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Running title: Role of **myeloperoxidase in psoriatic children**

ABSTRACT

Background: Psoriasis, a chronic inflammatory skin disease, is associated with oxidative stress of serum lipoproteins.

Objectives: In psoriatic children we evaluated the activity and levels of myeloperoxidase, the activity of paraoxonase-1 (PON1) and biochemical markers of lipid peroxidation, to investigate wether an unbalance between oxidant-antioxidants occurs very early in psoriasis.

Materials and Methods: A total of 52 patients affected by psoriasis and 48sex-age matched healthy controls were enrolled. Serum MPO levels were measured using ELISA method. MPO and PON1 activities (paraoxonase, arylesterase and lactonase) were evaluated by spectroscopic methods.

Results: Our results demonstrated a significant increase of MPO levels and activity in psoriatic subjects. PON1 activities were found to be significantly decreased. A positive correlation has been established between the MPO/PON1 ratio and levels of lipid peroxides in all psoriatic patients.

Conclusions: These results suggest that an unbalance between MPO and PON1 can reflect in higher oxidative stress in serum lipoproteins.

KEY WORDS

Myeloperoxidase, paraoxonase-1, high density lipoproteins,pediatric psoriasis, lipid peroxidation.

INTRODUCTION

Psoriasis (PS) is a chronic inflammatory skin disease characterized by increased keratinocyte proliferation and alterations in dermal and epidermal T-cells, monocytes-macrophages and neutrophils [1]. Increased cardiovascular and metabolic co-morbidity [2,3] related to alterations of plasma lipoprotein levels and composition has been described [4-8]. A relationship between psoriasisand oxidative stress has also been demonstrated with higher levels of biochemical markers of plasma lipid and protein oxidation[4,9-11], including higher levels of lipid peroxidation markers in very low density and low density lipoproteins in adult patients with a history of disease that lasts for years [12]. High titers of autoantibodies against oxidized low density lipoproteins (ox-LDL) confirm that *in vivo* oxidation of LDL occurs in plasma of psoriatic patients [13]. Furthermore, an accumulation of ox-LDL has been detected in the upper epidermis of the involved skin from psoriatic patients by direct immune-fluorescent method [14]. Compositional and functional alterations of high density lipoproteins (HDL) have also been studied in psoriasis and recently reviewed [15-18]. A decrease of cholesterol efflux from macrophages, higher levels of lipid hydroperoxides and a decrease of the anti-inflammatory and antioxidant properties has been reported in HDL from adult psoriatic patients [16,18].In detail, the activity of paraoxonase 1 (PON1), a multitasking enzyme associated to HDL [19], is significantly lower in adult PS patients and a relationship with disease activity has been observed [11, 20].

The study of the molecular mechanisms that could trigger oxidative damage to lipoproteins *in vivo*in psoriasis has not been previously investigated. A role of the enzyme myeloperoxidase (MPO) in oxidative damage of plasma lipoproteins has been recently reported in atherosclerosis and inflammatory diseases[21]. Myeloperoxidase (MPO), secreted by activated monocytes, is a pro-oxidative and pro-inflammatory hemeprotein [22], which catalyzes the conversion of chloride and hydrogen peroxide to hypochlorite [22]. MPO generates other reactive oxygen species such as hydroxyl radical and singlet oxygenand cross-links proteins [21]. ROS generated by activated monocytes oxidatively modify LDL and HDL *in vitro*[22]. Previous studieshave suggested that the ratio between serum levels of myeloperoxidase and paraoxonase 1 activity could be a potential indicator of dysfunctional high-density lipoprotein [23]. We studied MPO levels and activity, PON1 activity and biochemical markers of lipid peroxidation in pediatric patients to investigate whether an unbalance between oxidant-antioxidants occurs very early in psoriasis.

MATERIALS AND METHODS

Subjects

52 psoriaticchildren (29/23 F/M mean age 9.8 ± 3.7)affected by psoriasis were included through consecutive recruitment from new referrals and follow-up visits at the Clinic of Dermatology ofthe Department of Clinical and Molecular Sciences of the Polytechnic University of Marche.

Inclusion criteria for pediatric patients were: a confident clinical diagnosis of psoriasis, age between 0–14 years and onset of disease within the past 12 months. Only scalp involvement or diaper rash was not regarded as sufficient for diagnosis. Diaper rash psoriasis was not included because of the difficulty in separating psoriatic diaper rash from other diaper rashes. None among the patients showed any clinical sign, or reported a history of psoriatic arthritis. Subjects with diabetes, clinical evidence of cardiovascular diseases, or receiving lipid-lowering drugs or antioxidant supplements were excluded from the study to avoid possible interferences on PON1 activity and plasma lipids. All selected subjects had avoided UVBnb, UVBbb, UVA or PUVA treatments and direct sun exposure for almost four weeks. Disease severity was quantified by the Psoriasis Area and Severity Index (PASI) (Table 1).

48 pediatric subjects (25/23 F/M mean age, 10.3± 2.7 years) ,age and sex matched ,without skin or systemic inflammatory disease (e.g. with nevi, molluscum contagiosum, warts) and without a family history of psoriasis or psoriatic arthritis were also recruited

Both controls and PS patients have comparable body mass index (BMI) (21.8 for control vs 22.5 for patients). All the procedures were in accordance with the Helsinki Declaration of 1975, as revised in 2000.The study was approved by “Ethics Committee, OspedaliRiuniti di Ancona”. Written informed consent for participation in the study was obtained from each patient’s parent with the approval of the attending physician.

Sample collection

Blood samples of controls and PS patients were collected at 8 a.m., after overnight fasting. Venous blood (about 10 ml) was placed in two tubes. An aliquot was incubated with heparin and plasma was separated by low speed centrifugation (3000 rpm) at 4°C for 20 min. Another aliquot was used for serum separation. A glass centrifuge tube containing blood (about 5 ml) without anticoagulant was left at room temperature for 30 min to allow formation of the clot, which was immediately removed. The tubes were centrifuged in a tabletop centrifuge for 10 min at a rotation speed of 2000 rpm. Both plasma and serum samples were divided in aliquots and stored immediately at −80°C.

Plasma lipid profile

Fasting levels of total cholesterol (TC), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C) and triglycerides (TG) were measured in plasma of controls and PS patients using commercially available kits (Roche Diagnostics, Switzerland).

Serum lipid peroxidation

The levels of lipid hydroperoxides were determined in serum of controls and psoriatic patients using FOX2 assay as previously described [11]. The levels of lipid hydroperoxides were quantified using a stock solution of t-butyl hydroperoxide. The results are shown as μmol of lipid hydroperoxides for L of serum.

Serum Total Antioxidant capacity

Serum total antioxidant capacity was assessed using the oxygen radical absorbance capacity (ORAC) assay [24].The oxygen radical absorbance capacity of serum employs the oxidative loss of intrinsic fluorescence of fluorescein induced by the free radical initiator 2,2'-azobis(2-amidinopropane)hydrochloride. Fluorescein fluorescence decay shows a lag or retardation in the presence of antioxidants, related to the antioxidant capacity of the sample. Trolox was used as a reference antioxidant for calculating the ORAC values. Results were expressed as μmol Trolox equivalents /L (μmol TE/L).

Serum PON1 Activities

PON1 activities were evaluated in serum of controls and psoriatic patientsusing three substrates [25] paraoxon for paraoxonase activity, phenylacetate for arylesterase activity and dihydrocoumarin for lactonase. All assays were performed in a 96 well plate, in a total reaction volume of 200 μL. *Paraoxonase Activity.* 10 μL of serum (non-diluted samples) were used. The basal assay mixture included 5mmol/L Tris-HCl, pH 7.4 containing 1 mmol/L $CaCl_2$ and 1.0 mmol/L paraoxon. Paraoxon hydrolysis was spectrophotometrically monitored for 8 min (every 15 s) at 412 nm. Non-enzymatic hydrolysis of paraoxon was subtracted from the total rate of hydrolysis. One unit of PON1 paraoxonase activity was equivalent to 1 nmol of paraoxon hydrolyzed/ min/ mL .

Arylesterase Activity. Serum samples were diluted 1:10 with 1 mmol/L $CaCl_2$ in 50 mmol/L Tris HCl, pH 8.0 and then, 5 μL was taken for a total reaction volume of 200 μL. After addition of the substrate phenyl acetate (1 mmol/L), the hydrolysis was monitored at 270 nm for 3 min (every 15 s). One unit of arylesterase activity was equivalent to 1 μmol of phenyl acetate hydrolyzed/min/mL.

Lactonase Activity. Serum samples were diluted 1:10 with 1 mmol/L $CaCl_2$ in 50 mmol/L Tris HCl, pH 8.0 and 3 µL were then taken for the assay. After addition of the substrate dihydrocoumarin (DHC) (1.0 mmol/L), the hydrolysis was monitored at 270 nm for 10 min (every 15 s). Non enzymatic hydrolysis of DHC was subtracted from the total rate of hydrolysis. One unit of lactonase activity was equivalent to 1 µmol of DHC hydrolyzed/min/mL.

All assays were performed in a 96 well plate, in a total reaction volume of 200 µL.

Myeloperoxidase levels and activity

Serum MPO levels were measured using a solid phase two-site MPO ELISA Kit from Mercodia (Uppsala, Sweden) according to instructions provided by the manufacturer (26).

MPO activity was evaluated by a colorimetric Activity Assay Kit (Sigma-Aldrich).

Statistical analysis

The results are reported as mean ± standard error (SE). For the comparison of normally distributed variables between groups, Student's t-test was used. Paraoxonase activity showed a non gaussian distribution; therefore we used a non-parametric test (Wilcoxon rank sum test). Pearson correlation coefficients and their significance levels were calculated for linear regression analysis. Differences were considered statistically significant at $p<0.05$ (Microcal Origin 5.0, OriginLab, Northampton, MA).

RESULTS

As shown in the table 1, plasma levels of total cholesterol, HDL-C, LDL-C were not significantly modified in paediatric patients compared to controls.

Lipid peroxides and total antioxidant capacity

Higher levels of lipid hydroperoxides (Table 2) and lower values of total antioxidant capacity were observed in serum of patients compared to sex-age matched healthy control children. The differences were statistically significant.

Activity of PON1 and levels of MPO

As reported in Table 2, lower activities of PON1 (paraoxonase, arylesterase and lactonase) were observed in sserum of patients compared to control subjects ($p<0.05$). In the same patients, a

significant increase of serum levels and activity ofmyeloperoxidase (MPO) was found in PS children ($p<0.05$,Table 2).The comparison of the ratio between serum MPO level /PON1 paraoxonase activity (MPO/PON1 ratio) showed higher levels in patients compared to controls ($p<0.05$, Table 2). In all groups of subjects, levels of serum PON1 paraoxonase activitywere negatively correlated with serum MPO concentration (Table 3). Furthermore a significant positive correlation was established between serum levels of lipid hydroperoxides and MPO/PON1 ratio (Table 3).

DISCUSSION

Higher levels of biomarkers of lipid peroxidation, lower total antioxidant capacity and lower PON1 activities in serum of psoriatic children have been demonstrated. The lower activity of PON1 is in good agreement with other studies in adult subjects [11,15, 20]. Our results, in absence of significant changes of plasma lipids, suggest that oxidative stress and an unbalance between oxidant-antioxidants occurs very early in psoriatic children.

Our study, for the first time, demonstrates also a significant increase in serum MPO levels and activity in psoriatic children and PON1 activity was negatively correlated with MPO levels. A higher ratio MPO/PON1 was observed in serum of pediatric patients compared to controls. Moreover a positive correlation has been established between the MPO/PON1 ratio and levels of lipid peroxides in all psoriatic patients. These results suggest that an unbalance between MPO and PON1 can reflect in higher oxidative stress in serum lipoproteins. All psoriatic children included in our study had a mild form of the disease. No correlation has been established between PASI scores and biochemical indexes of lipid peroxidation or PON1 activities in psoriatic children. In adult patients a negative correlation between PON1 activity and PASI score has been reported in subjects with PASI values ranging from moderate to severe disease by other authors [26-28]. However, other studies did not find significant relationship between PON1 activities and severity of the disease [29]. These results are likely related to disease duration ranging from few months to several years.

Some hypotheses can be formulated to explain the potential molecular mechanisms involved in the alterations of PON1 activities in psoriatic children. We suggest that the higher MPO levels and activity could contribute to alterations of HDL and paraoxonase. This hypothesis is supported by previous studies which have demonstrated that among molecular mechanism able to trigger lipid peroxidation of lipoproteins, an emerging role is reserved to the enzyme MPO [21-23]. High MPO levels and/or activity have recently been demonstrated in a psoriatic animal model [30]. Moreover

in adult human subjects psoriatic lesions are characterized by a focal dense infiltration of neutrophils, T lymphocytes and macrophages that migrate from the vascular to the dermal compartment and through all layers of the epidermis up to the stratum corneum [31]. Furthermore Dylek et al [32] have recently demonstrated that neutrophils in psoriasis lesions are actively producing MPO [32]. *In vitro* studies confirm that MPO and reactive oxygen species generated by neutrophils trigger lipid peroxidation of LDL and HDL [22]. In particular MPO mediates modifications of apoAI with formation of chlorotyrosine and nitrotyrosine from tyrosine residues [33-35]. Other mechanisms could be involved. A considerable number of inflammatory cytokines have been shown to be elevated in lesional psoriasis skin in adult subjects [36]. Previous studies have shown that inflammation in both humans and rabbits leads to the loss of PON1 activity and a decreased ability to protect LDL against oxidation [19]. TNF and IL-1 leads to a decrease in PON1 mRNA levels in liver and a decrease in serum PON1 activity [37].

In conclusion, our data demonstrate that psoriasis in pediatric patients, is associated with higher levels of MPO, oxidative damage of plasma lipids and lipoproteins, a decrease in antioxidant defensesand a significant decrease of PON1.The higher ratio MPO/ PON1 suggests dysfunctional high-density lipoprotein in psoriatic pediatric patients. HDL has a number of important functions (anti-oxidant, anithrombotic) that could reduce the risk of CVD and which may be adversely impacted by inflammation [38]. As aforementioned, PON1 is a multitasking protein localized at the HDL surface and is associated with protection against oxidative stress- related diseases [19, 39], in fact it exerts a protective role against lipid peroxidation of biological membranes, HDL and LDL [19, 39, 40]. We suggest that whenever the activity of the antioxidant enzyme PON1 is lowered, it will be unable to prevent oxidation of membranes and LDL and coud be involved in the higher oxidative stress in psoriasis.

Figure 1 summarizes our hypothesis of the potential role of MPO and PON1 in inflammation and lipid peroxidation in psoriasis. The relationship between psoriasis, oxidative stress,inflammation and alteration of lipoprotein functions is supported by previous studies, which have demonstrated that drug treatments decrease inflammation, lipid peroxidation and recover HDL functions in psoriatic adult patients [17, 20]. It as to be stressed that modifications of HDL composition, PON1 activity and MPO levels realize early in pediatric patients, even in absence of modification of plasma lipids

Although further studies are necessary to evaluate whether the lower PON1 activities are primary events or a consequence of abnormal metabolism of inflamed skin in pediatric patients, we suggest

that an intensive multidisciplinary lifestyle intervention on inflammatory biomarkers could positively affect risk factors for cardiovascular disease in psoriatic children.

Financial support: NONE.
Conflict of Interest. NONE.

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FIGURE LEGEND

Figure 1. Schematic representation of potential molecular mechanisms involved in lipid peroxidation, lipoprotein dysfunction and alterations in inflamed skin in psoriasis .

(1) The higher production of superoxide anion and MPO from activated PMN contributes to lipid peroxidation of LDL and HDL.
(2) MPO catalyzes the conversion of chloride and hydrogen peroxide to hypochlorite, a strong reactive oxygen species (ROS).
(3) Oxidized LDL (ox-LDL) and oxidized HDL (ox-HDL) show compositional and functional alterations. In particular ox-LDL exert pro-inflammatory properties and activate migration and degranulation of PMN. Ox-HDL have lower PON1 activity and exibit lower antioxidant and anti-inflammatory activity.

Table 1: Clinical characteristics and plasma parameters in controls and subjects affected by psoriasis. TG, triglycerides; TC, total cholesterol; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol

	Healthy subjects	**PsoriaticPatients**
Age (years)	9.8 ± 3.7	10.3± 2.7 years
Fastingglucose (mg/dL)	81.1±7.7	73.4±15.8
TG (mg/dL)	74.3±18.4	75.2±31.0
TC (mg/dL)	165.9±26.7	158.2±25.5
HDL-C(mg/dL)	51.6±7.3	49.21±6.5
LDL-C (mg/dL)	89.9±20.9	90.1±24.1
BMI	21.8±3.5	22.7±3.1
PASI	-	9.8± 4.3

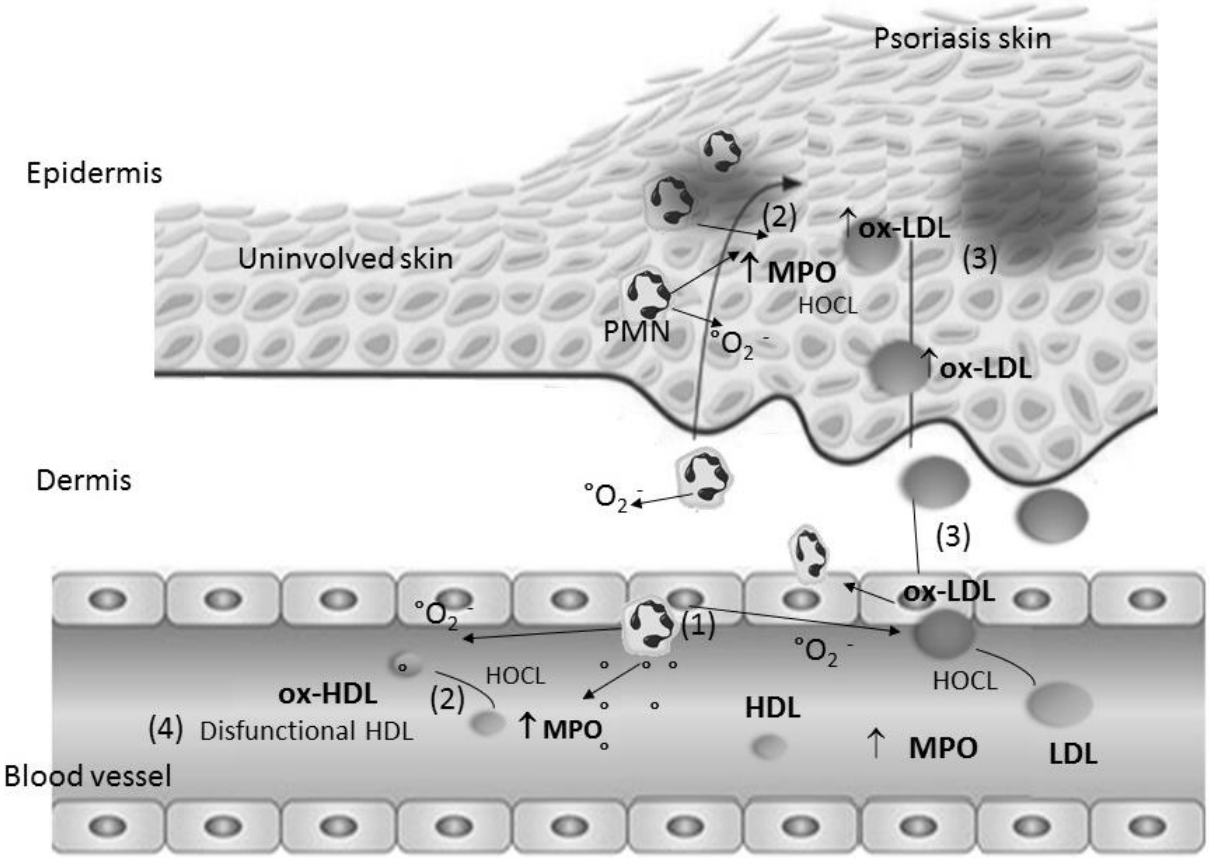
Table 2: PON1 activities (paraoxonase, arylesterase, lactonase) , MPO activity and levels in controls and psoriatic patients *p<0.05 vs healthy subjects

	Healthy subjects	**Psoriatic patients**
Lipid hydroperoxides (µmol/L)	2.56 ± 0.7	5.2 ± 1.4*
Total antioxidant capacity (mmol TE /L)	13.2 ± 1.9	8.78 ± 4.1*
PON-1 – paraoxonase (U/mL)	211.1 ± 13.9	94.7±9.6*
PON-1 – arylesterase (U/mL)	76.3± 2.6	51.2±3.0*
PON1 –lactonase (U/mL	27.2± 1.4	18.3±1.5*
MPO levels (ng/mL)	101.8±12.3	149.6±14.8*
MPO activity	9± 3	14± 2*
MPO /PON1 (paraoxonase) ratio	0.7± 0.09	1.85± 0.31*

Table 3 : Correlations between PON1 paraoxonase activity and MPO levels and between MPO/ PON1 ratio and lipid hydroperoxide levels in serum of control subjects and of patients affected by psoriasis.

	Healthy subjects	**Psoriaticpatients**
PON1 activity *vs* MPO levels	r= -0.64,p<0.004	r= -0.57, p<0.01
MPO/ PON1 ratio *vs* lipid hydroperoxides	r=0.46, p<0.03	r=0.69, p<0.006

Figure 1


Psoriasis skin
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