate the inflammatory response [4]. T cells produce gamma-interferon that inhibits collagen production by smooth muscle cells. Also, data suggests that mast cells, natural killer cells, dendritic cells also appear to contribute to atherosclerosis [5]. Various gene knockouts and transgenic experiments have underscored the importance of the various cytokines, chemokines, and adhesion molecules in atherogenesis, emphasizing the pivotal role of inflammation in atherosclerosis [1, 2].

Numerous inflammatory biomarkers have been shown in various studies to predict cardiovascular events. These include cell adhesion molecules, cytokines, chemokines, and acute-phase reactants such as fibrinogen, serum amyloid A (SAA), and C-reactive protein (CRP). In this review, we discuss the inflammatory marker CRP, since the largest amount of published data supports a role for CRP as a robust and independent risk marker for cardiovascular disease (CVD) [6, 7]. In addition to being a risk marker, there is much evidence suggesting that CRP may indeed be a culprit in atherogenesis [8].

TLR, Inflammation, Diabetes, and CVD

Toll-like receptors (TLR) are pattern recognition receptors and members of the innate immune system that contribute to inflammation and act as central integrators of a wide variety of signals responding to diverse agonists [9–11]. There are 11 members of the TLR family identified in humans of which TLR2 and TLR4 play key roles in atherosclerosis. Monocytes often function as control switches of the immune system maintaining the balance between pro and anti-inflammatory activities [12]. Monocytes express abundant amounts of TLR2 and TLR4. TLRs mainly signal through the adapter protein MyD88 via activation of NF-κB, resulting in the increased transcription of inflammatory genes (IL-1β, IL-6, IP-10, MCP-1, and tumor necrosis factor alpha (TNF-α)). In addition, a MyD88-independent pathway involving Trif-IRF3 is essential to TLR3 and TLR4 signaling resulting in the production of type 1 interferon [12]. In two recent studies [13, 14], we showed the functional activation of both Myd88 dependent and independent pathways in Monocytes of both T1DM and T2DM patients (Table 1).

TLR2 and TLR4 bind to components of gram positive and gram negative bacteria, respectively [15]. Ligands for TLR2 and TLR4 include the high-mobility group B1 protein (HMGB1); heat shock protein-60 (HSP60); heat shock protein-70; endotoxin; hyaluronan; advanced glycation end products; and extracellular matrix components. HMGB1 is considered as a "late" pro-inflammatory mediator and alarming for damaged cells. Both HMGB1 and HSP60 act as endogenous ligands of TLR2 and induce the production of proinflammatory cytokines [16, 17]. Low-molecular weight degradation products of hyaluronan elicit pro-inflammatory responses in murine alveolar macrophages in rheumatoid arthritis models and other chronic inflammatory conditions [18, 19]. Endotoxin is the most important ligand

Table 1 Significance of TLR2 and TLR4 in type I diabetes mellitus compared to controls

Parameters	TLR2	TLR4
Cell surface expression (Flow Cytometry)	↑	↑
mRNA expression	↑	↑
↑HbA_{1c}	Significant correlation (r=0.52)	Significant correlation (r=0.38)
↑Carboxymethyllysine (CML)	Significant correlation (r=0.29)	Significant correlation (r=0.35)
↑NF-κB	Significant correlation (r=0.48)	Significant correlation (r=0.74)
↑IL-1β	Significant correlation (r=0.55)	Significant correlation (r=0.54)
↑TNF-α	Significant correlation (r=0.50)	Significant correlation (r=0.52)

TLR toll-like receptor, *mRNA* messenger ribonucleic acid, *Hb* hemoglobin, *NF-KB* nuclear factor kappa B, *IL* interleukin, *TNF* tumor necrosis factor

required for TLR4 activation [20], and its levels are significantly increased in diabetics.

Studies in animal models implicate TLR2 and TLR4 in the pathogenesis of diabetes and atherosclerosis. Mohammad et al. [21] showed increased TLR2 expression in NOD mice macrophages and this correlated with increased NF-κB activation resulting in increased pro-inflammatory cytokines. Song et al. [22] reported increased TLR4 mRNA expression in differentiating adipose tissue of *db/db* mice. TLR2 expression is upregulated in atherosclerotic plaque macrophages and in endothelial cells of mice. TLR2KO/$LDL^{-/-}$ and TLR2KO/$ApoE^{-/-}$ mice are protected from the development of atherosclerosis [23, 24]. Furthermore, $MyD88^{-/-}$ mice (myeloid differentiation factor 88: a key downstream TLR adapter protein) showed a reduction in plaque size, lipid content, and decreased expression of IL-1β and TNF-α [25, 26]. In atherosclerosis, TLR2 and TLR4 mRNA and protein were shown to be increased in the endothelium and in areas infiltrated with inflammatory cells. Interestingly, TLR2 and TLR4 expression also co-localizes with nuclear NF-κB [27]. Recent reports have also established a protective role of TLR2 deficiency in mice during I/R injury to maintain coronary endothelial function or left ventricular function [28]. These studies further confirm a role for TLRs in diabetes and atherosclerosis, with atherosclerosis-prone mice deficient in TLR2 or TLR4 showing reduced atherosclerosis development when compared with those animals with functional receptors.

High TLR2 expression level on monocytes was suggested to be an independent risk factor for atherogenesis [29]. Mizoguchi et al. [30] recently showed significant correlation between angiographic vessel score/Gensini score (indicating the extent and severity of coronary atherosclerosis) with $CD14^{+}$ monocytic TLR2 and TLR4 expression in 62 stable angina patients, suggesting the TLR2/4 association with severity of CAD. Monaco et al. [31] recently reported that TLR2 MyD88-mediated inflammation and matrix degradation plays a significant role in human atherosclerosis.

The independent association between increased expression of TLR4 in monocytes and poor outcome after stroke in humans is consistent with previous experimental data indicating that TLR4-deficient mice had smaller infarctions and less inflammatory response after an ischemic insult [32]. Studies have also been done to determine whether mutations in the genes for TLRs and their signaling pathways have an effect on CAD and acute coronary syndrome [33]. Patients with acute myocardial infarction (MI) and unstable angina had significantly higher expression of TLR4/$CD14^{+}$ monocytes than stable angina or control patients [34, 35]. Given the pivotal role of TLR2 and TLR4 in the pathogenesis of CVD, it is important to examine the status of TLR2 and TLR4 in psoriasis.

C-Reactive Protein

CRP is the prototypic marker of inflammation in humans and a member of a highly conserved family of proteins called the pentraxins. CRP comprises five noncovalently associated protomers arranged symmetrically around a central pore and has a molecular weight of 118,000 Da [36, 37]. It is a nonglycosylated protein in humans, and its gene has been mapped to chromosome 1.

To date, in phagocytes, CRP has been shown to bind Fc-gamma receptors (FcgR) I and II, and its function appears to clear apoptotic and necrotic cells (opsonophagocytosis). It has been proposed that distinct forms of CRP are made during inflammation. Conformationally rearranged CRP, which expresses many epitopes not seen in native CRP, is referred to as modified or monomeric CRP (mCRP). mCRP antigens have been reported to be detected in the wall of normal human blood vessels [38]. However, the presence of mCRP in serum and atheroma has not been reported

CRP is predominantly synthesized in the liver (hepatocytes) as an acute-phase reactant and is transcriptionally driven by IL-6, with synergistic enhancement by IL-1. Some recent data challenge the dogma that CRP is exclusively produced by the liver, however, and suggest that it is also produced in the atherosclerotic lesion (especially by smooth muscle cells and macrophages), the kidney, neurons, and alveolar macrophages [39–41]. mRNA and protein for CRP is expressed in arterial plaque tissue, and both CRP mRNA and protein levels are tenfold higher in plaque compared with the normal artery [39]. We have also shown that human aortic endothelial cells (HAECs) synthesize and secrete CRP [42]. The most potent agonist for CRP production from HAECs is the combination of IL-1 and IL-6. Thus, synthesis

and secretion of CRP by cells in the atherosclerotic lesion by paracrine/autocrine loops could result in local concentrations of CRP far in excess of plasma concentrations and could contribute to proinflammatory, proatherogenic effects. Ouchi et al. have demonstrated CRP mRNA in human adipose tissue [43]. Our group has reported recently that adiponectin, an adipocytokine, significantly decreases CRP RNA and protein levels, whereas leptin has been shown to enhance CRP synthesis in endothelial cells incubated with IL-1 and IL-6 [44, 45].

Several prospective studies have shown a consistent and robust association between levels of high-sensitivity CRP (hsCRP) and the risk of future cardiovascular events and have indicated a 1.5–2-fold higher relative risk (95% confidence interval, 1.6–2.5) for major coronary events between the upper and lower tertiles of hsCRP independent of clinical risk assessment or lipid profiles [46]. CRP adds to traditional risk factors for prediction of major coronary events, and is additive to the Framingham Risk Score. From the available data, the Centers for Disease Control and Prevention and the American Heart Association Scientific Statement on Markers of Inflammation and Cardiovascular Disease has recommended that hsCRP may be measured at the physician's discretion in asymptomatic people with an intermediate risk of CAD (class IIa recommendation) to optimize the global assessment of CVD risk. Patients can be categorized using CRP-based risk categories of low (<1 mg/L), average (2–3 mg/L), and high (>3 mg/L) on the basis of the average of two measurements taken optimally at least 2 weeks apart [47].

Several reports indicate a pro-atherogenic and prothrombotic role for CRP [7, 8]. CRP promotes endothelial dysfunction in vivo and in vitro by uncoupling and decreasing eNOS, increasing prostacyclin, increasing PAI-1 and ET-1, IL-8 release, and increasing monocyte-endothelial cell adhesion and transmigration. In monocyte macrophages, CRP increases tissue factor release, increases release of reactive oxygen species, promotes oxidized LDL-C uptake and matrix metalloproteinases and increases AT1 receptors and smooth muscle cell proliferation. CRP appears to exert these effects via binding to FC gamma receptors 1 and 2 [48]; however, these studies need to be confirmed and the relevance of these findings to human CAD needs to be elucidated. In summary, CRP appears to contribute to atherogenesis [7, 8]. CRP is a risk marker for cardiovascular disease and may be used in primary prevention. Recently, the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), a landmark primary prevention trial, was published [49, 50]. The major objective of JUPITER was to investigate whether treatment with rosuvastatin, 20 mg daily, compared to placebo, would decrease the rate of first major cardiovascular events in healthy subjects with normal LDL-C but elevated CRP levels (Table 2). JUPITER was a randomized, double-blind, placebo-controlled, multicenter trial conducted at 1,315 sites in 26 countries. Men, 50 years of age or older and women, 60 years of age or older, were eligible for the trial if they did not have a history of CVD and if, at the initial screening visit, they had an LDL-C level of <130 mg/dL (3.4 mmol/L) and a high-sensitivity CRP level of >2.0 mg/L. Eligible subjects were randomly assigned in a 1:1 ratio to receive either rosuvastatin, 20 mg daily, or matching placebo. The primary outcome was the occurrence of a first major CVD event, defined as nonfatal MI, nonfatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from CVD causes.

Table 2 Hazard ratios for incident of cardiovascular events according to magnitude of reduction in high-sensitivity C-reactive protein (hsCRP) in Rosuvastatin treated group

Parameters	Placebo	Rosuvastatin (hsCRP>2mg/L)	Rosuvastatin (hsCRP<2mg/L)	*p* value
Events/ patients	189/7,832	72/4,305	31/3,411	–
Event rate	1.11	0.77	0.42	–
HR (95% CI)[a]	1	0.68	0.36	<0.0001

HR hazard ratio, *CI* confidence interval

[a] Fully adjusted for age, baseline LDL cholesterol, baseline hsCRP, baseline HDL cholesterol, blood pressure, sex, body mass index, smoking status, and parental history of premature coronary heart disease

Treatment with rosuvastatin significantly reduced the primary composite end point at 44% compared to placebo. There was also a significant 20% reduction in total mortality. For participants who had elevated levels of high-sensitivity CRP but who were nonsmokers, were not overweight (had a body mass index <25 kg/m^2), did not have the metabolic syndrome, had a calculated Framingham risk score of 10% or less, or had an LDL-C level of 100 mg/dL (2.6 mmol/L) or lower, the observed relative reductions in the hazard ratio associated with rosuvastatin for the primary end point were similar to those in higher-risk groups. Most interestingly, among patients with no other major CVD risk factor other than increased age, rosuvastatin therapy resulted in a significant 37% reduction in CVD events. Whereas rosuvastatin reduced LDL-C by 50%, the reduction in CVD events in JUPITER was almost twice that predicted based on LDL-C reduction on the basis of previous statin trials. It is important to point out that CRP levels were significantly reduced by 37% to a median value of 2.2 mg/L.

This study provides further support in human subjects that CRP appears to be an active participant in atherothrombosis and that specifically targeting CRP in the future may prove beneficial. The Adult Treatment Panel III guidelines will need to consider these important results by deciding whether to recommend CRP testing to intermediate-risk patients so that we can better identify candidates at greater

risk. Increased CRP levels integrate a myriad of metabolic abnormalities, including increased adiposity, diabetes, smoking, end-stage renal disease, hypertension, and metabolic syndrome. If high-sensitivity CRP is recommended as a screening test, it is important that the test be performed on two occasions at least a week apart, with the patient being in a steady state. If levels exceed 10 mg/L, then one should search for a nidus of inflammation and then repeat the test once the inflammatory episode has resolved.

Lipoprotein-Associated Phospholipase A_2

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2), also known as platelet-activating factor acetylhydrolase (PAF-AH), was initially identified as the enzyme responsible for hydrolyzing and inactivating the proinflammatory phospholipid PAF [51]. Lp-PLA_2 in plasma is predominantly bound to LDL-C (80%), primarily to highly atherogenic small, dense LDL-C particles, with the remaining amount bound to HDL-C and VLDL-C. It preferentially cleaves oxidized phospholipids by hydrolyzing the sn-2 fatty acid. On oxidized LDL-C, this action results in the generation of lysophosphatidylcholine (lyso-PC) and oxidized free fatty acids, both of which are proatherogenic. Lyso-PC, for example, upregulates CAM expression and enhances chemo-attraction for monocytes. Lp-PLA_2 is expressed in macrophage-rich regions of early to advanced atherosclerotic lesions. Macrophages and T cells appear to be the primary sources of Lp-PLA_2 in these lesions, inasmuch as only low levels of expression are seen in smooth muscle cells [52].

Several studies have shown that Lp-PLA_2 is generally associated with LDL-C and apolipoprotein B but not with hsCRP or other markers. After adjusting for other risk factors, these studies provide some evidence that Lp-PLA_2 may be an independent CAD risk factor. Lp-PLA_2 enzyme activity in blood was determined in 3,148 patients who were hospitalized for coronary angiography [53]. Of these, 2,524 patients had angiographically confirmed CAD and the remaining 694 subjects served as controls. Lp-PLA_2 activity showed the strongest correlations with LDL-C (r=0.517, p<0.001) and apolipoprotein B (r=0.644, p<0.001), and weaker but significant correlations with other lipid parameters, white blood cells, and SAA (all p<0.001). When adjustments were made for age, gender, BMI, smoking, LDL-C, diabetes, hypertension, hsCRP, SAA, fibrinogen, and use of aspirin, beta-blockers, and digitalis, the highest Lp-PLA_2 quartile still had 1.85 times higher CAD risk (95% CI, 1.23–2.78; p=0.003) than did the lowest quartile. Thus, Lp-PLA_2 was independently associated with CAD risk in patients not taking lipid-lowering drugs in this study.

Lp-PLA_2 was measured using an enzyme-linked immunosorbent assay in a case–control analysis of the West of Scotland Coronary Prevention Study [54]. A total of 580 men with a coronary event during follow-up were each matched for age and smoking status with two control subjects who had not had a coronary event. Lp-PLA_2 levels were weakly correlated with LDL-C (r=0.21, p<0.001) and fibrinogen (r=0.086, p<0.01) in this cohort. Lp-PLA_2 levels were significantly associated with increased risk of the composite end point of nonfatal MI, cardiac death, or first revascularization, with each 0.52 mg/L increasing risk by 20% (p<0.001). This risk estimate was unaffected by adjustment for CRP, white cell count, or fibrinogen (p=0.002) or for age, systolic blood pressure, LDL-C, or HDL-C (p=0.005). When grouped according to quintiles of Lp-PLA_2, patients in the highest quintile had a 1.8-fold higher CVD risk than did those in the lowest quintile after adjustment for the other factors.

In the ARIC study, in 608 patients with a CAD event (nonfatal MI, CAD death, or revascularization) and 740 controls [55], Lp-PLA_2 correlated with LDL-C (r=0.36, p<0.0001) and inversely with HDL-C (r=−0.33, p<0.0001) but not with hsCRP, BMI, or blood pressure. After adjusting for age, sex, and race, patients in the highest tertile of Lp-PLA_2 had a 1.8-fold greater risk of CAD (95% CI, 1.33–2.38) than did those in the lowest tertile. When the analysis focused solely on individuals with LDL-C <130 mg/dL, both Lp-PLA_2 and hsCRP independently predicted CAD risk. The highest tertile of Lp-PLA_2 was associated with a 2.08-fold higher risk (95% CI, 1.20–3.62), whereas hsCRP levels >3 mg/L were associated with a 1.76-fold higher risk (95% CI, 1.02–3.03). Notably, the increased risk associated with these markers was seen only in patients who had both high Lp-PLA_2 and high hsCRP. This study suggests that Lp-PLA_2 and hs-CRP may be complementary markers for identifying patients with low LDL-C who are at high CAD risk.

The results of these studies provide a conflicting view of the role of Lp-PLA_2 as a risk factor for CAD. Lp-PLA_2 independently predicts CAD risk, with patients at the highest levels having approximately twice the risk as those at the lowest levels. The predictive power of Lp-PLA_2 appears strongest in patients who are not taking lipid-lowering drugs and in patients with low LDL-C levels. Even when Lp-PLA_2 predicts CAD risk, it appears, however, to be unable to discriminate between stable and unstable disease. It should be noted that different Lp-PLA_2 assays were used in these studies and enzyme levels or activity were measured and thus, its measurement needs to be standardized [56].

In addition to its association with CAD, Lp-PLA_2 activity has been shown to be an independent predictor of ischemic stroke in the general population in a prospective population-based study [57]. Subjects in the highest quartile had an almost doubled risk of a future ischemic stroke compared with those in the lowest quartile. Because total cholesterol is not associated with risk of stroke, the association between Lp-PLA_2 activity and stroke suggests that Lp-PLA_2,

although carried by LDL-C, may convey a different risk [57].

Izaki et al. [58] examined PAF, as well as PAF-AH or Lp-PLA2 activity in plasma of patients with psoriasis. In a normal healthy group (n=12) PAF level was 25.9±6.5 pg/0.1 ml plasma [mean±standard error of the mean (SEM)], and this was elevated in patients with psoriasis (68.1±11.8, n=25, p<0.01), without a change in the PAF-AH level. PAF in psoriasis significantly decreased after treatment (70.9±17.1 to 25.1±5.5, p<0.05) and this was moderately correlated (r=0.298) with clinical improvement as indicated by the psoriasis area and severity index (38.5±7.5 to 10.9±4.2, p<0.01). The results obtained suggest a role of PAF in psoriasis. As the priming effects of PAF have been shown, for leucocytes and endothelial cells, to enhance their inflammatory response, we assume that PAF has roles in the acute phase of psoriatic inflammation. However, larger prospective studies need to be conducted to elucidate the role of Lp-PLA2 in psoriatic inflammation and its contribution to CVD.

Psoriasis, Inflammation, and Heart Disease

Psoriasis is an inflammatory skin disease affecting 2–3% of the general population and mainly characterized by keratinocyte hyperplasia leading to erythematous oval plaques with adherent silvery scales. The precise etiology of psoriasis remains poorly understood, and appears to result from a complex interplay between genetics, environment, skin barrier disruption, and immune dysfunction. A common comorbidity associated with psoriasis is psoriatric arthritis (PsA) [59]. This is an inflammatory arthritic condition that is characterized by pain, swelling, and tenderness of the joints surrounding ligaments and tendons. Between 25% and 34% of patients with psoriasis have PsA [59]. PsA can present with a wide range of symptoms from mild to severe and can have a waxing and waning course that may result in debilitating polyarticular arthritis with joint destruction [60].

Psoriasis has been associated with an increased risk of atherosclerosis, including CAD and stroke, for decades [61–63]. Patients with psoriasis have a 5-year shorter life expectancy, most frequently due to CVD causes [64]. The prevalence of CVD risk factors, including type 2 diabetes mellitus, dyslipidemia, smoking, obesity, and metabolic syndrome is substantially higher in patients with psoriasis than in the general population [65–68]. Furthermore, the prevalence of these risk factors appears to increase from mild to severe psoriasis (Table 3) [65, 66]. In the National Health and Nutrition Examination Survey, 2003–2006, the prevalence of the metabolic syndrome was 40% among patients with psoriasis and 23% among controls (Table 4) [69]. Patients with severe psoriasis have an increased risk of CVD mortality that is independent of traditional CVD risk factors [70]. CVD and their risk factors are also more common in other inflammatory arthritides, including ankylosing spondylitis and rheumatoid arthritis [71].

Studies suggest that psoriasis is associated with a chronic inflammatory state [72, 73]. Patients with PsA have a higher prevalence of subclinical atherosclerosis as determined by carotid artery intima-media thickness, a marker of macrovascular atherosclerotic disease [74, 75]. Patients with PsA also have a significantly increased prevalence and severity of coronary artery calcifications [76]. Activated inflammatory cells and pro-inflammatory cytokines contribute to the development of psoriatic lesions and play an important role in the rupture of atherosclerotic plaques [77]. The extravasation of T cells through the epithelium occurs in both psoriatic and atherosclerotic plaques.

Risk factors for CVD were compared for 102 consecutive PsA patients and 82 controls, adjusting for BMI [78]. They also assessed the role of inflammation on CVD risk by using a BMI and hsCRP-adjusted model. PsA patients had higher CVD risk even after adjustment for BMI; however, further adjustment for hsCRP levels rendered the risk nonsignificant. Thus, it appears that CRP may play a pathophysiological role in inflammation and CVD in this population; however, further studies need to be done in this area. Methotrexate therapy in patients with psoriasis will prove instructive because the drug lowers CRP in these patients who appear to be at increased risk for CVD events.

Izaki et al. [58] examined PAF, as well as PAF acetylhydrolase (PAF-AH) or Lp-PLA2 activity in plasma of patients with psoriasis. In a normal healthy group (n=12), PAF level was 25.9±6.5 pg/0.1 ml plasma [mean±SEM], and this was elevated in patients with psoriasis (68.1±11.8, n=25, p<0.01) without a change in the PAF-AH level. PAF in psoriasis significantly decreased after treatment (70.9±17.1 to 25.1±5.5, p<0.05) and this was moderately correlated (r=0.298) with clinical improvement as indicated by the psoriatic area and

Table 3 Prevalence odds ratios of individual cardiovascular risk factors in mild and severe psoriasis patients

Variable	Mild psoriasis model (95% CI)[a]	Severe psoriasis model (95% CI)[a]
Diabetes	1.13 (1.08–1.18)	1.62 (1.3–2.01)
Lipids	1.16 (1.12–1.21)	1.04 (0.84–1.28)[NS]
Hypertension	1.03 (1.01–1.06)	1.00 (0.87–1.14)[NS]
Smoking	1.31 (1.29–1.34)	1.31 (1.17–1.47)
BMI (25–30)	1.12 (1.1–1.14)	1.27 (1.14–1.42)
BMI (>30)	1.27 (1.24–1.31)	1.79 (1.55–2.05)

BMI body mass index, *CI* confidence interval, *NS* not statistically significant

[a] Adjusted for age, sex, person-years, diabetes, hypertension, hyperlipidemia, smoking, and BMI

Table 4 Prevalence of different metabolic abnormalities in presence of psoriasis in the National Health and Nutrition Examination Survey (NHANES)

Variable	No psoriasis (95% CI)	Psoriasis (95% CI)	ODDs ratio (OD) (95% CI)[a]
Hypertryglyceridemia	27.2 (24.9–29.6)	44 (33.8–54.2)	2.08 (1.39–3.11)
Low HDL cholesterol	23.9 (21.3–26.4)	33.9 (23.7–44.1)	1.63 (0.98–2.71)
High blood pressure	22.2 (20.4–24)	28.4 (14.8–41.9)	1.33 (0.63–2.79)
Abdominal obesity	47.9 (45.3–50.5)	62.9 (51.3–74.5)	1.72 (1.03–2.86)
High fasting glucose (modified)	28.5 (25–32)	30.5 (16.9–44.1)	1.06 (0.56–1.99)

CI confidence interval, *HDL* high-density lipoprotein, *OR* odds ratio

[a] Odds ratios are adjusted for age, sex, and race/ethnicity

severity index (38.5±7.5 to 10.9±4.2, $p<0.01$). The results obtained suggest a role of PAF in psoriasis. As the priming effects of PAF have been shown for leucocytes and endothelial cells to enhance their inflammatory response, we assume that PAF has roles in the acute phase of psoriatic inflammation. However, larger prospective studies need to be conducted to elucidate the role of Lp-PLA2 in psoriatic inflammation and its contribution to ASCVD.

Recognizing the increased prevalence of CVD disease, the National Psoriasis Foundation has recommended screening for CVD risk factors as early as age 20 in patients with psoriasis who do not have known CVD risk factors [79]. The National Psoriasis Foundation has also issued a consensus statement that alerts providers that patients with psoriasis may represent an emerging high-risk CVD population and thus patients with moderate to severe psoriasis should be screened for CVD risk factors [80]. This consensus statement further recommends that appropriate lifestyle and pharmacologic therapies be prescribed for patients with psoriasis who are at increased risk for CVD. If dermatologists or rheumatologists

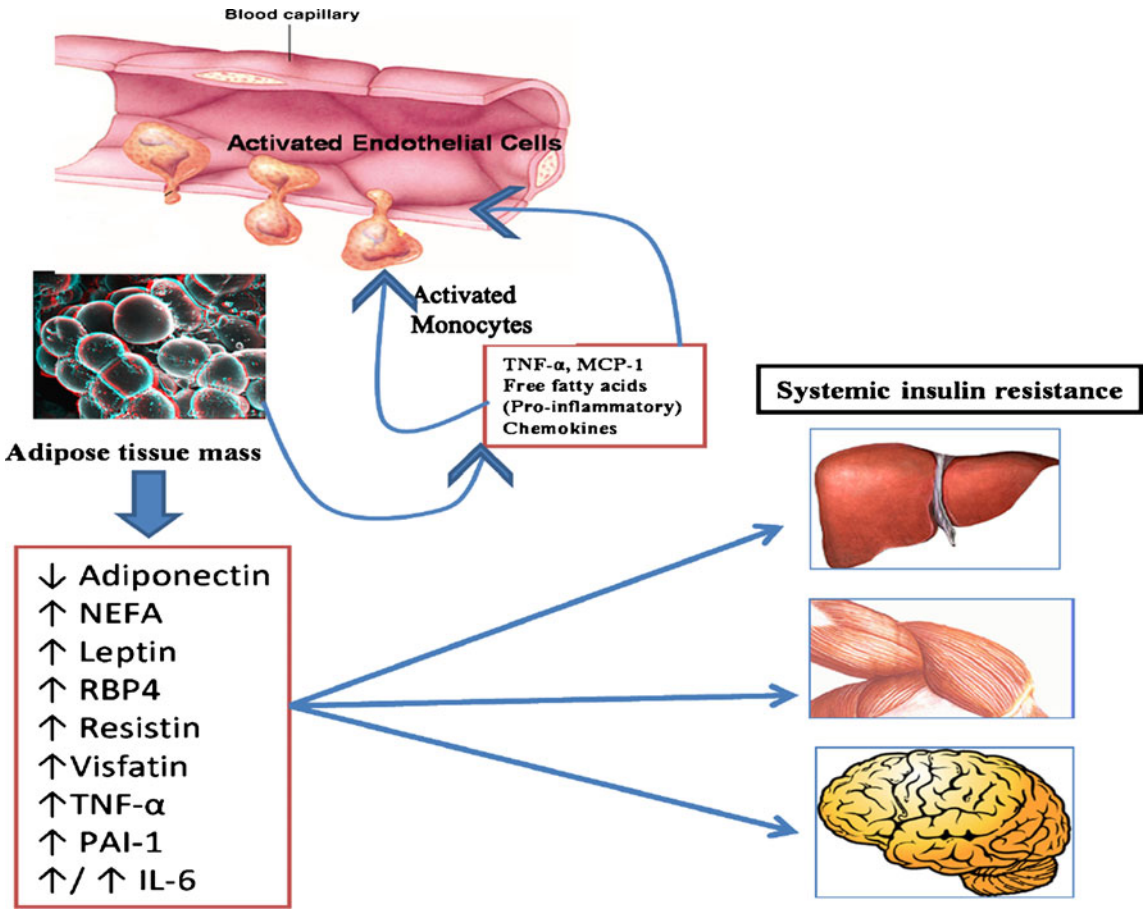

Fig. 1 Adipose tissue associated inflammatory cytokines and its effect on systemic insulin resistance, monocyte activation and inflammation of blood vessels. MCP-1, monocyte chemoattractant protein-1; TNFα-, tumor necrosis factor-; PAI-1, plasminogen activator inhibitor-1; ATM, adipose tissue mass; NEFA, nonesterified fatty acids; RBP4, retinol-binding protein- 4; IL-6, interleukin-6

cannot assume this responsibility, these patients should be referred to other providers who can.

Obesity, Adipocytokines, and Insulin Resistance in Psoriatic Disease

Activated white adipose tissue increases the synthesis of pro-inflammatory cytokines, such as interleukins and TNF-α, IL-18; synthesis of regulatory cytokines, such as IL-10, is decreased [81, 82]. IL-6 stimulates the hepatic production of CRP. A positive correlation has been found between CRP levels and abdominal obesity [83]. Furthermore, pro-inflammatory cytokines stimulate adipocytes to synthesize neuropeptides, such as substance P and nerve growth factor that have been shown to be critical in the pathogenesis of psoriatic disease [84]. Thus, the influence of obesity on psoriatic disease seems to stem from a complex interaction of inflammatory and metabolic factors. Insulin resistance is strongly influenced by several proinflammatory signals. Both insulin resistance and the presence of a proinflammatory status may account for the development of endothelial dysfunction, an early step in the atherogenesis process observed in patients with psoriasis. Metabolic syndrome and obesity are known risk factors for psoriasis [69].

Adipocytokines have been linked to obesity, insulin resistance, inflammation, and CAD (Fig. 1). Adipocytokines are cytokines associated with adipose tissue including TNF-α; the most widely studied are leptin, adiponectin, resistin, and visfatin. In Table 5, the source and functions of individual adipocytokines are listed. Leptin plays a key role, not only in the regulation of appetite and body weight, but also in the modulation of immune responses. Circulating leptin concentrations are increased in obesity; these increased levels are associated with the development of inflammation, insulin resistance, and subclinical coronary atherosclerosis. Leptin also interacts with insulin in several ways that may act to either facilitate or inhibit atherosclerosis. Elevations in resistin and visfatin are also associated with increased inflammation, insulin resistance and cardiovascular risk. In contrast, adiponectin is antiinflammatory and increased concentrations of adiponectin are inversely associated with obesity, insulin resistance and cardiovascular risk. Pro-inflammatory adipokines appear to contribute to the "low-grade inflammatory state" of obese subjects, setting up a cluster of metabolic aberrations including cardiovascular complications and autoimmune inflammatory diseases. Some adipokines such as leptin have neuroendocrine functions. Leptin receptors are expressed on monocytes/macrophages, T cells and natural killer cells. In isolated monocytes/macrophages, leptin induces the production of TNF-α and IL-6. Leptin-deficient mice are less prone than nonleptin-deficient mice to develop inflammatory diseases [85, 86].

Table 5 Sources and functions of key adipokines

Different adipokines	Source (s)	Receptor (s)	Function (s)
Leptin	Adipocytes	Leptin receptor	Control of appetite through central nervous system
Lipocalin 2	Macrophages, adipocytes	Unknown	Influences insulin resistance and inflammation through TNF secretion from adipocytes
RBP4	Liver, adipocytes, macrophages	Retinol, transthyretin	Role in systemic insulin resistance
Adiponectin	Adipocytes	Adiponectin receptor 1 and 2, Tcadherin, calreticulin-CD91	Insulin sensitizer, anti-inflammatory
Resistin	Human: blood mononuclear cells Rodent: adipocytes	Unknown	Influences insulin resistance and inflammation through IL-6 and TNF secretion from macrophages
TNF	Adipocytes, stromal vascular fraction cells	TNF receptors	Inflammation, antagonism of insulin signaling
ANGPTL2	Adipocytes, other cells	Unknown	Local and vascular inflammation
IL-18	Stromal vascular fraction cells	IL-18 receptor, IL-18 binding proteins	Inflammation
IL-6	Adipocytes, stromal vascular fraction cells, Liver, Muscle	IL-6 receptor	Different functions depending upon source and target tissue
CXCL 5	Stromal vascular fraction cells (macrophages)	CXCR2	Antagonism of insulin signaling through JAKSTAT pathway
CCL2	Adipocytes, stromal vascular fraction cells	CCR2	Recruitment of monocytes
NAMPT	Adipocytes, macrophages, other cells	Unknown	Chemotactic to monocytes
SFRP5	Adipocytes	WNT5a	Suppression of proinflammatory signaling through WNT

ANGPTL2 angiopoietin like protein 2, *CCL2* CC-chemokine ligand 2, *CXCL5* CXC-chemokine ligand 5, *NAMPT* nicotinamide phosphoribosyltransferase, *RBP4* retinol-binding protein 4, *SFRP5* secreted frizzled-related protein 5, *STAT* signal transducer and activator of transcription, *JAK* Janus kinase, *TNF* tumor necrosis factor, *IL* interleukin

In light of these novel actions of adipocytokines on inflammation and the metabolic Syndrome, extensive research work is currently going on to elucidate the role of adipocytokines in inflammatory diseases. Several studies have reported that expressions of genes which regulate both skin and lipid metabolism are altered in psoriatic skin and have provided evidence for altered fatty acid metabolism [87] and accumulation of ox-LDL in the skin of patients with psoriasis [88]. Further, early reports suggest that leptin and resistin may be involved in the pathogenesis of psoriasis in overweight individuals, possibly by augmenting the cytokine expression by the inflammatory infiltrate [89, 90]. Leptin is known to play a major role in CVD and recent observations suggest that leptin is an independent risk factor for CAD [91]. Other adipocytokines, including resistin, gherelin, adiponectin, and cachectin, may also contribute to the pathogenesis of atherosclerotic CVD [91, 92]. In diabetics and the associated metabolic syndrome, these adipocytokines have been related to risk factors for atherosclerosis, correlate well with inflammatory markers, and are predictive of the development of CVD [91, 92]. Thus, adipocytokines in psoriatic disease may be one of the common pathways for the pathogenesis of psoriatic disease and atherosclerosis.

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References

1. Ross R (1999) Atherosclerosis an inflammatory disease. N Engl J Med 340:115–26
2. Hansson GK, Libby P (2006) The immune response in atherosclerosis: a double-edged sword. Nat Rev Immunol 6:508–19
3. Jialal I, Devaraj S (2001) Inflammation and atherosclerosis: the value of the high-sensitivity C-reactive protein assay as a risk marker. Am J Clin Pathol 116:S108–15
4. Libby P, Okamoto Y, Rocha VZ, Folco E (2010) Inflammation in atherosclerosis: transition from theory to practice. Circ J 74:213–20
5. Packard RR, Lichtman AH, Libby P (2009) Innate and adaptive immunity in atherosclerosis. Semin Immuno Pathol 31:5–22
6. Verma S, Szmitko PE, Ridker PM (2005) C-reactive protein comes of age. Nat Clin Pract Cardiovasc Med 2:29–36
7. Verma S, Devaraj S, Jialal I (2006) Is C-reactive protein an innocent bystander or proatherogenic culprit? C-reactive protein promotes atherothrombosis. Circulation 113:2135–50
8. Devaraj S, Singh U, Jialal I (2009) The evolving role of C-reactive protein in atherothrombosis. Clin Chem 55:229–38
9. Takeda K, Kaisho T, Akira S (2003) Toll-like receptors. Annu Rev Immunol 21:335–76
10. Uematsu S, Akira S (2006) Toll-like receptors and innate immunity. J Mol Med 84:712–25
11. Kawai T, Akira S (2006) TLR signaling. Cell Death Difference 13:816–25
12. Hill HR, Hogan NA, Rallison ML, Santos JI, Charette RP, Kitahar M (1982) Functional and metabolic abnormalities of diabetic monocytes. Adv Expt Med Biol 69:621–8
13. Devaraj S, Dasu MR, Rockwood J, Winter W, Griffen SC, Jialal I (2008) Increased toll-like receptor (TLR) 2 and TLR4 expression in monocytes from patients with type 1 diabetes: further evidence of a proinflammatory state. J Clin Endocrinol Metab 93:578–3
14. Dasu MR, Devaraj S, Park S, Jialal I (2010) Increased toll-like receptor activation and TLR ligands in recently diagnosed type 2 diabetes subjects. Diabetes Care 33:861–8
15. Tsan MF, Gao B (2004) Endogenous ligands of toll-like receptors. J Leukocyte Biol 76:514–9
16. Wagner H (2006) Endogenous TLR ligands and autoimmunity. Adv Immunol 91:159–73
17. Ohashi K, Burkart V, Flohe S, Kolb H (2000) Cutting edge: heat shock protein 60 is a putative endogenous ligand of the toll-like receptor-4 complex. J Immunol 164:558–61
18. Laurent TC, Fraser JR (1992) Hyaluronan. FASEB J 6:2397–404
19. Noble PW, McKee CM, Cowman M, Shin HS (1996) Hyaluronan fragment activate an NF-κB/I-κBα autoregulatory loop in murine macrophages. J Exp Med 183:2373–8
20. Akashi S, Shimazu R, Ogata H, Nagai Y, Takeda K, Kimoto M, Miyake K (2000) Cutting edge: cell surface expression and lipopolysaccharide signaling via the toll-like receptor 4-MD-2 complex on mouse peritoneal macrophages. J Immunol 164:3471–5
21. Mohammad MK, Morran M, Slotterbeck B, Leaman DW, Sun Y, Grafenstein H, Hong SC, McInerney MF (2006) Dysregulated toll-like receptor expression and signaling in bone marrow-derived macrophages at the onset of diabetes in the non-obese diabetic mouse. Int Immunol 18:1101–13
22. Song MJ, Kim KH, Yoon JM, Kim JB (2006) Activation of toll-like receptor 4 is associated with insulin resistance in adipocytes. Biochem Biophys Res Commun 346:739–45
23. Liu X, Ukai T, Yumoto H, Davey M, Goswami S, Gibson FC 3rd, Genco CA (2007) Toll-like receptor 2 plays a critical role in the progression of atherosclerosis that is independent of dietary lipids. Atherosclerosis 196:146–54
24. Michelsen KS, Wong MH, Shah PK, Zhang W, Yano J, Doherty TM, Akira S, Rajavashisth TB, Arditi M (2004) Lack of toll-like receptor 4 or myeloid differentiation factor 88 reduces atherosclerosis and alters plaque phenotype in mice deficient in apolipoprotein E. Proc Natl Acad Sci USA 101:10679–84
25. Bjorkbacka H, Kunjathoor VV, Moore KJ, Koehn S, Ordija CM, Lee MA, Means T, Halmen K, Luster AD, Golenbock DT, Freeman MW (2004) Reduced atherosclerosis in MyD88-null mice links elevated serum cholesterol levels to activation of innate immunity signaling pathways. Nat Med 10:416–21
26. Edfeldt K, Swedenborg J, Hansson GK, Yan ZQ (2002) Expression of toll-like receptors in human atherosclerotic lesions: a possible pathway for plaque activation. Circulation 105:1158–61
27. Leemans JC, Stokman G, Claessen N, Rouschop KM, Teske GJ, Kirschning CJ, Akira S, van der Poll T, Weening JJ, Florquin S (2005) Renal associated TLR2 mediates ischemia/reperfusion injury in the kidney. J Clin Invest 115:2894–903
28. Favre J, Musette P, Douin-Echinard V, Laude K, Henry JP, Arnal JF, Thuillez C, Richard V (2007) Toll-like receptors 2-deficient mice are protected against postischemic coronary endothelial dysfunction. Arterioscler Thromb Vasc Biol 27:1064–71
29. Kuwahata S, Fujita S, Orihara K, Hamasaki S, Oba R, Hirai H, Nagata K, Ishida S, Kataoka T, Oketani N, Ichiki H, Iriki Y, Saihara K, Okui H, Ninomiya Y, Tei C (2010) High expression level of Toll-like receptor 2 on monocytes is an important risk factor for arteriosclerotic disease. Atherosclerosis 209:248–54
30. Mizoguchi E, Orihara K, Hamasaki S, Ishida S, Kataoka T, Ogawa M, Saihara K, Okui H, Fukudome T, Shinsato T, Shirasawa T, Ichiki H, Kubozono T, Ninomiya Y, Otsuji Y, Tei C (2007)

Association between toll-like receptors and the extent and severity of coronary artery disease in patients with stable angina. Coron Artery Dis 18:31–8
31. Monaco C, Gregan SM, Navin TJ, Foxwell BM, Davies AH, Feldmann M (2009) Toll-like receptor-2 mediates inflammation and matrix degradation in human atherosclerosis. Circulation 120:2462–9
32. Caso JR, Pradillo JM, Hurtado O, Lorenzo P, Moro MA, Lizasoain I (2007) Toll-like receptor 4 is involved in brain damage and inflammation after experimental stroke. Circulation 115:1599–608
33. Ameziane N, Beillat T, Verpillat P, Chollet-Martin S, Aumont MC, Seknadji P, Lamotte M, Lebret D, Ollivier V, de Prost D (2003) Association of the toll-like receptor 4 gene Asp299Gly polymorphism with acute coronary events. Arterioscler Thromb Vasc Biol 23:e61–4
34. Fukushima R, Soejima H, Fukunaga T, Nakayama M, Oe Y, Oshima S, Sugiyama S, Ogawa H (2009) Expression levels of toll-like receptor genes in coronary atherosclerotic lesions of patients with acute coronary syndrome or stable angina pectoris. Circ J 73:1479–84
35. Bajaj M, Suraamornkul S, Piper P, Hardies LJ, Glass L, Cersosimo E, Pratipanawatr T, Miyazaki Y, DeFronzo RA (2004) Decreased plasma adiponectin concentrations are closely related to hepatic fat content and hepatic insulin resistance in pioglitazone-treated type 2 diabetic patients. J Clin Endocrinol Metab 89:200–6
36. Thompson D, Pepys MB, Wood SP (1999) The physiological structure of human C-reactive protein and its complex with phosphocholine. Structure 7:169–77
37. Khreiss T, József L, Potempa LA, Filep JG (2005) Loss of pentameric symmetry in C-reactive protein induces interleukin-8 secretion through peroxynitrite signaling in human neutrophils. Circ Res 97:690–7
38. Calabro P, Willerson JT, Yeh ET (2003) Inflammatory cytokines stimulated C-reactive protein production by human coronary artery smooth muscle cells. Circulation 108:1930–2
39. Yasojima K, Schwab C, McGeer EG, McGeer PL (2001) Generation of C-reactive protein and complement components in atherosclerotic plaques. Am J Pathol 158:1039–51
40. Kobayashi S, Inoue N, Ohashi Y, Terashima M, Matsui K, Mori T, Fujita H, Awano K, Kobayashi K, Azumi H, Ejiri J, Hirata K, Kawashima S, Hayashi Y, Yokozaki H, Itoh H, Yokoyama M (2003) Interaction of oxidative stress and inflammatory response in coronary plaque instability: important role of C-reactive protein. Arterioscler Thromb Vasc Biol 23:1398–404
41. Dong Q, Wright JR (1996) Expression of C-reactive protein by alveolar macrophages. J Immunol 156:4815–20
42. Venugopal SK, Devaraj S, Jialal I (2005) Macrophage conditioned medium induces the expression of C-reactive protein in human aortic endothelial cells: potential for paracrine/autocrine effects. Am J Pathol 166:1265–71
43. Ouchi N, Kihara S, Funahashi T, Nakamura T, Nishida M, Kumada M, Okamoto Y, Ohashi K, Nagaretani H, Kishida K, Nishizawa H, Maeda N, Kobayashi H, Hiraoka H, Matsuzawa Y (2003) Reciprocal association of C-reactive protein with adiponectin in blood stream and adipose tissue. Circulation 107:671–4
44. Devaraj S, Torok N, Dasu MR, Samols D, Jialal I (2008) Adiponectin decreases C-reactive protein synthesis and secretion from endothelial cells: evidence for an adipose tissue vascular loop. Arterioscler Thromb Vasc Biol 28:1368–74
45. Singh P, Hoffmann M, Wolk R, Shamsuzzaman AS, Somers VK (2007) Leptin induces C reactive protein expression in vascular endothelial cells. Arterioscler Thromb Vasc Biol 27:e302–7
46. Bassuk SS, Rifai N, Ridker PM (2004) High-sensitivity C-reactive protein: clinical importance. Curr Probl Cardiol 29(8):439–93
47. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, Fadl Y, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC, Taubert K, Tracy RP, Vinicor F (2003) Markers of inflammation and cardiovascular disease. Application to clinical and public health practice. Circulation 107:499–511
48. Devaraj S, Du Clos TW, Jialal I (2005) Binding and internalization of C-reactive protein by Fcgamma receptors on human aortic endothelial cells mediates biological effects. Arterioscler Thromb Vasc Biol 25:1359–63
49. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, Macfadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ (2009) Reduction in CRP and LDL-C and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet 373:1175–82
50. Jialal I, Devaraj S (2009) Jupiter to Earth: CRP promotes atherothrombosis. Metab Syndr Relat Disord 7:1–3
51. Dada N, Kim NW, Wolfert RL (2002) Lp-PLA2: an emerging biomarker of coronary heart disease. Expert Rev Mol Diagn 2:17–22
52. Hakkinen T, Luoma JS, Hiltunen MO, Macphee CH, Milliner KJ, Patel L, Rica SQ, Tew DG, Karkola K, Yia-Herttuala S (1999) Lipoprotein-associated phospholipase A(2), platelet-activating factor acetylhydrolase, is expressed by macrophages in human and rabbit atherosclerotic lesions. Arterioscler Thromb Vasc Biol 19:2909–17
53. Winkler K, Winkelmann BR, Scharnagl H, Hoffmann MM, Grawitz AB, Nauck M, Bohm BO, Marz W (2005) Platelet-activating factor acetylhydrolase activity indicates angiographic coronary artery disease independently of systemic inflammation and other risk factors: the Ludwigshafen Risk and Cardiovascular Health Study. Circulation 111:980–7
54. Packard CJ, O'Reilly DS, Caslake MJ, McMahon AD, Ford I, Cooney J, Macphee CH, Suckling KE, Krishna M, Wilkinson FE, Rumley A, Lowe GD (2000) Lipoprotein-associated phospholipase A2 as an independent predictor of coronary heart disease. West of Scotland Coronary Prevention Study Group. N Engl J Med 343:1148–55
55. Ballantyne CM, Hoogeveen RC, Bang H, Coresh J, Folsom AR, Heiss G, Sharrett AR (2004) Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident coronary heart disease in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. Circulation 109:837–42
56. Zalewski A, Nelson JJ, Hegg L, Macphee C (2006) Lp-PLA2: a new kid on the block. Clin Chem 52:1645–50
57. Oei HH, Van Der Meer IM, Hofman A, Koudstaal PJ, Stijnen T, Breteler MM, Witteman JC (2005) Lipoprotein-associated phospholipase A2 activity is associated with risk of coronary heart disease and ischemic stroke: the Rotterdam Study. Circulation 111:570–5
58. Izaki S, Yamamoto T, Goto Y, Ishimaru S, Yudate F, Kitamura K, Matsuzaki M (1996) Platelet-activating factor and arachidonic acid metabolites in psoriatic inflammation. Br J Dermatol 134:1060–4
59. Gladman DD (2004) Psoriatic arthritis. Dermatol Ther 17:350–63
60. Gladman DD, Shuckett R, Russell ML, Thorne JC, Schachter RK (1987) Psoriatic arthritis (PSA)—an analysis of 220 patients. Q J Med 62:127–41
61. Prodanovich S, Kirsner RS, Kravetz JD, Ma F, Martinez L, Federman DG (2009) Association of psoriasis with coronary artery, cerebrovascular, and peripheral vascular diseases and mortality. Arch Dermatol 145:700–3
62. Kimball AB, Guerin A, Latremouille-Viau D, Yu AP, Gupta S, Bao Y, Mulani P (2010) Coronary heart disease and stroke risk in patients with psoriasis: retrospective analysis. Am J Med 123:350–7
63. Tobin AM, Veale DJ, Fitzgerald O, Rogers S, Collins P, O'Shea D, Kirby B (2010) Cardiovascular disease and risk factors in patients with psoriasis and psoriatic arthritis. J Rheumatol 37:1386–94

64. Abuabara K, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM (2010) Cause-specific mortality in patients with severe psoriasis: a population-based cohort study in the U.K. Br J Dermatol 163:586–92
65. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB (2006) Risk of myocardial infarction in patients with psoriasis. JAMA 296:1735–41
66. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM (2006) Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol 55:829–35
67. Gottlieb AB, Dann F (2009) Comorbidities in patients with psoriasis. Am J Med 122:1150
68. Raychaudhuri SK, Chatterjee S, Nguyen C, Kaur M, Jialal I, Raychaudhuri SP (2010) Increased prevalence of the metabolic syndrome in patients with psoriatic arthritis. Metab Syndr Relat Disord 8:331–4
69. Love TJ, Qureshi AA, Karlson EW, Gelfand JM, Choi HK (2011) Prevalence of the metabolic syndrome in psoriasis: results from the National Health and Nutrition Examination Survey, 2003–2006. Arch Dermatol 147:419–24
70. Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM (2010) Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. Eur Heart J 31:1000–6
71. Han C, Robinson DW Jr, Hackett MV, Paramore LC, Fraeman KH, Bala MV (2006) Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. J Rheumatol 33:2167–72
72. Nestle FO, Kaplan DH, Barker J (2009) Psoriasis. N Engl J Med 361:496–509
73. Gladman DD, Ang M, Su L, Tom BD, Schentag CT, Farewell VT (2009) Cardiovascular morbidity in psoriatic arthritis. Ann Rheum Dis 68:1131–5
74. Balci DD, Balci A, Karazincir S, Ucar E, Iyigun U, Yalcin F, Seyfeli E, Inandi T, Egilmez E (2009) Increased carotid artery intima-media thickness and impaired endothelial function in psoriasis. J Eur Acad Dermatol Venereol 23:1–6
75. Tam LS, Shang Q, Li EK, Tomlinson B, Chu TT, Li M, Leung YY, Kwok LW, Wong KC, Li TK, Yu T, Zhu TY, Kun EW, Yip GW, Yu CM (2008) Subclinical carotid atherosclerosis in patients with psoriatic arthritis. Arthritis Rheum 59:1322–31
76. Ludwig RJ, Herzog C, Rostock A, Ochsendorf FR, Zollner TM, Thaci D, Kaufmann R, Vogl TJ, Boehncke WH (2007) Psoriasis: a possible risk factor for development of coronary artery calcification. Br J Dermatol 156:271–6
77. Späh F (2008) Inflammation in atherosclerosis and psoriasis: common pathogenic mechanisms and the potential for an integrated treatment approach. Br J Dermatol 159:10–7
78. Tam LS, Tomlinson B, Chu TT, Li M, Leung YY, Kwok LW, Li TK, Yu T, Zhu YE, Wong KC, Kun EW, Li EK (2008) Cardiovascular risk profile of patients with psoriatic arthritis compared to controls—the role of inflammation. Rheumatology (Oxford) 47:718–23
79. Kimball AB, Gladman D, Gelfand JM, Gordon K, Horn EJ, Korman NJ, Korver G, Krueger GG, Strober BE, Lebwohl MG (2008) National Psoriasis Foundation clinical consensus on psoriasis comorbidities and recommendations for screening. J Am Acad Dermatol 58:1031–42
80. Friedewald VE, Cather JC, Gelfand JM, Gordon KB, Gibbons GH, Grundy SM, Jarratt MT, Krueger JG, Ridker PM, Stone N, Roberts WC (2008) AJC editor's consensus: psoriasis and coronary artery disease. Am J Cardiol 102:1631–43
81. Ouchi N, Parker JL, Lugus JJ, Walsh K (2011) Adipokines in inflammation and metabolic disease. Nat Rev Immunol 11:85–97
82. Olefsky JM, Glass CK (2010) Macrophages, inflammation, and insulin resistance. Annu Rev Physiol 72:219–46
83. Florez H, Castillo-Florez S, Mendez A, Casanova-Romero P, Larreal-Urdaneta C, Lee D, Goldberg R (2006) C-reactive protein is elevated in obese patients with the metabolic syndrome. Diabetes Res Clin Pract 71:92–100
84. Raychaudhuri SP, Jiang WY, Raychaudhuri SK (2008) Revisiting the Koebner phenomenon: role of NGF and its receptor system in the pathogenesis of psoriasis. Am J Pathol 172:961–71
85. Matarese G, Di Giacomo A, Sanna V, Lord GM, Howard JK, Di Tuoro A, Bloom SR, Lechler RI, Zappacosta S, Fontana S (2001) Requirement for leptin in the induction and progression of autoimmune encephalomyelitis. J Immunol 166:5909–16
86. Otero M, Lago R, Lago F, Casanueva FF, Dieguez C, Gómez-Reino JJ, Gualillo O (2005) Leptin, from fat to inflammation: old questions and new insights. FEBS Lett 579:295–301
87. Romanowska M, al Yacoub N, Seidel H, Donandt S, Gerken H, Phillip S, Haritonova N, Artuc M, Schweiger S, Sterry W, Foerster J (2008) PPAR delta enhances keratinocyte proliferation in psoriasis and induces heparin-binding EGF-like growth factor. J Invest Dermatol 128:110–24
88. Tekin NS, Tekin IO, Barut F, Sipahi EY (2007) Accumulation of oxidized low-density lipoprotein in psoriatic skin and changes of plasma lipid levels in psoriatic patients. Mediators Inflamm 2007:78454
89. Cerman AA, Bozkurt S, Sav A, Tulunay A, Elbaşi MO, Ergun T (2008) Serum leptin levels, skin leptin and leptin receptor expression in psoriasis. Br J Dermatol 159:820–6
90. Johnston A, Arnadottir S, Gudjonsson JE, Aphale A, Sigmarsdottir AA, Gunnarsson SI, Steinsson JT, Elder JT, Valdimarsson H (2008) Obesity in psoriasis: leptin and resistin as mediators of cutaneous inflammation. Br J Dermatol 159:342–50
91. Matarese G, Mantzoros C, La Cava A (2007) Leptin and adipocytokines: bridging the gap between immunity and atherosclerosis. Curr Pharm Des 13:3676–80
92. Rizzo M, Rizvi AA, Rini GB, Berneis K (2009) The therapeutic modulation of atherogenic dyslipidemis and inflammatory markers in the metabolic syndrome: what is the clinical relevance? Acta Diabetol 46:1–11