

Serum lipid metabolism in psoriasis and psoriatic arthritis – an update

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Abstract

Introduction: Psoriasis and psoriatic arthritis (PSA) are chronic, inflammatory, systemic diseases characterized by metabolic abnormalities, including an increased cardiovascular risk and an oxidative imbalance. This study assessed blood parameters of lipid metabolism and markers of oxidative stress in patients with psoriasis and PSA.

Material and methods: The study included 93 patients with psoriasis (31 patients with PSA and psoriasis, 62 patients with psoriasis vulgaris), and 60 healthy, age-matched controls. Serum concentrations of the glucose and the following lipid metabolism parameters were measured: triglycerides (TG), total cholesterol (TC), low-density lipoproteins (LDL), very low-density lipoproteins (VLDL), high-density lipoproteins (HDL), and apolipoproteins A and B (ApoA, ApoB). Oxidative status was determined as serum concentrations of ox-LDL/MDA Adduct. The Psoriasis Area and Severity Index (PASI) was used to determine disease severity.

Results: Among the three studied groups, controls had the highest HDL concentration ($p < 0.001$), patients with PSA had the highest ApoB concentration ($p < 0.05$), ApoA : ApoB ratio ($p < 0.05$), ox-LDL/MDA adduct concentration ($p < 0.001$), and TC: HDL and LDL : HDL ratios (accordingly $p < 0.05$, $p < 0.01$). In patients with psoriasis or PSA, oxidative status correlated positively with TC and ApoB concentrations.

Conclusions: In line with previous research, among patients with psoriasis and PSA, we found lipid metabolism abnormalities and an oxidative imbalance, which might be due to chronic inflammation in these conditions. Effective treatment of patients with psoriasis or PSA could reduce the risk of cardiovascular diseases.

Key words: oxidative stress, cholesterol, apolipoprotein, lipid metabolism.

Introduction

Psoriasis is a chronic, inflammatory, systemic disease that has many clinical forms. Psoriasis presents most commonly as plaque psoriasis, but some patients have psoriatic arthritis (PSA) [1–5]. Psoriatic arthritis involves inflammatory changes in the joints (arthritis) and ligament attachments (enthesitis), which can precede or accompany psoriatic lesions, or occur as the only symptom of the disease [6]. Typically, the rheumatoid factor is absent in patients with PSA, but the human leukocyte antigens (HLA) b27 or cw6 are present. In Poland, of 800,000–1,000,000 patients with psoriasis, at least 13,600 have PSA [3, 4]. An increasing number of pediatric patients with different types of PSA has also been observed [7].

In psoriasis, chronic inflammation may lead to oxidative stress and other metabolic alterations. For instance, in patients with psoriasis, leukocyte enzymes, such as proteolytic enzymes or myeloperoxidase, produce an excess of reactive oxygen species (ROS), which leads to oxidative stress. In the epidermis and psoriatic plaques, ROS oxidize lipids, proteins, and low-density lipoproteins (LDLs), which results in cell damage [2]. Notably, in contrast to normal skin, the skin of patients with psoriasis contains oxidized LDLs (oxLDLs) [8]. Because LDL oxidation is one of the earliest stages of atherosclerosis, oxLDLs, which contain hundreds of different oxidized lipoproteins, can serve as atherosclerosis markers [1, 5, 9].

In addition to oxidative stress, metabolic risk factors such as atherosclerosis, hyperlipidemia, or insulin resistance are common among patients with psoriasis [1, 10–15]. In patients with psoriasis or PSA, several groups have found numerous lipid alterations, including changes in concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), or lipoprotein Lp(a), or decreased concentrations of high-density lipoprotein cholesterol (HDL-C) [5, 16, 17]. Moreover, patients with psoriasis or PSA have dysfunctional LDLs or HDLs, low-volume LDLs, and LDL efflux disturbances [5, 11, 18]. Additionally, patients with PSA might have apolipoprotein or oxLDL abnormalities, and PSA severity could be related to the concentration of small, dense LDLs [9].

Dyslipidemia is the most widespread cardiovascular (CV) risk factor. Available results of scientific research point to a direct link between the concentrations of TC, LDL-C and non-HDL-C (total cholesterol concentration minus HDL cholesterol concentration) and the risk of myocardial infarction (MI), stroke and fatal cardiovascular disease (CVD) [19]. Pol-SCORE is a useful tool used for the estimation of total CV risk of patients in primary prevention. The VARO study demonstrated improved identification of high-risk individuals and

greater adherence to current treatment guidelines and modern drug therapy [20]. Psoriasis is a factor increasing CV risk which is not included in Pol-SCORE. Patients with these diseases have higher CV morbidity and mortality rates compared with the general population [19].

It is worth noting that in the general population children of parents who had coronary heart disease (CHD) had significantly higher levels of TC, low-density LDL-C, glucose, and body weight as compared to those without a parental history. This emphasizes the need for greater attention to be paid to primary prevention efforts to control risk factors in children of CHD patients [21], especially with coexisting psoriasis.

Because oxidative stress and lipid alterations can co-occur in psoriasis or PSA, this study investigated parameters of lipid metabolism and oxidative stress in patients with psoriasis and PSA [22].

Material and methods

Participants

This study was approved by our local Bioethics Committee. All participants signed informed consent before enrolment to the study. The study consisted of 31 patients with PSA and 62 patients with psoriasis. The control group comprised 60 healthy, age-matched volunteers without psoriasis or other systemic diseases. We excluded participants who received medications that could affect lipid metabolism (thiazides, β -blockers, local or systemic hormonal formulations, statins, fibrates). Patients did not receive local retinoids or dithranol. PSA was diagnosed according to the “Classification Criteria for Psoriatic Arthritis” (CASPAR). The Psoriasis Area Severity Index (PASI) was used to determine the severity of psoriatic skin lesions in patients with psoriasis or PSA. The percentage of skin affected by psoriatic lesions was determined with an assumption that a patient’s hand represented 1% of the total body surface area.

Laboratory studies

Blood samples were collected after an overnight 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 according

to the Friedewald formula. We used the Cobas Integra 400 analyzer with commercially available reagents (Roche Diagnostics, Japan).

The remaining measurements were performed in frozen serum samples, which were stored at -80°C before use. Serum levels of apolipoproteins A and B (ApoA and ApoB) were determined by an immunonephelometric method in a Behring nephelometer (BNA) and ox-LDL/MDA Adduct concentration was measured with an enzyme-linked immunosorbent assay (ox-LDL/MDA Adduct ELISA Kit, Immundiagnostik AG, Germany).

Moreover, the following cardiovascular risk parameters were calculated: the TC : HDL ratio (Castelli index I); the LDL-C : HDL-C ratio (Castelli index II), the ApoB : ApoA ratio, the LDL-C : ApoB ratio, and the Atherogenic Index of Plasma (AIP) calculated according to a standard formula: $\log(\text{TG} : \text{HDL-C})$ [22].

Statistical analysis

The Shapiro-Wilk test was used to test for normality. For comparisons between two groups, Student's *t*-test or the Mann-Whitney test was used depending on data distribution. For comparisons among more than two groups, the Kruskal-Wallis test was used, and the multiple comparisons of mean ranks test was used for *post hoc* comparisons when significant differences were found in the Kruskal-Wallis test. Correlations were as-

essed with the Spearman rank correlation coefficient. *P*-value < 0.05 was considered significant. The Statistica 10.0 software was used for all calculations.

Results

Table I presents the mean age, body mass index (BMI), and systolic and diastolic blood pressure in patients with psoriasis, patients with PSA, and controls.

Table II presents clinical characteristics of patients with psoriasis and patients with PSA. Disease duration and disease severity, assessed with the PASI, were statistically important greater in patients with PSA than in patients with psoriasis (Table II). Among the three studied groups, controls had the highest HDL-C concentration ($p < 0.001$) and patients with PSA had the highest ApoB concentration ($p < 0.05$), ApoA:ApoB ratio and ox-LDL/MDA Adduct concentration (respectively $p < 0.05$, $p < 0.001$). The studied groups did not differ significantly with respect to the remaining laboratory parameters (Table III). Moreover, patients with PSA had the highest TC : HDL-C and LDL-C : HDL-C ratios (respectively $p < 0.05$, $p < 0.01$; Table IV). In the combined group including patients with psoriasis and PSA, the ox-LDL/MDA Adduct, indicating the oxidative status, correlated with the TC ($R_s = 0.34$; $p < 0.05$) and ApoB concentrations ($R_s = 0.39$; $p < 0.01$; Table V). These correlations were non-significant in controls.

Table I. Mean age, body mass index, and systolic and diastolic blood pressure in the studied groups

| Parameter | Psoriatic arthritis (<i>n</i> = 31) | | Psoriasis vulgaris (<i>n</i> = 62) | | Controls (<i>n</i> = 60) | | <i>P</i> -value |
|--------------------------|---|--------------------|--|--------------------|------------------------------|--------------------|-----------------|
| | Mean | Standard deviation | Mean | Standard deviation | Mean | Standard deviation | |
| Age [years] | 40.68 | 7.38 | 40.87 | 11.05 | 41.02 | 9.84 | 0.9880 |
| BMI [kg/m ²] | 27.52 | 4.13 | 26.48 | 4.34 | 26.31 | 4.08 | 0.2514 |
| SBP [mm Hg] | 126.71 | 16.39 | 126.34 | 16.57 | 127.15 | 11.39 | 0.6119 |
| DBP [mm Hg] | 83.35 | 10.63 | 79.82 | 14.60 | 82.33 | 8.11 | 0.3689 |

BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure.

Table II. Clinical features of patients with psoriasis and psoriatic arthritis

| Parameter | Psoriatic arthritis (<i>n</i> = 31) | | Psoriasis vulgaris (<i>n</i> = 62) | | <i>P</i> -value |
|---|---|--------------------|--|--------------------|-----------------|
| | Mean | Standard deviation | Mean | Standard deviation | |
| Duration of psoriasis vulgaris [years] | 16.75 | 13.19 | 9.25 | 10.12 | < 0.001 |
| Duration of psoriatic arthritis [months] | 10.35 | 12.91 | – | – | – |
| PASI | 28.07 | 5.87 | 26.00 | 6.54 | < 0.05 |
| % of total body surface affected by psoriatic lesions | 38.64 | 13.95 | 35.83 | 15.59 | 0.2438 |

PASI – Psoriasis Area Severity Index.

Table III. Laboratory characteristics in the studied groups

| Parameter | Psoriatic arthritis (n = 31) | | Psoriasis vulgaris (n = 62) | | Controls (n = 60) | | P-value |
|-----------------------|---------------------------------|--------------------|--------------------------------|--------------------|----------------------|--------------------|---------|
| | Mean | Standard deviation | Mean | Standard deviation | Mean | Standard deviation | |
| Glucose [mg/dl] | 89.97 | 14.77 | 83.55 | 11.06 | 81.65 | 11.06 | 0.0519 |
| TC [mg/dl] | 214.27 | 40.08 | 193.54 | 39.75 | 203.42 | 39.23 | 0.0637 |
| HDL-C [mg/dl] | 45.69 | 11.59 | 48.40 | 12.15 | 53.07 | 11.69 | < 0.001 |
| LDL-C [mg/dl] | 129.56 | 32.92 | 112.92 | 27.93 | 118.31 | 35.23 | 0.0798 |
| VLDL [mg/dl] | 33.00 | 19.25 | 25.09 | 10.42 | 25.50 | 15.47 | 0.1268 |
| TG [mg/dl] | 157.21 | 98.01 | 127.70 | 52.95 | 132.17 | 84.70 | 0.4156 |
| ApoA [mg/dl] | 1.31 | 0.40 | 1.31 | 0.41 | 1.26 | 0.40 | 0.7500 |
| ApoB [mg/dl] | 1.13 | 0.42 | 0.98 | 0.33 | 0.90 | 0.27 | < 0.05 |
| ApoA : ApoB ratio | 0.90 | 0.27 | 0.24 | 0.76 | 0.76 | 0.27 | < 0.05 |
| Ox-LDL [μ mol/l] | 420.79 | 335.79 | 390.26 | 311.04 | 84.99 | 83.81 | < 0.001 |

TC – total cholesterol, HDL-C – high-density lipoprotein cholesterol, LDL-C – low-density lipoprotein cholesterol, VLDL – very low-density lipoprotein, TG – triglycerides, ApoA – apolipoprotein A, ApoB – apolipoprotein B, Ox-LDL – oxidized LDL.

Table IV. Cardiovascular risk parameters in the studied groups

| Parameter | Psoriatic arthritis (n = 31) | | Psoriasis (n = 62) | | Controls (n = 60) | | P-value |
|---------------------|---------------------------------|--------------------|-----------------------|--------------------|----------------------|--------------------|---------|
| | Mean | Standard deviation | Mean | Standard deviation | Mean | Standard deviation | |
| TC : HDL-C ratio | 5.00 | 1.68 | 4.17 | 1.15 | 4.01 | 1.15 | < 0.05 |
| AIP | 0.48 | 0.31 | 0.40 | 0.22 | 0.33 | 0.31 | 0.0541 |
| LDL-C : HDL-C ratio | 3.03 | 1.07 | 2.47 | 0.87 | 2.33 | 0.89 | < 0.01 |
| ApoB : ApoA ratio | 0.88 | 0.28 | 0.77 | 0.20 | 0.76 | 0.27 | 0.0534 |
| LDL-C : ApoB ratio | 125.33 | 43.57 | 125.76 | 41.12 | 144.41 | 47.01 | 0.0755 |

TC – total cholesterol, HDL-C – high-density lipoprotein cholesterol, LDL-C – low-density lipoprotein cholesterol, ApoB – apolipoprotein B, ApoA – apolipoprotein A, AIP – atherogenic index of plasma.

Discussion

Our study confirmed that patients with psoriasis or PSA have lipid metabolism alterations and an oxidative imbalance. In our study, we found significant alterations of the HDL-C, ApoB, and ox-LDL/MDA Adduct concentrations, which were elevated in patients with psoriasis or PSA. Moreover, among patients with psoriasis or PSA, oxidative stress was associated with higher TC and ApoB concentrations.

Psoriasis and PSA are systemic diseases associated with an increased risk of metabolic syndrome, cardiovascular diseases, and major cardiovascular events [1–3, 5, 10, 12, 15–17, 19, 23–25]. In the 1920s, Ishimaru and Lortat-Jacob described lipid metabolism abnormalities among patients with psoriasis and showed how these abnormalities influenced the disease course. In the 1930s, Grutz and Burger hypothesized that lipid intestinal

absorption might be related to skin function, and they referred to psoriasis as “lipoidosis”. In 1963, Melczer described a relationship between the progression of psoriasis and lipid metabolism [26]. Subsequent research confirmed that patients with psoriasis or PSA have numerous lipid profile alterations, with increased serum concentrations of TC, LDL-C, and TG being the most frequent abnormalities. Moreover, patients with psoriasis tend to have reduced HDL-C, ApoA, and ApoB concentrations [8, 10, 17, 16]. In a recent study performed in Spain among 358 patients with psoriasis (disease length, 10–25 years), 41.6% had hypercholesterolemia, including 65 patients who received lipid-lowering medications; moreover, 47.6% of patients with PSA had hypercholesterolemia, compared to 39.8% of patients with psoriasis. In addition, in that study, 20.7% of patients had documented prior cardiovascular events [12].

Table V. Correlation between oxidative activity and the studied parameters in patients with psoriasis or psoriatic arthritis and in controls

| Parameter | Patients with psoriatic arthritis or psoriasis | | Controls | |
|---------------------|--|------------------|-----------------------|-----------------|
| | <i>R</i> _s | <i>P</i> -value | <i>R</i> _s | <i>P</i> -value |
| TC | 0.34 | < 0.05 | 0.21 | 0.2549 |
| HDL-C | 0.23 | 0.1224 | 0.06 | 0.7384 |
| LDL-C | 0.23 | 0.1187 | 0.27 | 0.1316 |
| VLDL | -0.02 | 0.8896 | 0.18 | 0.3122 |
| TG | -0.07 | 0.6210 | 0.18 | 0.3122 |
| ApoA | 0.26 | 0.0900 | 0.12 | 0.5263 |
| ApoB | 0.39 | < 0.01 | -0.07 | 0.7091 |
| ApoA : ApoB ratio | 0.25 | 0.0939 | -0.08 | 0.6582 |
| TC : HDL-C ratio | 0.08 | 0.5777 | 0.11 | 0.5618 |
| API | -0.15 | 0.3076 | 0.10 | 0.5878 |
| LDL-C : HDL-C ratio | 0.11 | 0.4475 | 0.12 | 0.5231 |
| ApoB : ApoA ratio | 0.24 | 0.1159 | -0.10 | 0.6100 |
| LDL-C : ApoB ratio | -0.25 | 0.0934 | 0.28 | 0.1253 |

TC – total cholesterol, HDL-C – high-density lipoprotein cholesterol, LDL-C – low-density lipoprotein cholesterol, VLDL – very low-density lipoprotein, TG – triglycerides, ApoA – apolipoprotein A, ApoB – apolipoprotein B, API – atherogenic index of plasma. Significant correlations are marked in bold.

A study involving 246 patients with psoriasis, performed in Poland, found that, compared to controls, patients with psoriasis had an abnormal concentration of HDL-C but not of other blood lipids [14]. In a study performed among 15,484 patients from South Korea, 10.94% had dyslipidemia, including 14.88% of patients with PSA and 10.39% of patients with psoriasis [15]. In line with previous research, our study found that patients with PSA had more atherogenic lipid profiles than patients with psoriasis [27, 28]. Moreover, in our study, patients with PSA or psoriasis differed from controls with respect to all the studied parameters, except for the ApoA concentration.

Evidence shows that chronic inflammation can cause structural protein changes, including creation of neo-epitopes, which, in turn, triggers autoantibody production and HDL alterations. Moreover, patients with an increased cardiovascular risk have elevated levels of autoantibodies against HDLs and apolipoprotein AI [29, 30]. These autoantibodies are regarded as biomarkers of cardiovascular diseases among patients with autoimmune disorders. Anti-aHDL and anti-Apo-AI antibodies were also detected in patients with psoriasis, and their presence correlated with greater disease severity [18]. Moreover, these autoantibodies could be involved in atherosclerotic plaque development in patients with psoriasis [30, 31]. However, among the many lipid alter-

tations observed in psoriasis, it is difficult to distinguish between those specific to psoriasis and those associated with dyslipidemia [31].

OxLDLs contribute to atherosclerosis progression because they activate monocyte infiltration and smooth muscle cell proliferation. Numerous studies have reported that patients with psoriasis have elevated oxLDL levels. Among 45 patients with moderate psoriasis severity (mean PASI: 14.0 ±8.3), Sunitha *et al.* found a correlation between the PASI and anti-oxLDL and oxLDL concentrations. Moreover, compared to controls, patients with psoriasis had a higher anti-ox-LDL : oxLDL ratio, which indicated greater oxidative stress [32]. Patients with psoriasis were found to have oxLDLs in the epidermis and serum [5, 8, 11, 24, 25, 32], as well as antibodies against HDLs or apolipoprotein AI [30, 31]. Tekin *et al.* also found significantly elevated oxLDL and anti-oxLDL concentrations in patients with psoriasis, particularly in the upper part of the epidermis; in contrast, normal skin did not contain oxLDLs or anti-oxLDL antibodies [8]. Also, in patients with psoriasis, the oxLDL concentration correlated with the BMI. In contrast to most studies on lipid alterations in psoriasis, Gerdes *et al.* and Gkalpakiotis *et al.* did not find significant differences between patients with psoriasis and controls with respect to the oxLDL concentration [24, 25].

It is hypothesized that an increased cardiovascular risk among patients with autoimmune dis-

eases could be associated with the duration and severity of inflammatory changes. For instance, dyslipidemia affects mostly patients with severe psoriasis or PSA [16]. However, in psoriasis, the exact mechanisms that link chronic inflammation to lipid metabolism alterations remain unknown. Moreover, it remains unclear whether chronic inflammation is the cause or the effect of lipid metabolism alterations. To date, numerous studies have investigated potential molecular mechanisms that could underlie the association between psoriasis and cardiovascular diseases, including shared genetic factors or inflammatory pathways, secretion of adipokines, insulin resistance, lipoprotein structure and function, angiogenesis, oxidative stress, microparticles, and hypercoagulability. Moreover, it is hypothesized that due to skin shedding with psoriatic plaques, patients with psoriasis lose numerous substances, such as interleukin 18 (human leukocyte elastase inhibitor), cathepsin G, C5a/C5adesarg, and lipids (ca. 60 g each month) [17, 33–36]. Moreover, compared to the non-lesioned skin, cholesterol concentration in psoriatic plaques is 5 times as high. Among patients with rheumatoid arthritis, Oliviero *et al.* found that the levels of ApoA1 and TC were reduced in serum but elevated in the synovial membrane [37]. Those authors suggested that HDLs may accumulate in the inflamed joints, which can inhibit pro-inflammatory cytokine production. Alternatively, ApoA1 sequestration in the inflamed joints could lead to low HDL serum levels, which would result in an elevated cardiovascular risk among patients with rheumatoid arthritis or PSA [37]. Orgaz-Molina *et al.* found that vitamin D concentration correlated with the levels of total cholesterol, LDLs, and TG only in patients with psoriasis who did not have joint involvement [27].

Currently, treatment targets in patients with PSA include not only preservation of joint function but also improvement of physical functioning, reduction of dactylitis, enthesitis, and reduction of skin and nail changes [6]. The occurrence of autoimmune, rheumatic or inflammatory diseases, such as psoriasis and PSA, is not an indication for the preventive use of lipid-lowering drugs. Measures for the prevention and treatment of dyslipidemia do not differ from generally applicable rules [19]. In view of current research, treating lipid alterations should also become part of care in patients with psoriasis. Studies show that moderate physical exercise increases antioxidative enzyme activity (e.g., superoxide dismutase) and reduces serum concentrations of total cholesterol, LDL-C, and oxidized lipids [38]. Because statins, in addition to lowering lipid serum concentrations, can reduce disease severity in psoriasis, some patients with psoriasis could benefit from statin treatment.

In conclusion, lipid metabolism abnormalities and oxidative stress are common among patients with psoriasis and PSA. Every patient should be evaluated to determine total CV risk for the purpose of ensuring appropriate patient education and making decisions on the intensity of treatment [19]. Effective treatment of patients with psoriasis or PSA could reduce the risk of cardiovascular diseases.

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Conflict of interest

The authors declare no conflict of interest.

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