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Commentary

Psoriasis & cardiovascular morbidity: The missing links?

Psoriasis is a chronic papulosquamous disorder with considerable morbidity. The prevalence of psoriasis varies between 0.09 and 11.43 per cent of the population[1]. It used to be considered a disorder of cutaneous hyperproliferation. However, over the course of the last two to three decades, psoriasis has also been found to be associated with a number of systemic abnormalities. Simultaneously, new hypotheses have been proposed which focus on the continued systemic inflammation and T-cell-mediated mechanisms to explain the cutaneous and joint manifestations. It primarily involves Th1- and Th17-mediated pathways, involving the release of proinflammatory cytokines such as interleukin-6 (IL-6), interferon-γ (IFN-γ) and tumour necrosis factor-alpha (TNF-α). TNF-α is one of the most important mediators in the pathogenesis of psoriasis, and many of the biologics used in the treatment of psoriasis are TNF-α antagonists[2].

Psoriasis has been conclusively proven to be associated with cardiovascular diseases such as myocardial infarction, heart failure and also metabolic syndrome[3]. In addition, hypertension, dyslipidaemia, insulin resistance and obesity have also been shown to be associated with psoriasis independently, apart from as components of metabolic syndrome[4].

Increased reactive oxygen species (ROS) production in neutrophils, keratinocytes and fibroblasts has been described in psoriasis[5]. In fact, ROS production can induce cell proliferation in different systems, possibly resulting in epidermal hyperproliferation in psoriasis[5]. In normal aerobic cells, antioxidant production balances out oxidative stress. Reduced glutathione (GSH) is a potent antioxidant, known to be depleted by free radical and other oxidative agents. Increased production of ROS as well as deficient antioxidant protection leads to oxidative stress. TNF-α can also act as an inducer of ROS production through impaired mitochondrial biogenesis and activation of NADPH oxidase. In psoriasis patients, increased ROS production may be due to deficient antioxidant mechanisms and in turn can lead to increased oxidation of polyunsaturated fatty acids[6]. The increased ROS production consequent to the inflammatory processes also causes increased formation of lipid oxidation and peroxidation products. Malondialdehyde (MDA) is one of the lipid peroxidation products.

Earliest event in the process of atherogenesis is abnormal oxidation of low-density lipoprotein (LDL) particles. Of the LDL sub-fractions, it is the small-dense LDL (sdLDL) which is more atherogenic. The sdLDL not only easily accumulates in the arterial walls to initiate atherosclerosis, but it also has a greater potential to get oxidised and get accumulated in macrophages. These lipid-laden macrophages known as foam cells play a pivotal role in the development of atherosclerotic plaque. Oxidised LDL (OxLDL), the product of oxidation of LDL, therefore, indicates the intensity of atherogenesis of the vessel wall. It also attracts macrophages and T-lymphocytes, damages the endothelial cells and stimulates the release of pro-inflammatory molecules[7].

C-reactive protein (CRP) belongs to the pentraxin superfamily of calcium-dependent ligand binding plasma proteins. It is synthesized in the liver in response to IL-6 which is in turn upregulated by IL-1 and TNF-α. Being an acute phase protein, CRP is a sensitive indicator of inflammation which shows a linear relationship between increase in the value and extent of inflammation and consequently tissue injury. CRP has been positively correlated with disease severity in psoriasis[8]. On the other hand, CRP is also an independent risk factor for cardiovascular diseases[8]. The possible mechanisms include binding of CRP to phosphatidylcholine of LDL and deposition of CRP in atherosclerotic plaques. It plays a central role in atherosclerosis from early stages of recruitment of

inflammatory cells to the final stage of plaque rupture. Therefore, CRP, which is indicative of the inflammatory process in psoriasis, could be the reason behind arterial stiffness and premature development of atherosclerosis in psoriasis patients. High-sensitivity CRP (hsCRP) refers to the lower detection limit of the assay and has been proven to be an independent vascular risk factor[8].

Cytokines of both Th1 and Th17 pathway increase generation of ROS in psoriasis patients. ROS generation occurs from two sources; exogenous sources such as cigarette smoking and endogenous sources such as leukocyte inflammatory responses[9]. Probably, chronic inflammation results in a condition of oxidative stress in psoriasis, which leads to oxidation of LDL-forming OxLDL. This OxLDL and CRP get incorporated in the atherosclerotic plaque, followed by rupture of the atherosclerotic plaque and formation of the thrombus[7].

Many studies have found higher OxLDL, MDA and hsCRP levels and lower GSH levels in psoriasis patients compared to controls, but the levels have not always correlated with the severity of psoriasis[10-15]. It has also been found that after TNF-α stimulation, human aortic smooth muscle cells and coronary artery endothelial cells show increased ROS generation, possibly by induction of NADPH oxidase[16].

In this background, the research work by Asha *et al*[17] published in this issue assumes significance. They compared LDL oxidising products such as OxLDL, OxLDL/LDL ratio, lipid peroxidation end-products such as serum MDA, antioxidant enzymes such as GSH and inflammatory markers such as hsCRP between 150 psoriasis patients and matched controls. As expected, serum cholesterol and triglyceride levels were significantly higher in psoriasis patients compared to controls. Interestingly, even though serum LDL of psoriasis patients was not significantly higher than controls, plasma OxLDL level as well as OxLDL/LDL ratio were significantly higher in psoriasis patients. MDA and hsCRP levels were significantly higher whereas GSH was significantly lower in psoriasis patients compared to controls. Therefore, the authors have suggested that psoriasis patients have deficient intrinsic antioxidant system, higher oxidative stress, higher risk of atherogenesis, increased inflammation of the atherosclerotic plaques as well as evidence of systemic inflammation. This clearly elucidates the link between psoriasis, oxidant/antioxidant imbalance, inflammation, atherosclerosis and increased cardiovascular morbidity. Further, they also showed a correlation between the severity of psoriasis and all these parameters, proving that as the severity of psoriasis increases, risk of oxidative stress, inflammation and atherosclerosis also increases. They also found that plasma MDA was positively correlated with OxLDL, which in turn was positively correlated with hsCRP.

An important aspect of cardiovascular risk in psoriasis patients will be assessment of effects of different psoriasis treatment modalities if any on the cardiovascular outcome. Treatments such as acitretin and cyclosporine may contribute to the development of cardiovascular risk factors such as hypertension and dyslipidaemia, whereas phototherapy and biologics are not known to have these side effects[7]. Assessment of effect of treatment for psoriasis was outside the scope of the case-control study conducted by Asha *et al*[17]. Therefore, a well-designed cohort study to assess the impact of different systemic treatments for psoriasis including biologics on oxidative stress, lipid profile and markers of systemic inflammation will be the logical next step in the future.

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