CLINICAL STUDY

Vaspin, neutrophil gelatinase-associated lipocalcin and apolipoprotein levels in patients with psoriatic arthritis

Colak S1, Omma A1, Sandikci SC1, Yucel C2, Omma T3, Turhan T2

Ankara Gulhane Training and Research Hospital, Department of Rheumatology, Etlik Quarter, Kecioren, Ankara, Turkey. sedayurumez@hotmail.com

ABSTRACT
OBJECTIVES: To examine the relationship between disease activity and vaspin, neutrophil gelatinase-associated lipocalcin (NGAL) and apolipoproteins in patients with psoriatic arthritis (PsA).

BACKGROUND: Psoriatic arthritis (PsA) is a chronic inflammatory arthritis, which is related with psoriasis. Adipokines are the mediators which play a role in metabolic homeostasis and inflammatory conditions.

METHODS: The levels of vaspin, NGAL, apolipoproteins and their correlations with disease activity were compared in 50 psoriatic arthritis patients and 36 healthy controls.

RESULTS: The levels of vaspin, NGAL, apolipoproteins and their correlations with disease activity were compared in 50 psoriatic arthritis patients and 36 healthy controls.

CONCLUSION: This is the first study to have compared vaspin and NGAL levels in patients with PsA. Vaspin, NGAL and dyslipoproteinemia are not correlated with disease activity (Tab. 3, Ref. 63).

KEY WORDS: apolipoprotein, disease activity, neutrophil gelatinase-associated lipocalcin, psoriatic arthritis, vaspin.

Introduction

Psoriatic arthritis (PsA) is a chronic, inflammatory and debilitating arthritis associated with the skin disease, psoriasis (1). The incidence of psoriatic arthritis is 2–3% in the general population and 30% among patients with psoriasis (2). Although the etiology of PsA is not fully known, some risk factors have been identified. It has been shown that psoriatic arthritis patients are at increased risk for metabolic syndrome, obesity, cardiovascular events (CVEs), type 2 diabetes mellitus, hypertension and hyperlipidemia (3–6).

Adipose tissue has an important role in the endocrine and immune systems by secreting adipokines. Some of these adipokines are anti-inflammatory, whereas some are pro-inflammatory (7).

Vaspin (visceral adipose tissue-derived serine protease inhibitor), a serine protease inhibitor, is a member of the adipokine group. Vaspin expression is increased in obesity. High vaspin levels are associated with increased glucose tolerance and insulin sensitivity and increased levels of vaspin are thought to play a protective role against the effects of insulin resistance (8).

Vaspin can be the redeeming particle of metabolic syndrome pathogenesis (9). In recent trials, low vaspin levels have been found in cardiovascular diseases (10,11). It has been shown that vaspin protects endothelial cells from the effects of free fatty acids and prevents these cells from undergoing apoptosis, thereby playing a protective role against atherosclerosis (12).

Neutrophil gelatinase-associated lipocalcin (Lipocalin-2, NGAL) is an immunomodulatory glycoprotein secreted by various cells, such as neutrophils, macrophages, adipocytes and hepatocytes. NGAL is a modulator of inflammatory response (20,21,22). NGAL levels have been found to be high in inflammation, metabolic syndrome, cardiovascular diseases, acute kidney injury, lupus nephritis and malignancies (13–17).

The glycoprotein part of lipoproteins, which are the structures that allow the lipids to move in the blood and dissolve in water, are called apolipoproteins. The main apolipoproteins of high-density lipoproteins (HDL) and low-density lipoproteins (LDL) are apolipoprotein A1 (apo A1) and apolipoprotein B (apo B), respectively. There is a negative correlation between serum apo A1 concentration and atherosclerosis. Apo B has been shown to be related with atherosclerosis (18,19).

The aim of this study was to evaluate the relationship between vaspin, NGAL levels, lipoproteins and disease activity in PsA patients.

Materials and methods

Patients and disease activity assessment

Samples were obtained from 50 PsA patients and 36 healthy control subjects between November 2017 and February 2018. Patients with PsA were defined according to the Classification Criteria
for Psoriatic Arthritis (CASPAR) (20). The study exclusion criteria were as follows: 1) age < 18 years 2) concomitant autoimmune or autoinflammatory disease, 3) acute or chronic infection, 4) malignancy, 5) pregnancy or up to 6 months postpartum period. The demographic features and clinical characteristics were recorded. Disease severity was assessed with the Psoriasis Area Severity Index (PASI) for skin disease. Arthritis activity was measured using the disease activity in PsA (DAPSA), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Visual Analogue Scale (VAS) and Minimal Disease Activity (MDA) (1, 21–23). Body mass index (BMI) was calculated and waist circumference (WC) was measured for each individual. The presence of metabolic syndrome was evaluated with the criteria of the National Cholesterol Education Program Adult Panel III (NCEP ATP III) (24).

The study protocol was approved by the Local Ethics Committee. The research protocol complies with the 2000 Declaration of Helsinki and written informed consent was obtained from all participants.

**Laboratory analysis**

Venous blood samples were collected from the participants after 12 hours of fasting and centrifuged at 1,500 g for 10 minutes. Separated sera were aliquoted into Eppendorf tubes and stored at −80 ºC until the time of analysis.

Serum levels of Vaspin and NGAL were detected with commercial ELISA (double antibody sandwich ELISA method) test kit (Elabscience Biotech Co. Ltd) according to the manufacturer’s protocol. HDL, cholesterol and triglyceride measurements were made with the enzymatic colorimetric method. LDL was calculated according to the Friedwald Formula. Apo B, Apo A1 and C reactive protein (CRP) values were detected with the immunoturbidimetric method. Erythrocyte sedimentation rate (ESR) was studied with Westergreen method.

**Statistical analysis**

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) program version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Conformity to normal distribution of the variables was investigated using visual and analytical methods. Normally distributed continuous values were expressed as mean ± standard deviation (SD) and categorical variables as number (n) and percentage (%). Parameters which were not normally distributed were stated as median values with interquartile range (IQR). Continuous parameters were analyzed using the Student’s t-test. Correlations were evaluated with the Pearson correlation coefficient. A value of p < 0.05 was considered statistically significant.

**Results**

Evaluation was made on the data of 50 PsA patients and 36 healthy control subjects. The groups were similar in respect of age and gender. Among PsA patients, metabolic syndrome, diabetes mellitus, hypertension and hyperlipidemia were seen in 21 (40 %), 8 (16 %), 13 (26 %) and 2 (4 %) patients, respectively.

**Tab. 1. Comparison of the demographic and clinical variables of the patient and control groups.**

| Variable          | PsA          | Healthy control | P     |
|-------------------|--------------|-----------------|-------|
| Male/Female       | 35/15 (70/30)| 25/11 (69.4/30.5)| 0.956 |
| Age               | 44.5 ± 13.88 | 43.08 ± 11.04   | 0.59  |
| Disease duration  |              |                 |       |
| Psoriasis         | 121.36±97.64 |                 |       |
| Psoriatic arthritis| 59.83±55.8  |                 |       |
| Involvement types |              |                 |       |
| Axial             | 14 (28)      |                 |       |
| Peripheral        | 45 (90)      |                 |       |
| Dactylitis        | 22 (44)      |                 |       |
| Enthesitis        | 9 (18)       |                 |       |
| ESR mm/h          | 20.2 ± 16.27 |                 |       |
| CRP mg/dl         | 9.28 ± 12.11 |                 |       |
| BMI (kg/m²)       | 29.78±5.42   | 26.31±4.86      | 0.003 |
| WC (cm)           | 98.86±13.68  | 89.2±10.67      | 0.001 |

PsA: psoriatic arthritis, ESR: erythrocyte sedimentation rate, CRP: C reactive protein, BMI: body mass index, WC: waist circumference. For the variables with , frequency (percent), without , mean±standard deviation was used.

**Tab. 2. Disease activity scores of patients.**

| Variable       | Mean/Standard deviation | Median (Minimum-Maximum) |
|----------------|-------------------------|-------------------------|
| DAPSA          | 19.5±18.63              | 11.65 (0–78)            |
| BASDAI         | 2.68±2.77               | 2.2 (0–10)              |
| BASFI          | 1.87±2.35               | 1.8 (0–9.6)             |
| PASI           | 7.91±13.6               | 1.5 (0–62.6)            |
| VAS            | 5.28±3.23               | 6 (0–10)                |

DAPSA: Disease activity in psoriatic arthritis, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, PASI: Psoriasis Area Severity Index, VAS: Visual analogue scale

**Tab. 3. Comparison of the adipokine and apolipoprotein levels of the patient and control groups.**

| Variable          | Patients       | Controls       | P     |
|-------------------|----------------|----------------|-------|
| Vaspin (ng/L)     | 391.63±436.4  | 176.67±122.75 | 0.001 |
| NGAL (ng/L)       | 5.2±2.67      | 1.94±2.09     | 0.014 |
| Apolipoprotein A1 (mg/dl) | 131.9±17.38  | 141.72±19.97 | 0.017 |
| Apolipoprotein B (mg/dl) | 102.52±27.29 | 92.55±34.21  | 0.137 |
| Apolipoprotein B/A1 | 0.78±0.21    | 0.66±0.27     | 0.023 |

NGAL: Neutrophil Gelatinase-associated Lipocalin

BMI and WC were significantly greater in the patient group. Of PsA patients, 21 (24.4 %) had metabolic syndrome. Demographic and clinical variables are shown in Table 1. The disease activity scores of patients are shown in Table 2. According to MDA criteria, 26 (52 %) patients were in remission.

Medications and the percentage of usage were analyzed. Twenty-one patients (42 %) were using corticosteroids, 31 patients (62 %) were using nonsteroidal anti-inflammatory drugs, 28 patients (56 %) were using methotrexate, 7 patients (14 %) were using salazopyrine, 5 patients (10 %) were using lefunomide, 1 patient (2 %) was using cyclosporine and 9 patients (18 %) were using anti tumour necrosis factor α blockers.

Vaspin and NGAL levels were higher in patients than in the healthy control group. The level of Apo A1 was lower and the Apo B/A1 ratio was higher in the patient group (p = 0.017 vs p = 0.023, respectively) (Tab. 3). Patients with metabolic syndrome had higher NGAL, Apo B and Apo B/A1 ratio (p < 0.05).
There was no statistically significant correlation between disease activity and vaspin, NGAL, and lipoprotein levels (p > 0.05).

NGAL levels had a negative correlation with disease duration of psoriasis and psoriatic arthritis (p < 0.05). There was no correlation between BMI and waist circumference and levels of vaspin, NGAL, and Apo A1 (p > 0.05). There was a positive correlation between Apo B, Apo B/A1 and BMI and WC (p < 0.05). Patients with metabolic syndrome had higher scores of DAPSA and PASI (p < 0.05).

Discussion

This study analyzed adipokines, apolipoproteins A and B, and their correlation with disease activity in patients with PsA. This is the first study to have assessed vaspin and NGAL levels and the correlations with disease activity in PsA.

The results of the study showed that BMI was higher in PsA patients, which was consistent with previous findings in literature (25–27). A recent study demonstrated that WC was higher in PsA patients which is similar to the current study findings (28). It is well known that metabolic syndrome is a common disorder among PsA patients (3, 4). In this study, metabolic syndrome was seen in 21 patients (24.4 %), which was a lower rate than previously reported in literature (29, 30).

Vaspin and NGAL levels were determined to be higher in PsA patients compared with the healthy control group. Vaspin plays a role in atherosclerosis, impaired insulin resistance, obesity and chronic inflammation (31, 32). Vaspin is known to have anti-inflammatory properties (33–35). The results of this study showed vaspin to be higher in the PsA patient group, but no correlation was determined between disease activity and vaspin levels. Mayer et al found that serum vaspin levels were associated with the development of arthritis in autoantibody positive individuals. In that study, vaspin levels were not associated with CRP (36). Metabolic syndrome, CVEs, and obesity are conditions known to increase in psoriasis and NGAL levels (49). The results of this study showed that vaspin levels did not differ from those of psoriasis patients (41). Ataseven et al showed that vaspin levels were lower in psoriasis compared with healthy control subjects and there was a positive correlation with PASI (42). Ozgen et al reported higher vaspin levels in RA patients, but there was no significant correlation between vaspin levels and disease activity. In the same study, vaspin levels were lower in active Behçet’s disease (43). In a study of juvenile idiopathic arthritis patients, vaspin levels did not differ from those of the control group and no significant correlation was found between vaspin levels and disease activity (44). Wang et al demonstrated low vaspin levels in ankylosing spondylitis patients (45). Various chronic inflammatory diseases present different vaspin responses. There is a need for further studies to be able to better understand the role of vaspin in chronic inflammatory diseases. In the current study, no correlation was found between vaspin and BMI or WC, which was similar to the findings in literature (36).

NGAL, a member of the adipokine superfamily, is secreted by neutrophils, macrophages, adipocytes and epithelial cells. This molecule plays a role in the regulation of inflammation, infections, immunity, ischaemia-induced injury and metabolic balance of the human body (46, 47). It is known that IL-17 is one of the major cytokines of PsA. Shen et al demonstrated that IL-17 induces NGAL secretion (48). Secretion of NGAL can be regulated either IL-17 or the interaction between IL-17 and TNF-α (46). Although NGAL can be secreted from adipocytes, no correlation was found in the current study between NGAL and BMI or WC. However, there was a positive correlation between the presence of metabolic syndrome and levels of NGAL. To the best of our knowledge there is no study which has examined NGAL in psoriatic arthritis patients with which the current study results could be compared. Serum and tissue NGAL levels have previously been found to be increased in patients with psoriasis (49, 50). NGAL was not correlated with PASI, BMI or WC in studies which were conducted in patients with psoriasis (49–51). Kamata and Stejak did not find a significant correlation between metabolic syndrome or its components and levels of NGAL in patients with psoriasis (50, 51). Romani et al showed a positive correlation between NGAL and PASI (52). Gulkesen et al reported that NGAL levels were higher in patients with RA than in the healthy control group and there was no correlation with disease activity (53).

In the current study, NGAL levels were negatively correlated with both psoriasis and psoriatic arthritis disease duration. In contrast, El Hadidi et al found no correlation between disease duration of psoriasis and NGAL levels (49).

Apolipoproteins provide transportation of lipids. Apo A1 is the major protein of HDL, which activates the enzyme, lecithin cholesterol acyltransferase (LCAT). This enzyme esterifies free cholesterol and removes cholesterol from peripheral cells. Apo A1 has antiatherogenic properties and prevents cross-interaction between macrophages and T cells. Changes in the protein and lipid structure of HDL occur in the presence of inflammation. Serum amyloid A is replaced by Apo A1 in HDL. Inflammation causes depletion of Apo A1. Apo B is the major protein of LDL, which provides transport of cholesterol from the liver to the periphery (18, 19, 54, 55). Although the exact value of the Apo B/A1 ratio is not fully known in literature, this ratio is considered to be a better predictor of cardiovascular risk than lipid and lipoprotein levels (56). In the current study, Apo A1 levels were found to be significantly lower and the Apo B/A1 ratio was significantly higher in the patient group. There was no significant correlation between apolipoprotein levels and disease activity. Apolipoprotein levels have been studied in various inflammatory diseases. Terkeltaub showed that Apo A1 levels were decreased in RA and increased in PsA patients (57). Gentile et al reported that Apo B levels were increased in patients with PsA (58), whereas Papagoras et al showed significantly lower Apo A1 levels in PsA patients and there were no significant differences in Apo B levels and ratio of Apo B/A1. There were no correlations between metabolic parameters and...
PASI, BASDAI, or DAS28. In the same study AS patients had lower Apo B and Apo B/A1 ratio. (59). Tam et al evaluated 31 PsA patients and reported higher Apo A1, Apo B and the ratio in PsA patients. According to that study, CRP had a negative correlation with Apo A1 and HDL, and a positive correlation with Apo B/A1 ratio (27). Semb and Jones showed that lipid subfractions do not change in PsA (60, 61). Another study demonstrated that PsA patients had higher Apo B and LDL levels, and conversely lower Apo A1 and HDL levels compared with the healthy control group (62). Similar findings were reported in another study of psoriasis patients (63). To be certain of the role of apolipoproteins in PsA, there is a need for further studies with larger samples. The contradictory results of the previous studies could be due to demographic characteristics, pathophysiology of diseases or risk of cardiovascular events.

The limitation to the current study was in the small sample size of the patient group. The cross-sectional design of the study and the fact that there was no follow-up of the patients can also be considered as limitations.

Conclusion

Vaspin and NGAL can be used as positive markers in patients with PsA. These adipokines can play a role in the inflammatory process of PsA. Apolipoprotein levels can be showing the increased risk for CVEs in patients with PsA. The contradictory results in literature indicate the need for future studies with larger samples.

Learning points
- High vaspin levels were found in patients with psoriatic arthritis.
- Neutrophil gelatinase-associated lipocalin was higher in psoriatic arthritis.
- Apolipoprotein A1 level is lower in the patient group.
- The ratio of apolipoprotein B/A1 is higher among the psoriatic arthritis patients.
- There was no correlation between disease activity and these biomarkers.

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