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Dislipidemia and oxidative stress in mild and in severe psoriasis as a risk for cardiovascular disease

Petronila Rocha-Pereira[a,b,*], Alice Santos-Silva[c,d], Irene Rebelo[c,d], Américo Figueiredo[e], Alexandre Quintanilha[d,f], Frederico Teixeira[b]

[a]*Departamento de Química da Universidade da Beira Interior, Rua Marquês d'Ávila e Bolama, 6200 Covilhã, Portugal*
[b]*Instituto de Farmacologia e Terapêutica Experimental da Faculdade de Medicina da Universidade de Coimbra, Coimbra, Portugal*
[c]*Departamento de Bioquímica da Faculdade de Farmácia da Universidade do Porto, Porto, Portugal*
[d]*Instituto de Biologia Molecular e Celular da Universidade do Porto, Porto, Portugal*
[e]*Serviço de Dermatologia do Hospital da Universidade de Coimbra, Coimbra, Portugal*
[f]*Departamento de Biologia Molecular do Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto, Porto, Portugal*

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Abstract

Psoriasis is a common chronic and recurrent inflammatory skin disorder that has been associated with oxidative stress, abnormal plasma lipid metabolism and with high frequency of cardiovascular events. 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. The aim of our work was to evaluate the development of oxidative stress and of dislipidemia in psoriasis, and to look for a correlation between their levels and worsening of psoriasis. We evaluated lipid profile, total antioxidant capacity, antioxidant vitamins A and E, and lipoperoxidation products. The study was performed in controls and in patients presenting mild and severe psoriasis. Patients presented risk changes in lipid profile (a rise in cholesterol ($P<0.01$), triglycerides ($P<0.001$), low density lipoprotein cholesterol ($P<0.01$), very low density lipoprotein cholesterol ($P<0.01$), apolipoprotein B ($P<0.001$) and lipoprotein(a) ($P<0.001$); and a reduction in high density lipoprotein cholesterol ($P<0.001$)), a rise in lipoperoxidation products ($P<0.001$) and a reduction in total antioxidant capacity ($P<0.001$) and in antioxidant vitamins A ($P<0.001$) and E ($P<0.05$). Moreover, we found that the worsening of psoriasis was associated with the enhancement of oxidative stress and of the lipid risk changes. Our data suggest that psoriasis patients must be considered as a group at risk for cardiovascular disease and that this risk seems to be higher in severe psoriasis. In addition, a possible benefit of an enriched diet or of a supplement of vitamins A and E in psoriasis patients should be further studied.

Keywords: Psoriasis; Risk factors; Cardiovascular disease; Oxidants; Antioxidants; Serum lipids

1. Introduction

Patients at risk for cardiovascular events often present hypertension and an abnormal lipid profile, namely hypercholesterolemia, hypertriglyceridemia, high lipoprotein (a), low density lipoprotein cholesterol and apolipoprotein B concentration, low high density lipoprotein cholesterol and apolipoprotein AI concentration. A rise in leukocytes has been also reported, suggesting that leukocytes play an im-

*Corresponding author. Tel.: +351-275-319-700; fax: +351-275-319-730/327-972.
E-mail address: petrorp@ciunix.ubi.pt: petronilarp@hotmail.com (P. Rocha-Pereira).

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portant role in the pathophysiology of cardiovascular diseases (CVD) [1,2]. Activated white blood cells (WBC) are known as important sources of oxygen metabolites and proteases that may impose oxidative changes to blood cells and to plasma constituents. According to the oxidative modification hypothesis for atherogenesis, oxygen metabolites contribute to the progression of the atherosclerotic process by modifying oxidatively low density lipoprotein cholesterol.

Increased production of oxygen metabolites is a common feature of most human diseases [3,4], including CVD and psoriasis, and usually triggers an up-regulation of the antioxidant defences. However, when the antioxidant capacity is overwhelmed an oxidative stress develops leading to oxidative damage of lipids and proteins.

Psoriasis is a common chronic and recurrent inflammatory skin disorder that has been associated with abnormal plasma lipid metabolism and with high frequency of cardiovascular events. This prevalence of cardiovascular events seems to be related to the severity of psoriasis, considering that it occurs much more frequently in patients presenting large areas of the body affected with psoriasis lesions [5].

The clinically active psoriasis lesions reveal infiltration of WBC, and several studies report high levels of WBC activation products in the peripheral blood of these patients [6,7]. Therefore, psoriasis patients may present, side by side with an abnormal lipid profile, a depletion in antioxidant defences, a rise in lipid peroxidation (LPO) and an imbalance of oxidants/antioxidants. These changes are all known as risk factors for cardiovascular events.

The aim of our work was to evaluate the lipid profile, the total antioxidant capacity as well as some plasma antioxidants, and the total plasma lipoperoxidation products in a healthy control and in a group of psoriasis patients. In addition, looking for a correlation between the severity of psoriasis lesions and an increased risk for cardiovascular events, we selected for the psoriasis group half of the patients with active psoriasis (more than 10% of the body area covered by lesions) and the other half with inactive psoriasis (less than 10% of the body area covered by lesions).

The study of the lipid profile included the evaluation of total cholesterol (Chol), triglycerides (TG), high density lipoprotein cholesterol (HDLc), low density lipoprotein cholesterol (LDLc), very low density lipoprotein cholesterol (VLDLc), apolipoprotein AI (Apo AI), apolipoprotein B (Apo B) and lipoprotein (a) (Lp(a)). To study the oxidant/antioxidant balance we evaluated total plasma antioxidant capacity and total plasma lipoperoxidation products. We also studied as plasma antioxidants the levels of vitamin A and vitamin E.

2. Materials and methods

2.1. Subjects

The protocol used for patients and controls was approved by the Committee on Ethics of the University Hospital of Coimbra. Patients and controls included 88 males and females presenting similar ages. The control group included 40 apparently healthy individuals (55% males and 45% females), aged 47 ± 13 years, with normal hematological and biochemical values, and with normal lipid profile. The pathological group included 48 individuals (62% males and 38% females), aged 47 ± 12 years, 24 presenting active psoriasis, and 24 presenting inactive psoriasis, with diagnosed psoriasis from 2 to 50 years before this study. Psoriasis disease was graded according to the area of the psoriasis lesions. Half of the patients presented severe psoriasis or active psoriasis (AP), in whom more than 10% of the body area was covered by psoriasis lesions, and the other half of the patients presented mild psoriasis or inactive psoriasis (IP), with less than 10% of the body area covered by psoriasis lesions. The body mass index and the ages were similar for both groups of patients and controls.

To assess the changes imposed by psoriasis per se, none of the patients had received any systemic or local steroid medication or any phototherapy treatment for at least 1 month prior to blood collection; none of them had any history of cardiovascular events and none of them presented *diabetes mellitus*, a condition that is usually associated with increased plasma lipid levels. In addition, the controls, as well as the patients, were not receiving any kind of medication, namely antioxidants or vitamins. None of the studied groups were under any dietary restriction.

2.2. Collection and preparation of blood samples

Blood samples were collected from the subjects, fasted for 12 h, with and without anticoagulant (heparin), and centrifuged to obtain plasma and serum, respectively. The recovered serum and plasma were sequentially analysed. To evaluate vitamin A and E light-protected tubes were used to collect and store the samples. None of the collected samples was icteric or hemolysed.

2.3. Assays

2.3.1. Lipid profile

Serum was used to study the lipid profile. Total Chol and TG concentrations were measured enzymatically using commercially available kits (CHOD-PAP and GPO-PAP, Boehringer, respectively) on an auto-analyser (Hitachi-704-Boeheringer Mannheim). HDLc was measured (using the method referred for total Chol) after precipitation of the lipoproteins that contained Apo B (LDL, VLDL and Lp(a)) by a phosphotungstic acid magnesium chloride mixture. LDLc was computed by Friedwald's formula: LDLc=total Chol−(HDLc+TG/5). VLDLc was calculated by the formula: VLDLc= TG/5 [8]. Apo AI and Apo B were measured by immunonephelometry (Kallestad QM300, Sanofi-Pasteur). Lp(a) was evaluated by an immunoturbidimetric assay (Tina-quant, Boehringer Mannheim).

2.3.2. Oxidative stress

The serum samples to measure vitamins A and E were stored frozen at −20°C in closed light-protected tubes for no more than 24 h after collection and handled light protected. None of the serum samples analysed was icteric or even hemolysed. Vitamin A and E serum levels were evaluated by high performance liquid chromatography (HPLC), using a commercially available kit (Vitamin A/E by HPLC reagent kit, Bio-Rad Lab. GMBH). Serum was mixed with an internal standard. Two phases were developed after the addition of ammonium sulphate solution and subsequent centrifugation (10 000×g/3 min). The upper phase was used immediately for HPLC analysis in an isocratic system. The samples were separated on a Reversed Phase Column with UV-detection and subsequent quantitative determination with the help of an internal standard (Sanofi Pasteur HP 1100).

Total plasma antioxidant capacity was evaluated by a colorimetric assay (TAS, Randox Laboratories, UK). Lipid peroxidation was estimated by thiobarbituric acid reactivity (TBA assay) [9].

2.4. Statistical analysis

The statistical analysis was performed using the SPSS package. To evaluate the differences between groups, we used the Student's t-test for the determinations presenting a gaussian distribution, and the Mann–Whitney test for those presenting a non-gaussian distribution. A P-value lower than 0.05 was considered statistically significant. The measurements are expressed as mean±standard deviation (S.D.).

3. Results

We analysed the obtained results in two ways, on the one hand to study the differences between healthy control and psoriasis patients, and on the other to evaluate the changes in the same studied parameters according to the activity of the disease (mild and severe psoriasis).

Table 1 presents the lipid profile found for control group, for total psoriasis patients (IP+AP) and for IP patients and AP patients. When compared to the control group we found that total psoriasis patients (IP+AP) presented significantly higher values for Chol ($P<0.01$), TG ($P<0.001$), LDLc ($P<0.01$), VLDLc ($P<0.01$), Apo AI ($P<0.01$), Apo B ($P<0.001$), Lp(a) ($P<0.001$) and for the ratio LDLc/Chol ($P<0.05$); significantly lower values were found for HDLc ($P<0.001$) and for the ratio HDLc/Chol ($P<0.001$).

When comparing the values presented by IP patients with those presented by the control group we found significantly higher values of Apo B ($P<0.01$) and Lp(a) ($P<0.001$); significantly lower values of HDLc ($P<0.05$). No significant differences were found in the other studied lipid parameters; however, IP patients showed a trend to increases in Chol, TG,

Table 1
Lipid profile (mean value±S.D. for each parameter) for control and psoriasis patients[a]

	Control (n=40)	IP+AP (n=48)	P-value IP+AP vs. Control	IP (n=24)	P-value IP vs. Control	AP (n=24)	P-value AP vs. Control	P-value IP vs. AP
Chol (mg/dl)	199.8±27.7	220.4±43.7	<0.01	208.9±47.1	ns	231.8±37.6	<0.001	<0.05
TG (mg/dl)	92.5±27.3	121.0±49.3	<0.001	100.6±47.2	ns	141.3±43.3	<0.001	<0.001
HDLc (mg/dl)	49.9±3.2	45.3±5.7	<0.001	46.8±6.2	<0.05	43.7±4.8	<0.001	<0.05
LDLc (mg/dl)	130.9±25.2	152.2±42.2	<0.01	143.0±44.6	ns	161.4±38.5	<0.001	ns
VLDLc (mg/dl)	18.6±6.3	24.0±9.9	<0.01	20.9±9.7	ns	27.0±9.3	<0.001	<0.05
Apo AI (mg/dl)	142.2±32.9	160.2±23.5	<0.01	155.6±21.0	ns	164.8±25.3	<0.01	ns
Apo B (mg/dl)	113.2±21.5	133.8±27.5	<0.001	129.3±26.7	<0.01	138.2±28.1	<0.001	ns
Lp(a) (mg/dl)	31.7±18.1	63.7±40.1	<0.001	69.5±47.1	<0.001	57.9±31.6	<0.001	ns
HDLc/Chol	0.26±0.04	0.22±0.06	<0.001	0.24±0.08	ns	0.19±0.04	<0.001	<0.01
LDLc/Chol	0.65±0.05	0.68±0.07	<0.05	0.67±0.07	ns	0.69±0.06	<0.01	ns

[a] Inactive psoriasis — IP; active psoriasis — AP; ns — non-significant.

LDLc, VLDLc, Apo AI and in the ratio LDLc/Chol; a trend to decrease was found in the ratio HDLc/Chol.

In AP patients we found more pronounced changes, than those presented by IP patients, when compared to the control group. Moreover, all the values presented significant differences: significantly higher values for Chol ($P<0.001$), TG ($P<0.001$), LDLc ($P<0.001$), VLDLc ($P<0.001$), Apo AI ($P<0.01$), Apo B ($P<0.001$), Lp(a) ($P<0.001$) and for the ratio LDLc/Chol ($P<0.01$); significantly lower values for HDLc ($P<0.001$) and for the ratio HDLc/Chol ($P<0.001$).

We have also studied the values according to the activity of psoriasis, by comparing the values presented by IP patients to those observed in AP patients (Table 1). We found that AP patients presented higher values of Chol ($P<0.05$), TG ($P<0.001$), VLDLc ($P<0.05$); significantly lower values were observed in HDLc ($P<0.05$) and in the ratio HDLc/Chol ($P<0.01$). No significant differences were found in the other studied lipid parameters; however, AP patients showed a trend to increases in LDLc, Apo AI, Apo B, and in the ratio LDLc/Chol, and a trend to reductions in Lp(a).

In Table 2 we show the mean values of total plasma lipid peroxides (TBA), total plasma antioxidant status (TAS), the balance between them, and, as plasma antioxidants, the levels of vitamin A and vitamin E, for control group, for total psoriasis patients (IP+AP), and for IP patients and AP patients.

When compared with the control group we found for total psoriasis patients (IP+AP) significantly higher values for TBA ($P<0.001$), TBA/TAS ($P<0.001$), TBA/vit A ($P<0.001$) and for TBA/vit E

Table 2
Lipid peroxidation and antioxidant defences (mean value±S.D. for each parameter) for control and psoriasis patients[a]

	Control (n=40)	IP+AP (n=48)	P-value IP+AP vs. Control	IP (n=24)	P-value IP vs. Control	AP (n=24)	P-value AP vs. Control	P-value IP vs. AP
TBA($\times 10^{-3}$ mM)	1.85±0.41	6.17±1.21	<0.001	5.40±1.06	<0.001	6.95±0.77	<0.001	<0.001
TAS (mM)	1.6±0.18	1.41±0.28	<0.001	1.55±0.21	ns	1.26±0.28	<0.001	<0.001
vit A (μg/dl)	47.8±13.9	17.5±5.1	<0.001	16.5±4.5	<0.001	18.4±5.6	<0.001	ns
vit E (μg/ml)	14.6±3.8	13.4±2.5	<0.05	13.6±3.0	ns	13.1±1.9	<0.05	ns
TBA/TAS	1.18±0.31	4.66±1.65	<0.001	3.54±0.80	<0.001	5.77±1.52	<0.001	<0.001
TBA/vit A	0.042±0.02	0.38±0.15	<0.001	0.35±0.11	<0.001	0.42 ± 0.17	<0.001	<0.05
TBA/vit E	0.135±0.05	0.48±0.14	<0.001	0.42±0.15	<0.001	0.53± 0.10	<0.001	<0.01

[a] Inactive psoriasis — IP; active psoriasis — AP; ns — non-significant.

($P<0.001$); significantly lower values were found for TAS ($P<0.001$), vit A ($P<0.001$) and for vit E ($P<0.05$).

In IP patients we observed significantly higher values of TBA ($P<0.001$), TBA/TAS ($P<0.001$), TBA/vit A ($P<0.001$) and of TBA/vit E ($P<0.001$); significantly lower values were found for vit A ($P<0.001$); no significant differences were found for TAS and vit E, though the IP patients showed a trend towards a decrease in their values.

When comparing the values presented by AP patients with those presented by the control group, we found significantly different values for all the studied parameters. AP patients presented significantly higher values, when compared to controls, for TBA ($P<0.001$), TBA/TAS ($P<0.001$), TBA/vit A ($P<0.001$) and for TBA/vit E ($P<0.001$); significantly lower values were found for TAS ($P<0.001$), vit A ($P<0.001$) and for vit E ($P<0.05$).

We have also compared the values presented by IP patients to those presented by AP patients (Table 2) and we found significant differences between them for almost all the studied parameters. We observed that AP patients presented higher values of TBA ($P<0.001$), TBA/TAS ($P<0.001$), TBA/vit A ($P<0.05$) and of TBA/vit E ($P<0.01$). A lower value for TAS ($P<0.001$) was also found. We observed a trend to increase in vit A and a trend to decrease in vit E.

4. Discussion

Although there have been extensive studies of serum lipids and apolipoprotein levels in psoriasis, their importance in the etiology or in the enhancement of the disease remains controversial [5,10–12]. It is accepted that there is a genetic predisposition to develop the disease and that several conditions may trigger an enhancement of the disease, with enlargement of psoriasis lesions, such as infections, skin traumas, sunlight, oxidant drugs and stress conditions [13,14]. Psoriasis is also frequently associated with some diseases, namely cardiovascular diseases, *diabetes mellitus* and to rheumatoid arthritis. The role and the importance of these pathologies in the etiology of psoriasis, or in its enhancement, are still controversial. It is interesting to notice that these commonly associated pathologies are known as ''oxidative stress conditions''. Psoriasis as a clinically inflammatory skin disease may per se impose an oxidative stress condition. The activation of the inflammatory cells, resulting in increased leukocyte activation products in the peripheral blood of psoriasis patients, may favour atherogenesis by promoting LDL oxidation. In addition, it is reasonable that the up-regulation of the antioxidant systems, triggered by the continuous skin inflammatory process, may lead to a decrease in the antioxidant capacity. Therefore, we believe that if psoriasis leads to high levels of oxidants, resulting from leukocyte activation and to a reduced antioxidant capacity, then psoriasis may favour the atherogenic process. Actually, the incidence of cardiovascular diseases in human populations that have low plasma antioxidant levels appears to be high, suggesting an important role in the progression of atherosclerosis [15–18].

Cardiovascular events occur frequently in psoriasis patients, particularly in those patients with a severe pattern and long duration of the disease. Considering the importance of an altered lipid profile and the development of an oxidative stress condition in atherogenesis, we tried, by evaluating these parameters in mild and severe psoriasis, to look for a correlation between psoriasis and its severity, with a rise in risk factors for cardiovascular diseases and the development of an oxidative stress.

We found that psoriasis patients (IP+ AP) present a significantly different lipid profile (Table 1), and that all the observed changes in that profile, excepting for Apo AI, are considered as modifications of risk for cardiovascular diseases. Our results (Table 2) also suggest that psoriasis is associated with the development of an oxidative stress, since psoriasis patients (IP+AP) presented significantly higher values for TBA, which almost triplicates the value presented by the control group, and significantly lower values for TAS. A significant rise in TBA/TAS, TBA/vit A and TBA/vit E ratios shows the imbalance between oxidants and antioxidants.

The comparative study of the lipid profile and of the oxidative stress between control and each of the pathologic groups, mild (IP) and severe (AP) psoriasis (Tables 1 and 2), showed that some significant atherogenic risk modifications and an imbalance between oxidants and antioxidants are already observed in mild psoriasis, and that in severe psoriasis

all the studied parameters become significantly different, suggesting that the worsening of the disease is associated with the enhancement of the oxidative stress and of the atherogenic risk.

Looking for a premature predictive index of the development of a psoriatic crisis, we compared the values obtained in mild (IP) and in severe psoriasis (AP). Our results suggest that the enlargement of psoriatic lesions are associated with a rise in oxidative stress, as showed by the imbalance between oxidants and antioxidants, and to more pronounced risk modifications in lipid profile.

Considering that the previous data suggested that the enlargement of psoriasis lesions are associated with a significant reduction in the antioxidant capacity and, obviously, with a rise in lipoperoxidation products, we evaluated some natural liposoluble antioxidants vitamins, namely vitamins A and E. These vitamins, being supplied by diet, may allow the control of their plasma levels by an enriched diet or even by a therapeutic vitamin supplementation [19,20], though some controversy exists about the therapeutic benefit of antioxidant vitamin supplementation [21–23].

We found that psoriasis patients (IP+AP) presented reduced plasma levels of vitamin A and vitamin E (Table 2), suggesting that the up-regulation of the antioxidant systems in psoriasis may lead to their depletion. Mild and severe psoriasis presented similar values (Table 2), suggesting that psoriasis per se seems to be associated with reduced values in these vitamins.

In summary, our data suggest that psoriasis patients must be considered as a group at risk for cardiovascular disease, since psoriasis per se seems to be associated with risk changes in the lipid profile and to the development of oxidative stress, as shown by the imbalance oxidants/antioxidants, resulting from a rise in lipoperoxidation products and a reduction in antioxidant capacity. In addition, we suggest that a regular evaluation of the oxidative stress and of the lipid profile, could provide early predictive indexes of a psoriatic crisis. Moreover, we believe it would be important to study the possible benefit of an enriched diet or of a therapeutic supplementation of natural antioxidant vitamins A and E.

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