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CONCISE COMMUNICATION

A novel approach in psoriasis: first usage of known protein oxidation markers to prove oxidative stress

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Abstract Oxidative stress may play a pivotal role in the pathogenesis of psoriasis, an inflammatory/hyperproliferative skin disease characterized by the cutaneous accumulation of neutrophils releasing reactive oxygen species, as revealed in a number of studies. This study was performed to demonstrate the presence of oxidative stress in psoriasis, as measured by protein oxidation markers. Twenty-nine psoriasis patients were selected based on disease severity assessment using body surface area as well as the psoriasis area severity index (PASI), and were grouped as mild (PASI $\leq$ 10) and moderate-to-severe (PASI $>$ 10). The measured parameters in psoriatic patients and fourteen healthy volunteers were as follows: erythrocyte sedimentation rate (ESR), high sensitive C-reactive protein (CRP), myeloperoxidase (MPO) activity, neopterin, total lipid hydroperoxides (LHP), pyrrolized protein (PP), protein carbonyl compounds (PCC), advanced oxidation protein products (AOPP), thiol levels, along with complete blood count. Except lower thiols, all parameters were found to be higher in total patients as well as in subgroups, compared to controls. There was no significant difference among the subgroups. In conclusion, protein oxidation in psoriatics, not only in moderate-to-severe, but also in mild patients, may be explained by the findings of inflammation, phagocytic cell oxidation, and MPO-hypochlorous acid-oxidation reactions; as reflected by increased total/differential leucocytes counts, CRP, ESR as well as MPO, neopterin, AOPP, PCC, PP, LHP, and decreased thiol levels. Demonstrating the AOPP and PP formation for the first time, oxidants from active neutrophils/monocytes may play an important role in the pathogenesis of psoriasis, leading to oxidative stress, especially by protein oxidation.

Keywords Psoriasis · Neutrophils/monocyte activation · Myeloperoxidase · Advanced oxidation protein products · Pyrrolized protein · Protein carbonyl compounds

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Introduction

Psoriasis is a chronic, inflammatory skin disease characterized by pathological skin lesions [35]. Increased production of reactive oxygen species (ROS) leading to oxidative stress is believed to be a key factor in psoriasis pathogenesis [5]. Oxidative stress in psoriasis patients has long relied solely on lipid peroxidation products such as lipid hydroperoxides (LHP), malondialdehyde (MDA), and hydroxynonenal (HNE), or on enzymatic/nonenzymatic antioxidants [33]. However, the data from these parameters are discordant; found to be increased, decreased or unchanged [5, 33].

Otherwise, the nature of ROS will play a significant role in determining whether to use lipids, DNA, or proteins as markers of oxidative stress [8]. For instance, hypochlorous acid (HOCl) induces the oxidation of proteins, however, causes little modification in DNA/lipids. Hence, when HOCl, the only in vivo source of which is myeloperoxidase (MPO) from activated neutrophils and monocytes [10], is the predominant ROS, specific protein oxidation products of HOCl should be used as the marker [8]. Furthermore, the usage of protein oxidation products as oxidative stress markers, such as pyrrolized protein (PP) [23], protein

carbonyl compounds (PCC) [28], or advanced oxidation protein products (AOPP) [36], may have some advantages due to their relatively early formation, greater stability, and reliability, as well as their longer life span. In addition, the oxidation of plasma thiols, located largely on albumin, is quantitatively the major manifestation of protein oxidation as well as of the plasma antioxidant system [17].

The objectives of this cross-sectional study were to prove the presence oxidative stress in psoriasis, and investigate whether the activation of neutrophils and/or monocytes is one of the main sources of oxidative stress leading to lipid and/or protein oxidations, and of inflammation in psoriatic patients. Therefore, MPO activity/neopterin levels as markers of activations of neutrophils/monocytes; total LHP as marker of lipid peroxidation; AOPP, PCC and PP as markers of protein oxidation; and thiols as marker of endogenous antioxidant system; and erythrocyte sedimentation rate (ESR), high sensitive C-reactive protein (hs-CRP) and complete blood count (CBC) as markers of inflammation were measured in the blood/serum/plasma samples of psoriatic patients.

Materials and methods

Subjects

Twenty-nine patients with psoriasis (vulgaris: 26, guttate: 3) and fourteen healthy volunteers were participated. All the participants gave written informed consent prior to the study. Disease severity was scored using body surface area (BSA) as well as the Psoriasis Area and Severity Index (PASI) by the same dermatologist; and the patients were grouped as mild (PASI $\leq$ 10) and moderate-to-severe (PASI $>$ 10). Clinical characteristics of the study groups were summarized in Table 1.

Routine biochemical analyses of the study groups were performed at baseline. Exclusion criteria were as follows: younger than 16 years of age, a history of any systemic or other skin diseases, hyperlipidemia, alcoholism, and concomitant (radio-, chemo-, immunosuppressive-) therapy. None had received any systemic therapy, local steroid medication, or any phototherapy for at least 1 month prior to blood collection.

Analytical procedures

Blood was collected without and with EDTA/heparin. Routine analyses were performed by an autoanalyzer (Synchron LX20; Beckman Coulter, CA, USA); CBC by an automated blood counter (XT-1800i Sysmex, Norderstedt, Germany); ESR by an ESR analyzer (Alifax; Polverara–Padova, Italy) and hs-CRP by an autoanalyzer (Dimension Arx, Dade Behring, Marburg, Germany), respectively. MPO activity [4], total LHP [24] and thiols [17] in heparinized-plasma; AOPP [36] in EDTA-plasma; PCC [28] and PP [14, 23] in serum were determined by spectrometric methods. The variation coefficient of the methods for MPO, AOPP, total LHP, PP, PCC, and thiol were 3.25, 4.06, 3.9, 2.29, 4.34, and 3.08 %, respectively. Serum neopterin was determined by ELISA (DRG, Germany. Catalog no: EIA-1476).

Statistical analyses

Data were evaluated by Statistical Package for Social Sciences (SPSS, version 16 for Windows, Chicago, IL, USA). When the normality of measured parameters was assessed by Shapiro–Wilk test, nonparametric statistical tests, "Kruskal–Wallis and Mann–Whitney *U*", were used only for ESR and hs-CRP comparisons. The other data were compared by the unpaired student's *t* test and the analysis of variance (ANOVA) and post hoc tests (Scheffe's procedure). Differences were considered significant at $p < 0.05$. Data were presented as mean $\pm$ SD, or median and minimum (min)—maximum (max) ranges in tstatistical anahe tables.

Results

There were no significant differences between controls and total patients in terms of age and gender. Patients' subgroups also did not differ with regard to age, gender, and duration of disease ($p > 0.05$; Table 1).

There were no significant differences in routine biochemical analyses among all groups ($p > 0.05$). White blood cell (WBC) count, neutrophils, and monocytes were significantly different higher in total patients than the controls ($p < 0.05$). Otherwise, WBC and neutrophils were significantly different, only in the "PASI $>$ 10" group ($p < 0.05$), and monocytes in two subgroups ($p < 0.05$). When the subgroups were compared, although not significant, moderate-to-severe patients had higher counts ($p > 0.05$). ESR and hs-CRP, in accordance with each other, were higher than control values in all psoriatic patients ($p < 0.05$); however, subgroups of the patients displayed similar levels ($p > 0.05$; Table 2).

MPO, neopterin, AOPP, total LHP, PP, and PCC levels were significantly higher, with thiols being lower, in total psoriatics as well as in mild and moderate-to-severe psoriasis patients compared to the controls ($p < 0.05$). No significant difference was observed between subgroups ($p > 0.05$; Table 3).

Table 1 Clinical characteristics of the study groups

	Control	Psoriasis patients		
		Total	(PASI ≤ 10) mild	(PASI > 10) moderate-to-severe
Volunteers (*n*)	14	29	14	15
Gender (M/F)	10/4	20/9	11/3	9/6
Age (years)	30–49	16–76	17–64	16–76
Mean age (years)	38.4 ± 5.4	39.1 ± 12.4	41.0 ± 14.1	38.0 ± 15.6
Disease duration (years)	–	0.5–39	0.5–30	0.5–39
Mean disease duration (years)	–	11.4 ± 9.3	9.7 ± 8.0	13.0 ± 10.4
PASI score	–	11.0 ± 6.4	6.8 ± 2.1	15.0 ± 6.7
PASI score (range)	–	2–36	2–10	10.9–36
BSA (mean %)	–	30 ± 18	22 ± 6	37 ± 22
BSA (range %)	–	10–100	10–30	20–100
Clinical type (*Proteus vulgaris*) (*n*/%)	–	26/89.7	13/92.9	13/86.7

Data were presented as mean ± SD

n the number of volunteers, *M*/*F* males/females, *BSA* body surface area, *PASI* Psoriasis Area and Severity Index

Table 2 Routine biochemical parameters of the study groups

Parameters	Control (*n*:14)	Psoriasis patients		
		Total (*n*: 29)	(PASI ≤ 10) (*n*: 14)	(PASI > 10) (*n*: 15)
WBC count (cell/μL)	6866 ± 1187	7645 ± 1011*	7362 ± 1253	7910 ± 656■
Neutrophils (cells/μL)	4463 ± 772	4969 ± 657*	4785 ± 814	5141 ± 427■
Monocytes (cells/μL)	240 ± 42	458 ± 60*	442 ± 75■	474 ± 39■
Glucose (mg/dL)	76 ± 29	87 ± 21	92 ± 27	83 ± 11
BUN (mg/dL)	12.8 ± 3.0	11.7 ± 3.7	11.5 ± 3.6	11.8 ± 3.9
Creatinine (mg/dL)	0.95 ± 0.13	0.87 ± 0.16	0.92 ± 0.16	0.83 ± 0.14
AST (IU/L)	25 ± 8	21 ± 6	20.6 ± 3.6	22.1 ± 7.9
ALT (IU/L)	29 ± 17	22 ± 8	24 ± 9	20 ± 7
ALP (IU/L)	78 ± 20	77 ± 29	75 ± 14	80 ± 39
hs-CRP (mg/L)	3.4 ± 0.8	6.5 ± 3.3	6.5 ± 3.5	6.5 ± 3.3
Med (min–max)	3.1 (3.1–5.2)	5.7 (3.0–15.0)●	4.5 (3.2–12.0)●	6.1 (3.0–15)●
ESR (mm/h)	7.8 ± 3.0	19.4 ± 7.3	20.5 ± 5.3	18.4 ± 8.8
Med (min–max)	8 (3–15)	19 (9–35)●	19 (13–35)●	15 (9–35)●

Data were presented as mean ± SD and median (min–max) (for gray line)

n number of volunteers, *BUN* blood urea nitrogen, *AST* aspartate transaminase, *ALT* alanine transaminase, *ALP* alkaline phosphatase, *WBC* white blood cell, *hs-CRP* high sensitive C-reactive protein, *ESR* erythrocyte sedimentation rate

Significant statistical comparisons:

Controls versus total patients (* $p < 0.05$) by unpaired *t* test

Controls versus total patients and Controls *vs* subgroups (● $p < 0.05$) by Kruskal–Wallis and Mann–Whitney *U* tests

Controls versus patients' subgroups (■ $p < 0.05$) by post-ANOVA test

Discussion

Psoriasis is a common skin disorder of which the main pathology is chronic inflammation [5, 35], however, the factors leading to inflammation are still being investigated and not fully understood. Inflammation is commonly attributed to the activation of circulating neutrophils and monocytes. The previous studies reported higher WBC counts [7, 20, 29], neutrophils [7, 25, 29], and monocytes [7]. In the present study, the number of WBC, neutrophils

Table 3 Oxidation parameters in the study groups

Parameters	Control (*n* 14)	Psoriasis patients		
		Total (*n* 29)	(PASI ≤ 10) (*n* 14)	(PASI > 10) (*n* 15)
MPO (U/L)	86.5 ± 24.9	207.1 ± 69.7*	198.6 ± 78.0■	215.1 ± 62.4■
Neopterin (nmol/L)	3.96 ± 0.89	7.61 ± 2.02*	8.16 ± 2.09■	7.11 ± 1.89■
AOPP (µmol/L)	36.1 ± 13.2	62.4 ± 20.6*	59.1 ± 17.4■	65.4 ± 20.6■
Total LHP (µmol/L)	14.3 ± 4. 9	30.5 ± 9.3*	32.6 ± 8.3■	28.4 ± 10.1■
PP (nmol/mg protein)	1.38 ± 0.38	2.33 ± 0.65*	2.19 ± 0.62■	2.46 ± 0.67■
PCC (nmol/mg protein)	0.99 ± 0.29	1.54 ± 0.43*	1.52 ± 0.46■	1.56 ± 0.42■
Thiol (µmol/L)	354 ± 54	208 ± 63*	195 ± 55■	220 ± 69■

Data were presented as mean ± SD

n number of volunteers, *MPO* myeloperoxidase, *AOPP* advanced oxidation protein products, *LHP* lipid hydroperoxides, *PP* pyrrolized protein, *PCC* protein carbonyl compounds

Significant statistical comparisons

Controls versus total patients (* $p < 0.05$) by unpaired *t* test

Controls versus patient' subgroups (■ $p < 0.05$) by post-ANOVA test

and monocytes were higher in psoriasis patients, regardless of the disease severity. Likewise, the findings of high CRP [7, 29] and ESR [20, 25, 29], possess great importance in terms of pointing out the chronic inflammatory nature of psoriasis. CRP [7, 29] and ESR [29] were also found to be increased with the severity of the disease, however, Ferretti et al. [13] reported similar CRP levels in total, mild, and severe patients, in accordance with the present study. These findings could indicate the presence of inflammation, even in patients with mild psoriasis.

Increased ROS production in neutrophils, keratinocytes, and dermal fibroblasts has been reported among the key factors of the inflammatory mechanism in psoriatics [5]. Psoriasis has also been suggested as an inflammatory condition in which mainly neutrophils seem to play a crucial role, and contributing to the development of oxidative and proteolytic stress [29]. The degranulation of activated neutrophils and the release of cytokines and neutral proteases appear to be important in the inflammatory response as well as in tissue damage in psoriasis. Indeed, higher circulating elastase [7, 25, 29], and increased NADPH oxidase activity as well as ROS production in WBC [3] were reported in psoriatics. Therefore, the activated neutrophils/monocytes may be the main sources of oxidative stress in psoriasis.

MPO is a pro-oxidative and pro-inflammatory enzyme; 95 % of circulating MPO is derived from neutrophils, to a lesser extent from monocytes [6, 10]. MPO, released during the respiratory burst, reacts with H_2O_2 and Cl^- ions to generate HOCl, with a greater toxicity. Inappropriate stimulation of oxidant formation by MPO (wrong place, wrong time, or excessive levels) may result in tissue damage [10]. An increase of MPO has been shown in skin tissues on a psoriatic mouse model [2], and in lesional psoriatic skin [6]. Although no significant change in circulating MPO was reported [12, 21], Cao et al. [6] have also first shown the increase in blood MPO; and suggested the contribution of lesional skin $CD11b^+$ leukocytes to circulating MPO levels. In the current literature, this study is the second report revealing the increased plasma MPO activity in psoriatics. One of the possible explanations may be the presence of activated neutrophils/monocytes generating oxidative damage in psoriatics. Monocyte activation in this study was also proved by higher neopterin levels, an early inflammation marker [16], as in the previous studies [18, 31]. Plasma neopterin has been demonstrated to be originated from sites of inflammation where HOCl is being released [16]. Thus, elevated neopterin levels might reflect the extent of oxidative stress in psoriasis.

Since HOCl has a relatively short half-life to be measured, specific products of HOCl may provide biomarkers of the activated neutrophils and monocytes. AOPP, first detected in the uremic plasma [36], may be a significant marker for monitoring phagocyte-mediated oxidative damage in psoriasis. AOPP, derived from plasma proteins, especially albumin, fibrinogen and lipoproteins, are defined as dityrosine-containing cross-linked products, and are considered to be reliable markers to estimate the degree of protein modifications [26, 36]. In addition, due to the structural similarity between AOPP and advanced glycation end products (AGE)-proteins, both have been shown to exert similar biological effects, and to accumulate in biological systems leading to similar clinical results [26].

This is the first study in the current literature revealing a significant increase in plasma AOPP of the psoriasis patients. However, AGE-peptides and carboxymethyl-/carboxyethyl-lysine antibodies [9], as well as protein adducts of methylglyoxal, an AGE precursor [22], were higher, and explained

as the indication for increased oxidative stress in psoriasis [9]. Higher AOPP, MPO and neopterin levels in the present study may be interpreted as the potential role of AOPP in the spread of inflammation, and also the oxidation of proteins due to glycosylation or neutrophil/monocyte-derived reactions in vivo.

PCC, the mostly accepted general biomarker of oxidative protein damage [8, 10], is considered to be a reliable marker regarding its occurrence in relatively early stage, and greater stability, and longer half-life in circulation [8]. Higher PCC was observed in the fibroblasts [11] as well as lesional [11, 19] and non-lesional [11] psoriatic tissue samples; and refer to the occurrence of oxidative damage prior to the appearance of typical psoriatic plaques [11]. In the current literature, there is only one study demonstrating higher plasma PCC levels in psoriatics [3], in accordance with the present study being the second report in the literature. Although PCC may occur via different mechanisms, HOCl has been shown to be the principal oxidant responsible for in vitro PCC formation [15]. Therefore, PCC formation will be inevitable under the conditions which generated HOCl as the main source of ROS.

Another example of in vivo protein oxidation is the formation of PP [14, 23, 34]. LHP, MDA, or HNE are capable of producing modified proteins, containing oxidized lipid/amino acid reaction products (OLAARPs), including pyrroles [34]. In the presence of proteins, OLAARP formation is accepted as an ultimate step in the lipid peroxidation, [14, 34]. Since the degree of pyrrolization associates with the number of ε-amino group of lysine residues, depending on the pyrrolization on plasma albumin [14]; PP has been suggested as a "plasma marker" of oxidative stress [14, 34]. In the present study, like that of AOPP, there is no study in the current literature, revealing higher serum PP levels in psoriatics. However, increased protein-bound pyrroles in plasma were detected in renal failure and atherosclerosis, these adducts were presented as the markers of disease-related oxidative injury [30]. Considering the above-mentioned etiology of these diseases, elevated PP levels may be an expected result in psoriasis patients.

The toxicity of lipid peroxidation has been attributed to the produced α, β-unsaturated or dicarbonylic aldehydes [8, 10]. LHP, the first primary stable product [24], may break down into reactive carbonyl-containing secondary products, resulting in the production of both OLAARPs as pyrroles [34] and PCC as AGE [28], with proteins. As in the present study, higher LHP was detected in psoriatics [1, 13, 22]. The co-existence of high LHP as well as PCC and PP in psoriatics may refer to the additional role of LHP in the enhanced protein oxidation.

Increased oxidative stress in psoriasis may also result from an insufficient antioxidant system. Thiols, derived from the cysteine-SH bound to proteins, especially albumin, are the most important member of the plasma antioxidant system [34]. It is well known that HOCl selectively chooses albumin as a target molecule [17], and in vitro thiol consumption with HOCl was found as high as 97 % [15]. Although there were many reports showing decreased [1, 3, 22, 29,] total antioxidant capacity in psoriatics, only two studies reported either unchanged [32], or lower [27] blood thiol in psoriatics in accordance with the present study. The decreased thiols may be ascribed to the thiol consumption through HOCl generated by neutrophils/monocytes. Consequently, low thiol levels in psoriasis indicate not only the deficiency in the antioxidant system, but also the presence of protein oxidation as well.

In conclusion, plasma protein oxidation in psoriatic patients, not only in moderate-to-severe but also in mild patients, may be explained by the findings of inflammation, phagocytic cell oxidation, and MPO–HOCl-oxidation reactions; as reflected by increased total/differential leucocytes counts, CRP, ESR as well as MPO, neopterin, AOPP, PCC, PP, LHP, and decreased thiol levels. Demonstrating the AOPP and PP formation for the first time, in our point of view, active neutrophils/monocytes may play an important role in the pathogenesis of psoriasis, and oxidants of neutrophil/monocyte origin may lead to oxidative stress, especially by protein oxidation.

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Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

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