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Original Research Article

Characterization and Comparison of oxidative and inflammatory biomarkers in psoriatic arthritis patients

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Abstract

Background: The aim of our research was to evaluate the oxidative and inflammatory biomarkers of oxidative stress (OS) in blood samples of patients with Psoriatic Arthritis compared to healthy controls.
Materials and Methods: Our study involved 40 patients with Psoriatic Arthritis and 40 generally healthy subjects matched by age and gender to the study group patients. In this study we have evaluated the haematological and lipid profiles in healthy control and patients group. We have also assessed the concentration/activity of antioxidant enzymes: Superoxide Dismutase (SOD), glutathione peroxidase (GPx), Catalase (CAT) and total antioxidative status (TAS), and lipid oxidation products: Malondialdehyde (MDA) were estimated. Serum ADA, hsCRP, SUA, and ESR were evaluated for patients and controls. The extent of disease severity was assessed using the Psoriasis Area and Severity Index (PASI) and Dermatology Quality Of Life Index (DLQI) and patients were grouped into having mild, moderate and severe disease using these scores.
Results: Comparison among healthy control and psoriasis patients; there were no statistical differences concerning age, body mass index, and fasting serum glucose level. A significant increase in malondialdehyde (MDA), Nitric Oxide end products (NOx) and hsCRP levels (p<0.001) was noted in Psoriasis patients as compared to controls. The concentration of GPx, CAT, and SOD was significantly higher in patients with Psoriatic Arthritis compared to healthy subjects.
Conclusions: Systemic biomarkers of oxidative stress can be relevant for assessment of psoriasis severity, for prediction of the outcome of therapy and of the development of co-morbidities. Our findings revealed that an imbalance of oxidative stress and antioxidant factors might contribute to the pathogenesis of psoriasis. Therefore, treatment based on antioxidant strategies might be beneficial in psoriasis management.

Keywords: Psoriatic arthritis, oxidative stress, lipid profile, inflammatory biomarkers

Introduction

Psoriatic Arthritis is a chronic recurrent systemic disease affecting 2-4% of the global population, in which inflammatory processes occur in the skin and are marked by the

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presence of abnormal skin patches that can significantly reduce the quality of life [1-3]. The pathophysiology of Psoriatic Arthritis is of a complex and dynamic nature, and its key role is played by immunological and genetic factors, acute bacterial and viral infections, and chronic inflammation [4].

The Psoriasis is a chronic, immune-mediated, inflammatory disease that affects the skin and joints. The prevalence of this disease varies between 0.6 and 4.8 percent. Although it can present at any age from birth to older age, the peak age ranges of onset are 15 to 20 and 55 to 60 years [1]. The exact aetiology of psoriasis remains unclear. However, genetic, immunological, psychological, hormonal, and environmental factors might be involved. The pathogenesis of psoriasis might be associated with abnormal interactions between innate immune cells, T-cells, and keratinocytes; activation of the immune system; the release of excess pro-inflammatory substances; and tissue or organ damage [3].

Oxidative Stress is caused by both increased production of reactive oxygen species (ROS) and decreased concentration/activity of antioxidants responsible for their neutralization [4]. Free radical generation, disturbances of antioxidant barrier, and lipid peroxidation have been reported in the typical picture of Psoriatic Arthritis. The early phase of active Psoriatic Arthritis is characterized by intradermal infiltrates of activated polymorphonuclear leucocytes, followed by increased production of superoxide anion and other ROS [5]. The available evidence has also shown a decreased level of antioxidants, such as total blood thiols and serum vitamin E as well as antioxidant enzymes, such as serum, plasma and erythrocyte superoxide dismutase (SOD), plasma and erythrocyte catalase (CAT) and erythrocyte glutathione peroxidase (GPx) [6-8]. Finally, the results of several studies revealed decreased total antioxidant capacity (TAC) in psoriasis patients compared to the controls. Some studies demonstrated an increased level of oxidative stress markers including plasma/- serum lipid hydroperoxides, protein carbonyl, and nitric oxide end products [6]. High levels of plasma and red blood cell malondialdehyde (MDA) resulting from decreased activity of CAT and GPx were reported as markers of Psoriatic Arthritis exacerbation [7-8]. Psoriatic Arthritis is accompanied by pathological changes in the oral homeostasis, increasing the risk of periodontitis. It is also worth mentioning that Psoriatic Arthritis has been linked to the dysfunction of salivary glands as well as changes in the saliva composition [9]. The pathogenesis of this disorder is not fully understood.

Previous studies have indicated a possible role of oxidative stress and antioxidant markers in the pathogenesis of psoriasis, but there are still some controversies in this area [6-8]. The objective of this cross-sectional study was to compare the serum levels of oxidative stress markers and antioxidant markers, including Superoxide Dismutase (SOD), glutathione peroxidase (GPx), Catalase (CAT) and total antioxidative status (TAS), and lipid oxidation products: malondialdehyde (MDA), between patients with psoriasis and healthy controls. This study evaluated different oxidant and antioxidant factors among patients with psoriasis. Identification of some risk factors can provide more valuable information about the treatment of this disease.

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.

Materials and Methods

This was a case-controlled study, carried out on 40 patients of psoriasis who attended Dermatology outpatient's clinic, a control group of healthy persons of 40 age and sex matched. Information includes demographics, medical history, lifestyle habits, and drugs use

and laboratory findings.

The inclusion criteria: Patients with severe Psoriatic Arthritis of 1-year duration, PASI score of more than.

The exclusion criteria: Significant cardiovascular disease, diabetics, hypertension, dyslipidaemia, and any patients with other types of psoriasis. The severity of psoriasis was assessed by PASI score.

After explaining purpose and contents of the study to subjects, written informed consent was obtained from each. A detailed history with special emphasis on psoriasis including age at onset, total duration, duration of present episode, remitting and relapsing factors, history of joint and nail involvement along with family history was recorded on a pre-designed case record form.

Dermatological examinations including morphological type of psoriasis, body surface area (BSA) involvement in percentage and psoriasis area severity index (PASI) were calculated for all patients.

BSA was calculated using the number of patient's hand areas affected. One hand area is equivalent to patient's one palm and fingers, and represents 1% of his entire body surface area. Psoriasis severity was assessed by PASI score.

Calculation of PASI Score: The body was divided into 4 sections (head (H) (10% of a person's skin); arms (A) (20%); trunk (T) (30%); legs (L) (40%)). For each section, the percent of area of skin involved was estimated and then transformed into a grade from 0 to 6: Within each area, three clinical signs estimated the severity: erythema (redness), induration (thickness) and desquamation (scaling). Severity parameters were measured on a scale of 0 to 4, from none to maximum.

Hence, the final formula for calculating PASI score is as follows:

$$\mathbf{PASI = 0.1(Eh + Ih + Dh)\,A + 0.2(Eu + Iu + Du)\,A + 0.3(Et + It + Dt)\,A + 0.4(El + Il + Dl)\,A}$$

The score can vary from 0 to 72. In our study: PASI score more than 12 was graded as severe.

Scoring of the clinical signs in each area is summed and is finally weighted according to the area's proportion of the body, which ranged from 0 to a theoretical maximum of 72.

1. Patients with a PASI > 12 have severe psoriasis.
2. Clinically significant plaques covering less than 10% of the integument is moderate plaque psoriasis and result in a PASI = 7.
3. If a patient with PASI < 7 as mild chronic plaque-type psoriasis.

We have calculated the body mass index which is the weight in kilograms (kg) which was divided by the square of the height in meters (m^2).

Laboratory studies: Under aseptic precaution blood samples were collected after an over-night fast (12-14 h) and deposited in additive-free vacutainer tubes to obtain serum by low-speed centrifugation at 4 °C. Lipid and glucose concentrations were determined in fresh serum samples. The TC concentration was measured with a colorimetric method with cholesterol esterase and oxidase, the HDL-C concentration was measured with a direct enzymatic-colorimetric method with polyethylene glycol (PEG)-modified cholesterol esterase and oxidase, and the triglyceride (TG) concentration was measured with an enzymatic-colorimetric method with phosphoglycerol oxidase. The LDL-C concentration was calculated

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according to the Friedewald formula. We used the Cobas Integra 400 analyzer with commercially available reagents (Roche Diagnostics, Japan).
CBC was measured by using CELL-DYN Emerald cell counter, ABBOTT, Germany. ESR was assayed using Westergren method. SUA was assayed by enzymatic colorimetric uricase method using SPINREACT, S. A/S. A. U Ctra. Santa Coloma, 7 E-17176 SANT ESTEVE DE BAS (GI) SPAIN according to the instructions of manufacturing company. The hsCRP was assayed by an enzyme-linked immunosorbent assay BIOS kit (Chemux Bio Science, Inc., California, USA). ADA was assayed through kinetic method using Ben Biochemical Enterprise (BEN) ADA quantitative ultraviolet assay kit, Milano, Italy. The principle of the assay was that ADA catalyzes the hydrolysis of the substrate adenosine with the liberation of ammonia that reacts with α-ketoglutarate and NADPH with means of glutamate dehydrogenase giving NADP. The decrease of absorbance in NADPH is monitored at 340 nm, which is proportional to the concentration of ADA in the sample [23]. The concentration of ADA was calculated using standard included in the kit.

Statistical analysis: Results on continuous measurements have been presented as mean ± SD and results on categorical measurements are presented in number and percentage (%).The significance of study parameters was calculated by student's t test for continuous data. The level of significance was taken as 0.05. The statistical software used was Microsoft excel and SPSS software version 16.0 for analysis of data and Microsoft word to generate graphs, tables etc.

Result

This study included 40 psoriasis patients classified according to PASI score into mild, moderate, and severe psoriasis group. Forty healthy subjects were included as a control group. There were no statistically significant differences of age and sex between different psoriasis groups and the control group. Demographic characteristics of the study population and disease characteristics are reported in Table 1. Patients and healthy controls were residents of various states of Southern India. The duration of psoriasis in our patients ranged from 1 year to 24 years while the psoriasis area and severity index (PASI) score of the 40 patients with psoriasis ranged from 1 to 30.

Table 1: Comparison of baseline parameters among control group and patient group

Parameters	Control Group (n=40)	Patient Group (n=40)	p-value
Age (years)	35.9 ±12.17	36.7 ±14.34	0.23
Gender			
Male n (%)	22(55%)	23 (57.5%)	0.62
Female n (%)	18 (45%)	17 (42.5%)	
Drug Abuse n (%)	1 (2.5%)	2 (5%)	
Alcohol use n (%)	7 (17.5%)	5 (12.5%)	
Smoking n (%)	11(27.5%)	9 (22.5%)	
Systolic blood pressure (mmHg)	130.0 ± 22.8	134.8 ± 20.4	0.02
Diastolic blood pressure (mmHg)	76.6 ± 8.4	72.0 ± 6.8	0.01
Weight (kg)	70.9 ± 13.1	72.4 ±13.1	0.02
Body mass index (kg m2)	26.4 ± 4.6	27.1 ± 4.6	0.004
Waist circumference (cm)	90.4 ± 11.7	92.3 ± 12.6	0.001
Waist-to-hip ratio	0.87 ± 0.04	0.88 ± 0.08	<0.001

This study was conducted on 40 patients with psoriasis and 40 healthy subjects in the control group. In total, 18 (45%) female and 22 (55%) male were enrolled in control group; on the other hand 17 (42.5%) female and 23 (57.5%) male were included in patient group. The mean

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age of the subjects was 35.9 ±12.17 years in the control group and 36.7 ± 14.34 years in the patient group (p=0.62). The mean body mass index in the patient group was significantly higher than that of the controls (27.1 ± 4.6 compared to26.4 ± 4.6kg/m^2; p=0.04). There were no statistical differences between controls and patients group concerning age, body mass index and fasting serum glucose level as in table.

Table 2: Comparison of haematological profiles between control group and patient group

Parameters	Control Group (n=40)	Patient Group (n=40)	p-value
RBC (10^6/μL)	4.63 ± 0.47	4.42 ± 0.57	0.052
WBC (10^3/μL)	7.08 ± 1.94	6.23 ± 1.47	0.815
PLT (10^3/μL)	257.50 ± 51.24	234.56 ± 49.27	0.07
HCT (%)	44.23±2.98	41.31 ± 2.57	0.02
Triglycerides (mmol)	129.77 ± 69.34	141.51 ± 80.16	<0.001
Total cholesterol (mmol)	144.84 ± 40.14	190.18 ± 20.58	0.006
LDL-cholesterol (mmol)	112.23 ± 29.82	103.59 ± 24.51	0.03
HDL-cholesterol (mmol)	38.66 ± 7.36	36.59 ± 7.21	0.001
Fasting blood sugar (mg/dL)	95.06±11.01	106.71±30.32	0.04

Patient group have shown significant decrease in RBC, WBC, Platelet and Hematocrit count compared to normal healthy control. Serum HDL in psoriasis patient was low in compare to controls which is statistically highly significant, Serum TG was high in psoriasis patient in compare to controls which is statistically highly significant, Serum LDL was high in psoriasis controls in compare to patients which is statistically highly significant, fasting blood sugar level was high in psoriasis patient in compare to controls which is statistically highly significant as in Table 2.

Table 3: Characterization and Baseline Clinical profile of psoriasis patients

Parameters	Patient Group (n=40)
Age of onset (years)	26.4 ± 9.63
Disease duration (years)	14.7 ± 8.6
Baseline PASI score	15.7 ± 8.4
Baseline DLQI score	17.4 ± 7.4
Severity of psoriasis (PASI score)	
Mild (1-5)	4 (10%)
Moderate (6-12)	9 (22.5%)
Severe (13-20)	16 (40%)
Very Severe (>20)	11 (27.5%)

Based on these findings, the mean age at onset of disease was 26.4 ± 9.63 years, and the mean disease duration was 14.7 ± 8.6 years. In the present study, 40 psoriasis patients were selected. Disease severity was assessed by Psoriasis Area Severity Index (PASI) score and grouped as mild, moderate and severe and compared with 40 healthy controls Table 3.

Table 4: Comparison of oxidative and inflammatory biomarkers between control group and patient group

Parameters	Control Group (n=40)	Patient Group (n=40)			
		Mild	Moderate	Severe	Very Severe
SOD (U/ml)	1.84 ± 0.19	1.65 ± 0.10	1.30 ± 0.07	0.98 ± 0.08	0.67 ± 0.14
GPx (U/ml)	4.17 ± 1.71	3.92 ± 1.06	3.51 ± 1.15	2.87 ± 1.05	2.31 ± 0.08
CAT (KU/l)	55.44 ± 3.11	48.56 ± 2.53	42.04 ± 3.92	36.15 ± 2.57	33.21 ± 1.05
Total Antioxidant Status (lmol/l)	966.66 ± 33.89	884.0 ± 24.16	798.33 ± 28.87	740.33 ± 18.52	698.42 ± 11.47

NO end products (lmol/l)	35.49 ± 6.31	43.41 ± 1.71	50.85 ± 3.68	62.24 ± 4.20	71.61 ± 3.89
MDA (nmol/ml)	1.54 ± 0.19	1.84 ± 0.24	3.11 ± 0.24	4.35 ± 0.45	5.97 ± 0.24
ESR (mm/h)	16.2 ± 0.92	22.83 ± 3.52	29.4 ± 2.49	30.2 ± 1.04	33.81 ± 0.94
SUA (mg/dl)	3.9 ± 0.24	4.6 ± 0.83	5.4 ± 0.72	6.2 ± 0.87	7.05 ± 0.72
hsCRP (ng/ml)	10.27 ± 2.43	28.46 ± 8.49	34.24 ± 9.46	48.36 ± 12.81	53.67 ± 9.61
ADA (U/L)	9.1 ± 1.53	17.43 ± 6.51	23.42 ± 7.81	27.59 ± 8.46	30.26 ± 6.43

ADA: Adenosine deaminase, hsCRP: High-sensitive C-reactive protein, SUA: Serum uric acid, ESR: Erythrocyte sedimentation rate, serum malondialdehyde (MDA), nitric oxide (NO•) end products, activity of erythrocyte-superoxide dismutase (SOD), catalase (CAT) and total antioxidant status (TAS).

Serum levels of malondialdehyde, nitric oxide end products and the activities of antioxidant enzymes such as erythrocyte-superoxide dismutase, catalase and total antioxidant status were investigated in these groups/subjects. As compared to controls, we found severity wise significantly increased serum malondialdehyde, nitric oxide end products with decrease in erythrocyte-superoxide dismutase activity, catalase activity and total antioxidant status in patients with psoriasis suggesting worsening of the disease.

ROS induced oxidation of polyunsaturated fatty acids in biological system results in the formation of lipid peroxidation product MDA which has been used as a biomarker of lipid peroxidation. Furthermore, we found severity wise increase in MDA levels in these patients indicating that, the degree of elevation of serum MDA is associated with the progression of psoriasis.

ADA, hsCRP, SUA and ESR showed a significant increase in each psoriasis group (mild, moderate, and severe) compared with the control group. No significant differences between ADA, hsCRP, SUA and ESR were found among different psoriasis groups. Furthermore, no significant correlation between PASI score and ADA, hsCRP, SUA and ESR was found Table 4.

Discussion

The present findings demonstrated associations between psoriasis and serum levels of different oxidative stress and antioxidant biomarkers. According to the results, the mean level of hsCRP in patients with psoriasis was significantly higher than that among healthy controls. It is known that psoriasis stimulates pro-inflammatory responses and chronic inflammation by activation of monocytes, macrophages, neutrophils, and endothelial cells. This activation of the immune system results in the production of more cytokines and reactive oxygen forms and the accumulation of hsCRP [9].

Psoriasis is common chronic inflammatory skin disorders. Many organs not only the skin affected by the inflammatory process including the cardiovascular system. Psoriasis disease has clear association with obesity and its related metabolic abnormalities. Clinical cardiovascular events provoked by dyslipidaemia, glucose intolerance and hypertension [10]. In our study, we have evaluated obesity by using BMI which was significantly increased in patients with psoriasis in comparison with controls. Abnormal lipid profile is a well-known cardiovascular risk factor. In our study we have observed highly significant elevated triglycerides and highly significant lower HDL levels which is inconsistent with other study which found increased serum HDL [11]. Decreased antioxidant activity with the process of chronic inflammation resulting from elevated cholesterol level. All these together with effects of drugs used in the treatment of psoriasis as cyclosporine and acitretin. There were highly significant statistical differences to those who were non hypertensive psoriasis patients in age, serum TG level, and serum LDL level, duration of disease and in the Psoriasis Area Severity Index. Many studies showed that the chronic inflammatory process responsible for

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hypertension as Huskic *et al*. found that psoriasis patients had increased concentration of tissue angiotensin-converting enzyme [12]. The Fasting glucose level was elevated and show highly significant differences between psoriasis patient and the control groups but there was negative correlation between the Psoriasis Area Severity Index and serum glucose level.

It is well established that the ROS induced oxidation of polyunsaturated fatty acids in biological system results in the enhancement of lipid peroxidation and MDA being one of its product, has been considered as a biomarker of lipid peroxidation [15]. These finding are in agreement with the observation of Gupta M *et al*. [16] and Gornicki A, [17] who noticed the elevated in serum MDA levels in psoriasis. Samuel V *et al*. [1] and Adam D *et al*. [11] have noticed concomitant increase in MDA with the severity of psoriasis. ROS may be produced during the inflammatory process, in psoriasis, affecting primarily lipid metabolism of cells [13].

Our study has also revealed a significant lowering in plasma activity of SOD and GPx in psoriasis patients as compare to the controls. SOD, an antioxidant enzyme, accelerates the dismutation of the toxic superoxide radicals produced during the oxidative energy processes into the less harmful molecules, hydrogen peroxide and molecular oxygen. It may be suggested that the lowering in SOD activity may result into more accumulation of superoxide anion radicals in neutrophils and such neutrophils may also get accumulated in psoriasis lesions where they are responsible for abundant superoxide production during the phagocytic reaction and also for the systemic activation of circulating neutrophils in psoriasis patients [14]. We also found a negative correlation between erythrocyte-SOD activity and serum MDA among the three different groups of psoriasis patients. Our study indicates the possibility that, in the pre-diagnostic stage, serum antioxidants are low because they have been used in reducing inflammatory products. Decreased SOD activity might be related to epidermal hyper proliferation, because the ROS are thought to induce cell proliferation in various cell systems.

We found a positive correlation between the PASI score of patients at the time of presentation with their levels of serum hsCRP with a highly significant. Also, when compared taking the mean PASI in each severity group (mild, moderate and severe) to the mean hsCRP in that group, the results were statistically highly significant in patients with moderate and severe psoriasis. It was also observed that the mean hsCRP was higher in the group with maximum severity of psoriasis.

As a potential regulator of keratinocyte growth and differentiation, the multifunctional signalling molecule NO• has been considered to be a strong candidate in the pathogenesis of psoriasis. NO• is an important marker of inflammation [15, 16]. In the present study, there was statistically significant increase in the levels of NO• end products in mild (P\0.01), moderate (P\0.01) severe (P\0.01) psoriasis patients when compared with healthy controls. Furthermore, NO• end product levels in moderate psoriasis patients were significantly higher (P\0.01) than the patients presenting with mild psoriasis, whereas, severe psoriasis patients exhibited significant rise in serum NO• end products (P\0.01) as compared to moderate psoriasis.

In vivo antioxidant status can be assessed by measuring individual plasma or tissue levels of antioxidants. Measuring the levels of these specific antioxidant molecules can yield valuable information, and low levels of such antioxidants provide suggestive, but not definitive, evidence of oxidative stress. However, determining total antioxidant capacity provides an index of the sum of the activities of all antioxidants [17, 18].

The decreased TAS may be possibly due to depressed state of antioxidant system or due to the exaggerated inflammatory processes and oxidative stress in these patients. Antioxidants prevent oxidative injury of structural lipids and proteins contributing to barrier integrity, which is essential for healthy skin condition. This suggests that cellular redox environment plays a pivotal role in skin homeostasis and that skin disease could result from an imbalance between pro-oxidant and antioxidant stimuli.

ISSN 2515-8260 Volume 09, Issue 08, 2022

Conclusions

We observed that the course of Psoriatic Arthritis is accompanied by redox imbalances with the prevalence of oxidation reactions. Oxidative damage plays an important role in the pathogenesis of this chronic inflammatory skin disease. Hence, we suggest that combined estimation of Serum hsCRP, 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.

We conclude that psoriasis patients considered at high risk for development of cardiovascular disease. Treatment of Dyslipidemias and dietary antioxidants supplementation should be considered in the management of psoriasis to reduce the morbidity from cardiovascular events.

In conclusion, this study provides an evidence for increased ROS production and decreased antioxidant defences in psoriasis, reflected by increased lipid peroxidation and decreased TAS as well as decrease in SOD activity and CAT activities. Increased NO• end products in these patients may be a result of immunological and inflammatory mechanism which are important in etiopathogenesis of psoriasis. Furthermore we found worsened oxidant and antioxidant status according to the progression of the psoriasis lesions, which may be the crucial point in the pathogenesis of psoriasis and need further elucidations.

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