

Dyslipidemia and oxidative stress in patients of psoriasis.

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Abstract:

Psoriasis is a common chronic inflammatory skin disease with an unknown etiology. The aim of this research was to determine the lipid profile and levels of lipid peroxidation as malondialdehyde (MDA), antioxidant enzymes glutathione peroxidase (GPx) and superoxide dismutase (SOD) in patients with psoriasis. The levels of lipid profile were significantly altered in the patient group. Levels of MDA were significantly increased ($p < 0.001$) where as the GPx and SOD were significantly decreased ($p < 0.001$) in patients with psoriasis. These results provide some evidence regarding the role of increased reactive oxygen species and decreased antioxidant activity in psoriasis.

Key words: Psoriasis, oxidative stress, lipid profile, antioxidant enzymes.

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Introduction

Skin is a major target of oxidative stress due to reactive oxygen species (ROS) that originate in the environment and in the skin itself. ROS generated during normal metabolism, are an integral part of normal cellular function, and are usually of little harm because of intracellular mechanisms that reduce their damaging effects. Antioxidants attenuate the damaging effects of ROS and can impair and/or reverse many of the events that contribute to epidermal toxicity and disease. However, increased or prolonged free radical action can overwhelm ROS defense mechanisms, contributing to the development of cutaneous diseases and disorders [1]. Although ROS play a role in diseases such as skin cancer, their biological targets and pathogenic mode of action are still not fully understood. In addition, strategies useful in the therapeutic management of ROS action in human skin are still lacking.

Psoriasis is a common chronic and recurrent inflammatory skin disorder [2] that has been associated with abnormal plasma lipid metabolism and high frequency of cardiovascular events [3]. This prevalence seems to be related to the severity of psoriasis, as it occurs more frequently in patients presenting large areas of the body affected with psoriasis lesions. Though dyslipidemia is known to occur, less is known about its status and association with oxidative stress in patients of psoriasis.

Malondialdehyde (MDA), is a marker of oxidative stress and specific enzymes that limit free-radical formation, such as glutathione peroxidase (GPX), superoxide dismutase (SOD) play an important role in the protection of cell membranes against oxidative damage and may be used as indicators of anti-oxidative status. There are several studies investigating the role of oxidant /antioxidant systems in the pathogenesis of psoriasis with discordant results [4,5].

Hence, this study was carried out to evaluate the oxidative stress and dyslipidemia in patients with psoriasis.

Methods and Material

A case control study, approved by the ethics committee was carried out at NKP Salve Institute of Medical Sciences, Nagpur. Fifty patients of psoriasis with a mean age of 42.13 ± 13.45 were included in the study. Fifty age and sex matched normal healthy controls with a mean age of 44 ± 12.74 were selected as controls. The patients were diagnosed by Auspitz sign, clinical features of psoriasis like erythema, itching, thickening and scaling of the skin. The clinical severity was determined according to the Psoriasis Area and Severity Index (PASI) score. Disease duration of the patients ranged from 1 month to 25 years. All the patients being treated only with topical agents such as corticosteroids, vitamin D analogues, dithanol during the six month period have been included in the study. Patients with any chronic inflammatory disease, diabetes mellitus, renal disorders, IHD, hypothyroidism,

Dyslipidemia and oxidative stress in patients of psoriasis.

nephritic syndrome, obstructive liver disease, any other skin disorder were excluded from the study. All the patients of systemic drug therapy of beta blockers, thiazides, retinoids, cyclosporine and lipid lowering agents in the recent 6 months were excluded from the study.

5 ml of venous blood samples was collected in EDTA bottle and plain bulb from patients with psoriasis and normal healthy individuals. Blood samples were centrifuged at 3000g for 10 minutes and were estimated for lipid profile, lipid peroxidation and antioxidant enzymes (glutathione peroxidase and superoxide dismutase).

Lipid profile estimation

Serum total cholesterol, triglyceride and HDL-cholesterol were measured by an enzymatic kit. LDL-C was calculated according to the following formulae: $VLDL-C = \text{Triglyceride}/5$ and $LDL-C = \text{Total cholesterol} - (VLDL-C + HDL-C)$.

Serum malondialdehyde estimation

This method was based on the fact that lipid peroxide condense with 1 methyl-2 phenyl indole (MPI) under acidic conditions resulting in the formation of a red chromophore. To determine specifically lipid peroxide in plasma, proteins are precipitated to remove water-soluble MPI reactive substance. The level of lipid peroxide is expressed in terms of malondialdehyde, which is unstable. Tetramethoxypropane, which is converted quantitatively to MDA in the reaction procedure is used as standard.

Erythrocytic Glutathione peroxidase assay

In the enzymatic kit method, GPx catalyses the oxidation of glutathione by cumene hydroperoxide. In the presence of glutathione reductase and NADPH the oxidized glutathione is immediately converted to reduced form with a concomitant oxidation of NADPH to NADP. The decrease in absorbance at 340 nm is measured.

Antioxidant superoxide dismutase assay

Assay was done by enzymatic kit method. The principle employs xanthine and xanthine oxidase (XOD) to generate superoxide radicals which react with 2-(4-iodophenyl)-3-(4-nitrophenol)-5-phenyltetrazolium chloride to form a red formazan dye.

Statistical analysis was done using t test. Correlation between the variables was estimated by Pearson's Correlation coefficients.

Result

As in Table 1, total cholesterol, triglycerides, VLDL, HDL-cholesterol and LDL-cholesterol were significantly altered ($p < 0.001$) in patients of psoriasis.

Table 2 depicts the levels of MDA ($p < 0.001$) which were significantly elevated in psoriatic patients as compared to normal healthy controls.

The levels of GPx and SOD antioxidants were significantly decreased ($p < 0.001$) in psoriatic patients as compared to normal healthy controls (Table 2).

Table 1. Lipid profile in patients with psoriasis

| | Group I (n=50)(controls) | Group II (n=50)(patients) |
|-------------------------|-----------------------------|------------------------------|
| Total cholesterol (mg%) | 142.02 ± 19.8 | 218.08 ± 16.5* |
| Triglyceride (mg%) | 131.4 ± 16.35 | 223.12 ± 16.55* |
| VLDL (mg%) | 26.71 ± 3.23 | 44.51 ± 3.51* |
| LDL (mg%) | 66.89 ± 11.98 | 134.27 ± 9.81* |
| HDL (mg%) | 48.43 ± 4.32 | 39.32 ± 4.68* |

* $P < 0.001$ when patients of group II compared with group I

Table 2. Values of Pro-oxidant and antioxidants in patients with psoriasis

| | Group I (n=50) | Group II (n=50) |
|---------------|-------------------|--------------------|
| MDA (nmol/ml) | 0.92 ± 0.24 | 1.74 ± 0.27* |
| SOD (U/gm Hb) | 6.83 ± 0.7 | 5.39 ± 0.36* |
| GPx (U/gm Hb) | 14.64 ± 1.43 | 13.27 ± 0.33* |

* $P < 0.001$ when patients of group II compared with group I

Discussion

Psoriasis is a chronic inflammatory skin disease characterized by pathological skin lesions due to various exogenous and endogenous factors and is associated with a number of biochemical and immunological disturbances. Psoriasis is considered to be an (auto) immune disorder, probably initiated by the overactive skin innate immune system, and maintained by immigrating activated type 1 T cells and abnormally proliferating and differentiating keratinocytes. A complex network of cytokines and chemokines mediates the pathological reaction, whereas the abnormal function of psoriatic regulatory T cells is likely responsible for the chronic nature of psoriasis [6].

Though conflicting reports are available regarding the serum lipid values in psoriasis [3,7,8,9,10], the potential role of lipid abnormality in psoriatic patients has been discussed. In our study, we found significantly high levels of total cholesterol, triglycerides, VLDL, and LDL-cholesterol in patients of psoriasis (Table I). Several mechanisms including an unhealthy lifestyle, activation of type 1 helper T cells, autoantibodies recognizing oxidized

LDL and some medications used to treat psoriasis such as oral retinoids and cyclosporine may induce dyslipidemia in psoriatic patients [9,11,12]. Also structural and functional abnormalities have been found in nearly all the segments of the gastrointestinal tract in psoriatic patients [13]. Moreover, the level of antibodies against oxidized LDL correlates with the disease severity. Thus, psoriasis is a risk factor for hyperlipidemia and its possible subsequent sequelae such as obstructive vascular disease cannot be excluded.

Increased production of free radicals may cause oxidative damage on biological biomolecules, cell membranes and tissues. The free radicals induced oxidation of polyunsaturated fatty acids results in the formation of lipid peroxidation products such as MDA. Our study indicates an increase in the level of MDA (Table 2) in psoriatic patients as compared to normal controls, which is in correlation with the studies of Gornicki A,[14] Rocha Pereira P et al [15] and Relhan V et al [16]. However, Yildirim et al [17] did not find any correlation in the levels of MDA in patients of psoriasis with that of controls. Correlation analysis reveals a significance in between the values of MDA and Total cholesterol (0.66, $p < 0.001$), LDL-C (0.74, $p < 0.001$) and VLDL-C (0.68, $p < 0.001$) in patients with psoriasis. Thus, our result supports the finding that psoriatic patients are associated with an increased mortality and morbidity from cardiovascular events [3,18,19].

Increased ROS production in patients of psoriasis [20] and decreased concentration of antioxidants leads to oxidative stress, which indicates lipid peroxidation. This may lead to cell damage by continuous chain reactions. In addition, it may be responsible for activation of phospholipase A₂, production of many mediators by arachidonate, deactivation of adenylate cyclase and activation of guanylate cyclase leading to decrease in the cAMP/cGMP ratio responsible for epidermal proliferation in patients of psoriasis [21].

Data suggests that sera from patients with psoriasis have an increased capacity to activate PMNs and induce increased superoxide anion ($O_2^{\cdot -}$) generation. Increased generation of superoxide anion radicals from neutrophils and neutrophil accumulation in psoriatic lesions results in superoxide production during the phagocytic reaction. Early and active psoriatic lesions are characterized by the intra-epidermal penetration of PMNL and thus superoxide, an oxygen derived material plays an important role [22]. Superoxide dismutase, an antioxidant enzyme, catalyzes the dismutation of superoxide into the less harmful molecules, oxygen and hydrogen peroxide. Our study reveals a decrease in the levels of antioxidant enzyme SOD (Table 2). This is in concordance with the studies of Yildirim [17], Pujari [23], Kural [22], Drewna

[25], and Kobayashi [26]. However, Utas [27] and Baz et al [5] found an elevated level of the antioxidant enzyme plasma SOD patients of psoriasis. In our study, the decrease in the levels of antioxidant SOD in patients of psoriasis is probably to counteract the stress caused by oxidation.

Cells contain enzymes GPx which change the hydroperoxide group to the much less toxic hydroxyl moiety. Similar to our GPx results as in Table 2, Kokcam [28] observed that GPx was found to be significantly decreased in patients with psoriasis as compared with the values from sex-age matched healthy controls. Selenium being an integral part of the enzyme GPx, reduction in the enzyme activity leads to the accumulation of hydroxyl radicals in inflamed tissue. Supplementation with Se has also shown to benefit patients with acne [29] and to reduce ultra violet-induced inflammation in hairless mice [30]. Michaelsson et al [31], and Farris et al [32] have also demonstrated a decrease in the levels of whole blood and plasma selenium in patients with psoriasis.

In conclusion, hyperlipidemia along with increase in lipid peroxidation and decrease in antioxidants levels are a feature of psoriasis. Inactivating the effects of free radicals and stabilization of the cell membranes thus preventing new epidermal destruction can be achieved by antioxidant supplementation, which can be used as a therapeutic approach.

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