commentary

Psoriasis: it's more than just the skin[1]

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Psoriasis is a skin disease that is accompanied by systemic inflammation and is one of the most common inflammatory disorders, estimated to effect between 1 and 3% of the population (1). It is characterized by epidermal hyperproliferation and dermal inflammation. The etiology of psoriasis is unknown but genetic factors play a role. Psoriasis may begin at any age but has two peak periods of onset: between 15 and 25 and between 50 to 60 years of age. In many patients, psoriasis affects only a small area of the skin (<2% of body surface area) whereas in other patients, the disease can be quite severe, affecting a large portion of the skin. The cutaneous manifestations lead to considerable morbidity and the emotional burden of severe psoriasis has been shown to be similar to that seen in patients with cancer, diabetes, and heart disease.

However, it is important to recognize that psoriasis is associated with systemic metabolic disorders including an increased prevalence of the metabolic syndrome, obesity, diabetes, dyslipidemia, and cardiovascular disease (CVD) (2–4). The increased risk of CVD in patients with psoriasis was first reported by McDonald and Calabresi in 1978 (5). They observed that patients with psoriasis had a 2.2-fold increase in CVD compared with controls. Since then, a large number of additional epidemiological studies have also shown that the risk of CVD is increased in patients with psoriasis [see Tobin et al. (4) for an excellent review of the literature] (2–5). Of note psoriasis still conferred an increased risk even when the studies controlled for the usual CVD risk factors such as age, sex, diabetes, hypertension, hyperlipidemia, smoking, and obesity, implying that psoriasis causes abnormalities that increase the risk of CVD that are not dependent on the usual risk factors (2–4). Moreover, studies have suggested that the more severe the psoriasis the greater the risk of CVD. Further, supporting the link of psoriasis with atherosclerosis are studies showing that patients with psoriasis have an increase in coronary artery calcium measured by CT and carotid intima media thickness measured by ultrasound (6–8).

A very large number of studies have compared serum lipid levels in patients with psoriasis to control subjects (2–4). Most of these reports included only a small number of subjects and the results have been extremely variable with some studies showing alterations in serum lipid levels in patients with psoriasis and other studies showing no changes. In general, there is a tendency for an increase in serum triglycerides and a decrease in HDL in patients with psoriasis. Additionally, a number of studies showed an increase in LDL and Lp(a) levels in patients with psoriasis (2–4). Some of the variability between studies maybe due to differences in the population of patients studied. Specifically, differences in the severity of the psoriasis and the prevalence of other abnormalities that affect lipid metabolism such as obesity and abnormalities in glucose metabolism could explain some of the variability between studies. Moreover, a number of drugs that in the past were frequently used to treat psoriasis, such as cyclosporine and retinoids, are well known to adversely affect serum lipid levels and could contribute to the differences between studies.

Psoriasis can be considered an ideal disease to study the effects of chronic inflammation on CVD, as the disease is localized to the skin, but there is systemic inflammation. It is now well recognized that an increased risk of atherosclerosis occurs in many chronic inflammatory disorders including HIV infection, chronic dental infections, Helicobacter pylori infection, chronic bronchitis, rheumatoid arthritis, and systemic lupus erythematous (9). Similar to psoriasis, the increased risk of CVD in these inflammatory disorders cannot be fully accounted for by the traditional risk factors. Also similar to psoriasis, these inflammatory disorders tend to lead to increases in serum triglyceride levels and decreases in HDL levels (10). Thus, the alterations in lipid and lipoprotein metabolism observed in patients with psoriasis may be a model relevant to a wide variety of disease states that lead to inflammation. Moreover, it is well recognized that obesity and many of the disorders associated with obesity such as the metabolic syndrome and type 2 diabetes are characterized by a low grade inflammatory state that may contribute to an increased risk of atherosclerosis (11).

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In this issue of the *Journal of Lipid Research*, Holzer and colleagues examine the structure and function of HDL in patients with psoriasis (12). First, using a proteomic approach they demonstrate that the protein composition of HDL is markedly altered in patients with psoriasis. Apo A1 and Apo M levels were decreased whereas the levels of several acute phase proteins such as SAA, prothrombin, α-2-HS-glycoprotein, and α-1-acid glycoprotein 1 were increased. Additionally, the lipid composition of HDL from patients with psoriasis was also altered with a decrease in total cholesterol, cholesterol ester, free cholesterol, phosphatidylcholine, and sphingomyelin. Second and most importantly, these investigators observed that the HDL from patients with psoriasis was less efficient at promoting cholesterol efflux from macrophages and that this defect in HDL function correlated with the severity of the psoriasis. Surprisingly, the antioxidant properties of HDL were similar in control and psoriatic HDL and PON activity was not altered. However, Lp-PLA2 activity was increased and correlated with disease activity.

The results presented in this manuscript first demonstrate that the HDL isolated from patients with psoriasis is altered (12). It has been well recognized that severe inflammation leads to alterations in the protein and lipid composition of HDL (10). What is notable in this paper is that the authors demonstrate changes in HDL composition in patients with relatively modest inflammation. The patients with psoriasis had a median CRP of only 2.7 mg/dl with an interquartile range of 1.2 to 5.6 mg/dl. These results suggest that relatively modest inflammation is associated with significant changes in HDL structure.

The second key observation relates to the function of HDL. The potential importance of reverse cholesterol transport in preventing atherosclerosis is widely recognized (13). Moreover, severe inflammation has been shown in animal models to decrease reverse cholesterol transport (14). There are a large number of steps involved in the reverse cholesterol transport pathway and in a recent commentary, we pointed out that all of the steps in the reverse cholesterol transport pathway were downregulated by acute severe inflammation (14). The first step in the reverse cholesterol transport pathway is the efflux of cholesterol from the macrophage to HDL. A decade ago, our laboratory demonstrated that HDL obtained from hamsters treated with LPS to induce a severe inflammatory state was defective in the removal of cholesterol from macrophages (15). Other investigators have shown that the administration of LPS to humans results in similar abnormalities (16). The paper by Holzer et al. demonstrates that a relatively mild chronic inflammatory state can similarly result in dysfunctional HDL leading to decreased cholesterol efflux from macrophages (12). A very recent paper examining the function of HDL from patients with rheumatoid arthritis reported that HDL from patients with severe rheumatoid arthritis (CRP 5.7 ± 8.7 mg/dl) also had a decreased ability to promote cholesterol efflux from macrophages, whereas HDL from patients with mild rheumatoid arthritis had a normal capacity to support efflux (17). There was an inverse correlation between markers of inflammation (sedimentation rate and CRP) and the ability of HDL to promote cholesterol efflux (17). Thus, inflammation, if of a sufficient magnitude, can lead to alterations in HDL resulting in a decreased ability to promote cholesterol efflux from macrophages.

Whereas reverse cholesterol transport is a very important anti-atherogenic function of HDL, other actions of HDL may also play an important role in preventing atherosclerosis. Specifically, the ability of HDL to protect LDL from oxidation maybe an important protective function (18). In the present study, HDL from patients with psoriasis did not demonstrate defective antioxidant properties (12). In contrast, studies in patients with other inflammatory disorders, rheumatoid arthritis, systemic lupus erythematous, and HIV infection have shown decreased antioxidant properties of HDL (19–21). The explanation for this difference could be that the assay employed to measure the antioxidant abilities of HDL is less sensitive or that the degree of inflammation in the patients studied was not of sufficient magnitude. It is also possible that the inflammatory stimuli produced by these different inflammatory disorders leads to subtle differences in cytokine and bioactive compound profiles resulting in the expression of different proteins and lipids leading to differences in HDL function.

In conclusion, numerous studies have demonstrated that inflammatory disorders increase the risk of CVD and that this increase cannot be totally accounted for by traditional risk factors. The present paper provides additional data demonstrating that psoriasis, a very common inflammatory disorder, alters the structure of HDL, resulting in functional changes that could contribute to an increased risk of atherosclerosis.

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