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Psoriasis, An inflammatory condition associated with oxidative stress

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ABSTRACT

Background: Psoriasis is a chronic inflammatory skin disease characterized by pathological skin lesions due to various exogenous and endogenous factors. Oxidative stress can be one of the causes for the occurrence of psoriasis as well as significant contributor to its progression. Skin exposure to a number of irritants or proinflammatory agents including UVA and UVB generates ROS through the oxidative burst in infiltrating leukocytes at the site of inflammation which damages the skin cells. Measurement of the oxidative stress marker like lipid peroxidation product Malondialdehyde (MDA) and Nitric Oxide end products ($NO_2 + NO_3$) along with the inflammatory marker hs-CRP in Psoriasis patients can uncover their role in disease causation, progression and development of various co-morbidities and timely prevention can significantly improve the quality of life of the psoriasis patients. **Aims and Objectives:** To measure the oxidative stress marker like lipid peroxidation product Malondialdehyde (MDA) and Nitric Oxide end products (NO2 + NO3) along with the inflammatory marker hs-CRP in Psoriasis patients to uncover their role in disease causation, progression and development of various co-morbidities and timely prevention to significantly improve the quality of life of the psoriasis patients. **Materials and Methods:** Fifty patients of psoriasis mainly plaque type of either sex, in the age group of 35 ± 15.5 (range: 7-79) years were taken following inclusion and exclusion criteria. To evaluate the oxidative stress lipid peroxidation product malondialdehyde (MDA) and Nitric Oxide end products (NO2 + NO3) were measured. hs-CRP was measured as an inflammatory marker and their correlation with the disease severity and duration was evaluated. **Results:** A significant increase in malondialdehyde (MDA), Nitric Oxide end products (NOx) and hs-CRP levels ($P < 0.001$) was noted in Psoriatic patients as compared to controls. There was a positive correlation between MDA, NOx and hs-CRP levels with the severity and duration of the disease. The correlation between hs-CRP and MDA and NOx also showed positive trend. **Conclusion:** Oxidative stress is one of the factors which can lead to the causation of Psoriasis and also significantly contribute to the disease progression and development of various co-morbidities. By measuring the oxidative stress marker and inflammatory marker in psoriasis patients early in the disease process we can employ preventive strategies for better management and improve the survival and quality of life.

Key words: Psoriasis; Oxidative stress; Malondialdehyde (MDA); Nitric Oxide end product (NOx); hs-CRP; PASI (Psoriasis area and severity index)

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INTRODUCTION

Psoriasis is a chronic inflammatory skin disease characterized by pathological skin lesions due to various exogenous and endogenous factors.[1,2] Skin exposure to a number of irritants or proinflammatory agents including UVA and UVB generates ROS through the oxidative burst in infiltrating leukocytes at the site of

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inflammation[3] which damages the skin cells. Psoriasis is a common chronic, inflammatory, proliferative skin disease that generally presents as chronic sharply demarcated, dull red, scaly plaques, particularly on extensor prominences and the scalp.[4] Skin cells mature and shed after about a month. However, in psoriasis, the normal cycle of replacing old skin cells with new one becomes unbalanced.[5] The causes of this disease are unknown, though genetic, metabolic, immune and environmental factors have been proposed.[6] The researchers are recently focused on oxidative stress as one of the important factor in pathogenesis of psoriasis.[7]

The skin is a potential target for oxidative injury, as it is continuously exposed to UV radiation and other environmental stresses generating reactive oxygen species (ROS).[8] Plasma membranes of the skin cells in the psoriatic lesion have a significant increase in arachidonic acid, which is the natural substrate for synthesis of malondialdehyde (MDA), an end product of lipid peroxidation [9] and also marker of oxidative stress.

Nitric oxide is an uncharged molecule having an unpaired electron, so it is a highly reactive free radical (NO▪), with very short half-life about 0.1 second. Nitric oxide is synthesized in cytoplasm from L-arginine by the enzyme nitric oxide synthase (NOS). On exposure to superoxide anion (O2-) nitric oxide is converted to a highly reactive free radical peroxynitrite, which causes lipid peroxidation, cell injury and cell death.

The keratinocytes, which make up the bulk of epidermis, constitutively express the neuronal isoform of Nitric Oxide Synthase (NOS I) whereas; the fibroblasts in the dermis and other cell types in the skin express the endothelial isoform (NOS III). Under certain conditions, virtually all skin cells appear to be capable of expressing the inducible NOS isoform (NOS II). The NO• liberated following UV irradiation plays a significant role in initiating melanogenesis, erythema and immunosuppression.[10] NO is the mediator of inflammation and the driving force behind the pathogenesis of psoriasis, as Psoriasis is an inflammatory condition, previous literature also proved that e.g., Gokhale et al, [11] Orem Asim et al.[12]

Inflammatory injuries may be worsened by ROS prolonged excessive release at the skin level, promoting chronic swelling. Therefore, there is a strict mechanism operated by a number of prooxidants and enzymatic antioxidants, which closely regulates cellular redox balance. Occurrence of chronic inflammation is an instance of antioxidant system depletion, allowing the prolongation of oxidative stress.[13,14]

C-reactive protein (CRP) is a hepatic acute phase reactant. Its synthesis is mainly controlled by IL-6, but IL-1 and TNF-α may also influence CRP levels. Hence serum CRP is an indirect marker of proinflammatory cytokine activity.[15] Increased oxidative stress in psoriasis arises due to increased inflammatory activity.[15]

So, assessment of lipid peroxidation product (MDA), NO' end products and C- reactive protein separately and their correlation with severity and duration of disease, is considered one of the best possible way to establish an inflammation associated with oxidative stress in psoriasis and this study was designed to with an aim to establish the association of inflammation with oxidative stress.

MATERIALS AND METHODS

The present cross-sectional study was conducted in the Department of Biochemistry and Department of Dermatology, IPGMER and SSKM hospital, Kolkata. A total of fifty patients with psoriasis mainly plaque type of either sex, in the age group of 35 ± 15.5 (range: 7–79) years who had not received any prior local or systemic treatment within two months were included in the study, after taking proper consent from the outdoor of Department of Dermatology, IPGMER and SSKM hospital, Kolkata. Fifty age and sex matched apparently healthy individuals were included in this study as control. Patients having acute illness such as fever, joint pain, abdominal complaint, malignancy, history of chest pain, deep fungal or disseminated localized gonococcal infection, taking active systemic therapy, of those having arthritis (rheumatoid factor positive), underlying diseases such as Diabetes mellitus, Hypertension, Hypothyroidism, known dyslipidemia other chronic inflammatory diseases, History of corticosteroid intake, chronic smokers or alcoholics, Patients receiving antioxidant therapy are excluded from the study. The Study protocol was approved by Research and Ethical committee, IPGMER and SSKM hospital, Kolkata. Oral informed consents were obtained from all subjects prior to the start of the study.

By taking all aseptic and antiseptic precautions, 5 ml of blood was drawn from the anti-cubital veins of the patients. Whole blood malondialdehyde is estimated by the method of Ohkawa et al [16] that is lipid peroxides are converted to malondialdehyde which react with thiobarbituric acid to produce a chromogen giving maximum absorbance at 530nm and is expressed as thiobarbituric acid reactive substance (MDA) in blood. Nitric oxide end products are measured in the blood by estimating its stable and non-volatile decomposition products Nitrates (NO_3) and Nitrites (NO_2) by Griess reaction where nitrite reacts under acidic conditions with sulfanilic acid ($HO_3SC_6H_4NH_2$) to form a diazonium cation ($HO_3SC_6H_4$–N- N+) which

subsequently couples to the aromatic amine 1-naphthylamine ($C_{10}H_7NH_2$) to produce a red–violet coloured ($\lambda max \approx 540$ nm), water-soluble azo dye ($HO_3SC_6H_4–N\,N–C_{10}H_6NH_2$).[17,18] Serum High sensitive C-reactive protein is measured by immunoturbidimetric method.

Severity of Psoriasis was assessed by Psoriasis Area and Severity Index (PASI). Patients with PASI score <10 have Mild psoriasis. Patients with PASI score >10 have Moderate to Severe psoriasis.

After the biochemical estimations, the results which were obtained were statistically analyzed by using statistical software, SPSS, 16. The results which were obtained were presented as Mean± SD and they were then compared between different groups of study by applying Students 't'– test. A probability (p) of less than 0.05 was considered as significant. Correlations were observed on using linear regression analysis.

RESULTS

Comparison of means of the different parameters (Table:1) revealed significantly higher values of malondialdehyde (MDA), Nitric oxide end products (NOx) and High sensitive C reactive protein (hs-CRP) in psoriatic patients as compared to control.

Table 1: Comparison of means of MDA, NOx and hs-CRP between psoriatic patients and Control

Parameters	Psoriatic patient (Mean±SD)	Control (Mean±SD)	P-Value
MDA (µMol/l)	42.33±3.69	6.51±0.87	<0.001*
NOx (µMol/l)	140.15±6.42	17.28±3.92	<0.001*
hs-CRP (mg/L)	6.58±0.68	2.34±0.79	<0.001*

(* significance at the level of P<0.001)

Table 2: Correlation of oxidative stress marker with PASI score and duration of disease

Parameters correlated	Correlation coefficient	Pearson's correlation significance
MDA vs PASI score	0.865	<0.001*
MDA vs Time (Years)	0.637	<0.001*
NOx vs PASI score	0.642	<0.001*
NOx vs Time (Years)	0.419	0.002**

(* significance at the level of P<0.001, ** significance at the level of P<0.05)

Table 3: Correlation of hs-CRP with disease severity and oxidative stress marker

Parameters correlated	Correlation coefficient	Pearson's correlation significance
hs-CRP vs PASI score	0.758	<0.001*
hs-CRP vs MDA	0.712	<0.001*
hs-CRP vs NOx	0.478	<0.001*

(* significance at the level of P<0.001, ** significance at the level of P<0.05)

Table 2 shows correlation of oxidative stress marker with Psoriasis Area and Severity Index (PASI) score. Serum

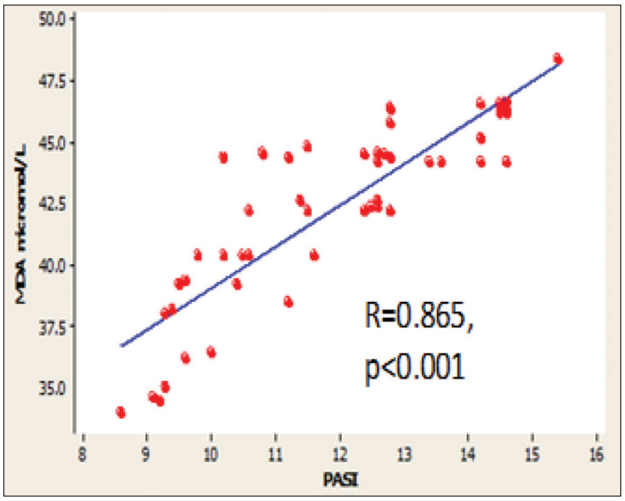

Figure 1: Correlation of MDA with PASI in patients

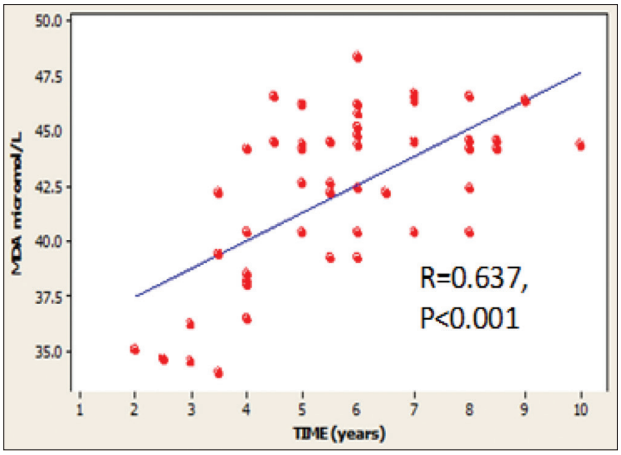

Figure 2: Correlation of MDA with time in patients

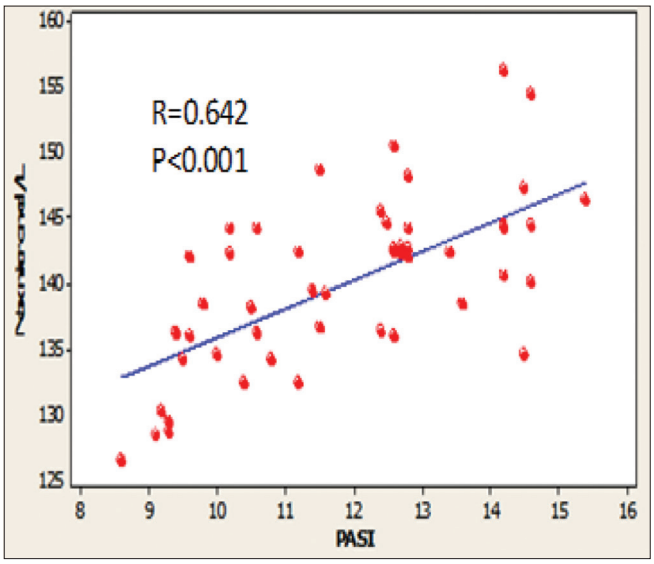

Figure 3: Correlation of Nox with PASI in patients

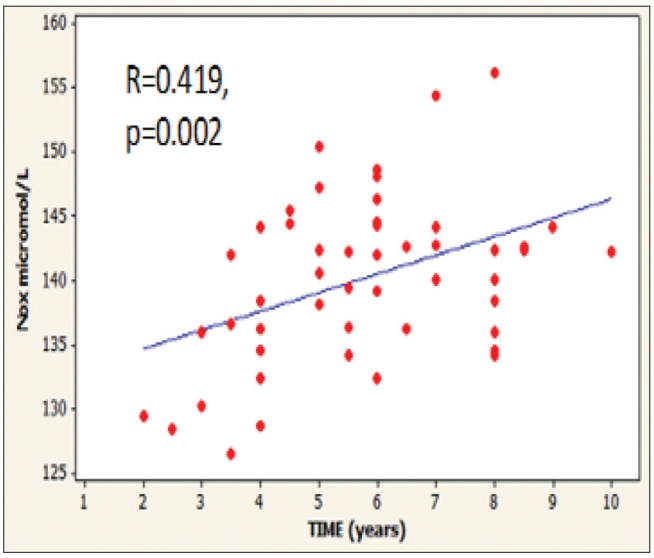

Figure 4: Correlation of Nox with time in patients

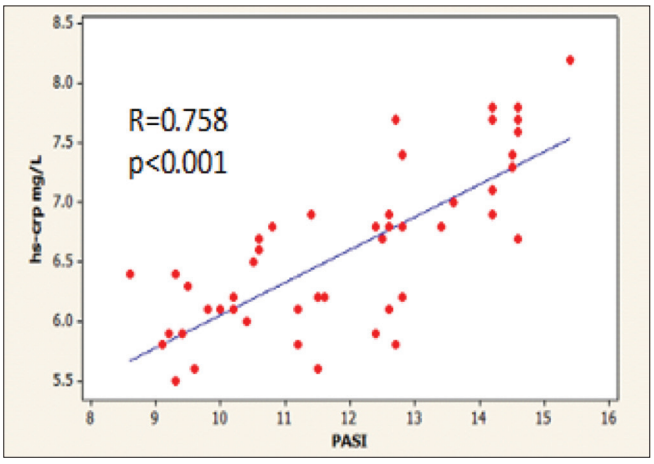

Figure 5: Correlation of hs-crp and PASI in patients

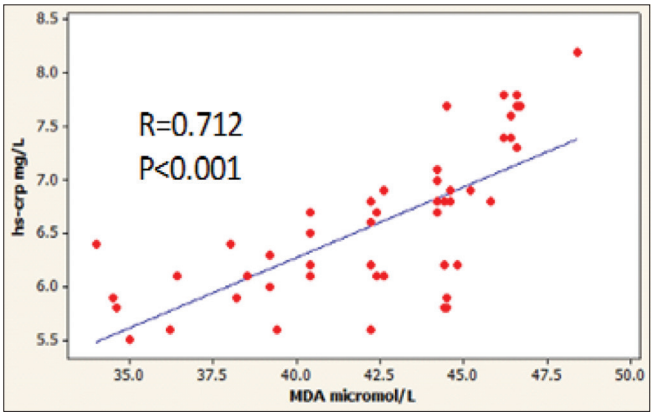

Figure 6: Correlation of hs-crp and MDA in patients

MDA and NOx value in psoriasis patients are positively correlated with PASI score and duration of disease, that means oxidative stress in psoriasis (as MDA & NOx are oxidative stress marker) increases with severity and duration of disease as depicted in Figures 1-4.

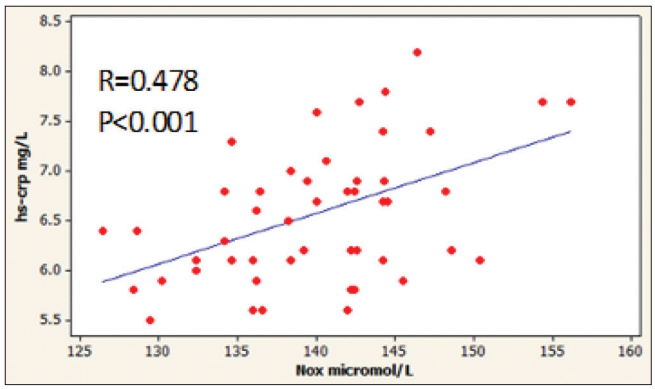

Figure 7: Correlation between hs-crp and Nox in patients

Table 3 shows Correlation of hs-CRP with disease severity and oxidative stress marker. Serum hs-CRP value positively correlated with PASI score, MDA and NOx as depicted in Figures 5-7.

DISCUSSION

In the present study it was found, that MDA levels is significantly ($p<0.001$) higher in patients of psoriasis 42.33±3.69 μMol/L than healthy controls 6.51 ±0.87. This indicates increased amount of oxidative stress in our patient group, which is similar with the findings of Rocha Pereira et al., [19] and Meffert et al.,[20] where higher level of lipid peroxidation product MDA in psoriasis patients than normal group were documented.

The skin is a potential target for oxidative injury, as it is continuously exposed to UV radiation and other environmental stresses generating reactive oxygen species (ROS)[21] also like any inflammatory disease, psoriasis often presents a rise in white blood cells (WBCs), namely in neutrophils in the epidermis. The activation of neutrophils triggers a set of functional and metabolic responses, including degranulation, enzyme release and generation of reactive oxygen species (ROS).[22] Psoriasis arises as a result of dysregulated interaction of the innate and adaptive immune system in the context of skin epithelium and connective tissues.[23] Dendritic cells , the key immune system sentinels drive the immune response in psoriasis by induction of auto proliferation of T-Cells and differentiation into Type-1 and Type 17 T-Helper cells respectively. Keratinocytes are activated by IL-17A, IL-17F and IL-22 from the Th17 associated pathway and TNF-α and IFN-γ from the Th1 pathway. These pathway leads to keratinocytes proliferation and production of proinflammatory cytokines (IL-1, IL-6, TNF-α).[24] ROS may be produced during the inflammatory process in Psoriasis, affecting primarily Lipid metabolism.[25] Increased generation of ROS coupled with decrease in the anti-

oxidant defence mechanism like superoxide dismutase, Glutathione peroxidase, catalase etc. increases oxidative stress resulting in peroxidation of membrane unsaturated fatty acids generating malondialdehyde (MDA), whose serum levels are increased in psoriasis. MDA is able to impair several physiological mechanisms of the human body through its ability to react with molecules such as DNA and proteins.[26,27]

There were significantly ($p<0.001$) increased levels of NOx in the psoriatic patients (140.15±6.42 μmol/l) as compared to controls (17.28±3.92μmol/l) which is in agreement with the previous studies Gokhale et al.,[28] Orem Asim et al.,[29] Gokhale et al.,[28] earlier showed that Nitric oxide levels were significantly increased in patients with psoriasis. Orem Asim et al., observed that nitrite levels and nitrite–nitrate ratios appear to be good indicators for the increased NO• production in patients and also showed a significant correlation with PASI score.[29] Nitric oxide (NO) is one of the mediators of inflammation and the driving force behind the pathogenesis of psoriasis. Expression of iNOS is involved in the pathogenesis of cutaneous inflammation in psoriasis.[30] Increase in mRNA expression of iNOS in skin lesions as compared to uninvolved skin have been reported. [31]

There was significant increase in the hsCRP (6.58±0.68 mg/l) levels in our patients than apparently healthy control (2.34±0.79 mg/l). The similar findings were documented by Pereira et al.[19] The inflammatory state in psoriasis releases pro inflammatory cytokines, which stimulate liver to produce acute phase reactants. CRP is one such acute phase reactant.[32] C-Reactive Protein concentrations in serum increase with increasing severity of psoriasis and show positive correlation with PASI. [33,34]

Therefore, psoriasis is not only having an immunological basis, but also associated with considerable amount of oxidative stress and inflammatory assault. This is indicated also in our observation.

The result of the study showed significant ($p<0.001$) correlation of serum MDA level and serum NOx level with duration of illness ($r=0.637$& $r=0.419$) and severity ($r= 0.865$& $r=0.642$) as depicted in Figures 1 to 4. These results are similar with the earlier studies conducted elsewhere Pereira et al.,[19] Jyothi et al.,[35] and also Orem Asim et al.,[29] Gokhale et al.[28]The above finding clearly shows that the oxidative stress in Psoriasis increases with the disease duration and severity.

Serum hs-CRP value is also well correlated positively with severity ($r=0.758$), serum MDA level ($r=0.712$) and serum NOx ($r=0.478$) as depicted in Figures 5-7. The result agrees with the previous studies by Pereira et al.,[19] Coimbra et al.,[36] Yiu et al.,[37] and Lucy Piper et al.[38]

Hence the inflammatory part of this disease is an intimate occurrence with its pathophysiology as well as with the oxidative stress. Timely monitoring of the oxidative stress and inflammatory marker in psoriasis patients may help in modifying the disease progression and also proper substitution of antioxidants in the diet can help in preventing the onset and progression of the disease there by reducing the disease burden in the community.

CONCLUSION

The present study is consistent with previous studies suggesting that there is increased oxidative stress in psoriasis patients. Oxidative damage plays an important role in the pathogenesis of this chronic inflammatory skin disease.

Hence, we suggest that combined estimation of Serum hs-CRP, MDA and NOx may be used as biomarkers for assessment of severity of psoriasis and early management by targeting oxidative stress can be a modality of treatment to reduce progression of disease. There is also scope for further study on beneficial effects of antioxidants like Glutathione, Vitamin E, Vitamin C, Vitamin A in preventing the onset and progression of disease in psoriasis patients.

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Author's contribution:
SP, UKB - Concept and Design of the study, prepared first draft of manuscript; **SS-**Interpretation of results, literature review; **IN -** Coordination, review of literature, final manuscript preparation**, UKB, AK -** Statistical analysis and interpretation, final revision of manuscript.

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