Original Article

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Investigation of Cardiovascular Disease and Metabolic Syndrome Risk with Copeptin in Psoriasis Patients: A Case-Control Study

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Abstract

Aim: Psoriasis is thought to result in vascular diseases, atherogenesis, peripheral insulin resistance, and cardiac comorbidities by causing metabolic function disorders, hypertension, and type 2 diabetes. To our best knowledge, there has not yet been a study evaluating psoriasis patients with regard to copeptin. The present study assesses cardiovascular disease in psoriasis patients based on metabolic function and copeptin levels.

Methods: The presented case-control study, which is a type of analytical observational study, included 45 psoriasis patients and an age-sex matched control group admitted to University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Dermatology, between March 2016 and May 2017. Patients' blood pressure, height, weight, body mass index, and waistline were measured for both groups. All subjects were also given complete blood count, fasting blood glucose (FBG), uric acid, lipid profile, insulin, C-reactive protein (CRP), copeptin levels, neutrophil-lymphocyte rate, and thrombocyte-lymphocyte rate were analysed. Copeptin was measured by an ELISA kit.

Results: Insulin and CRP averages were statistically significantly higher in psoriasis patients than in the control group (p=0.001 for both). The neutrophil-lymphocyte and thrombocyte-lymphocyte rates were significantly higher in psoriasis patients (p=0.008). Insulin resistance was also higher in psoriasis patients (p=0.001). In both the patient and control groups, there was no statistically significant relationship found between copeptin level, general characteristics, and laboratory parameters.

Conclusion: To our best knowledge, this is the first study evaluating psoriasis patients with regard to copeptin. Psoriasis patients should be followed up with easily accessible parameters such as neutrophil-lymphocyte rate, thrombocyte-lymphocyte rate, insulin levels, FBG, and uric acid levels.

Key Words: Psoriasis, copeptin, metabolic disease, cardiovascular disease

Introduction

Psoriasis is a T-cell-mediated inflammatory disease with an incidence rate of 2-3% (1,2). While in the past it was believed only to affect the skin and joints, (3) in recent years it has been frequently researched that psoriasis causes cardiac diseases by affecting the metabolic system, blood pressure, and sugar-insulin resistance that causes atherosclerosis (4-6). Its an increasingly accepted

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opinion that the comorbidities should be considered when planning therapy and follow-ups for psoriasis (7,8).

Arginine vasopressin (AVP) is a neurohormone secreted from the neurohypophysis, protecting homeostasis by ensuring water reabsorption from the kidneys. As its half-life is low in plasma, the c-terminal fragment of the AVP precursor (copeptin) is used to determine AVP levels. It has a long half-life and is thought to be a marker of cardiac disease and mortality risk in population-based studies (9,10). Copeptin is also a good diagnostic and prognostic marker in metabolic diseases (diabetes mellitus, metabolic syndrome, insulin resistance) (11) and cardiovascular events in clinical practice (12). El Dayem et al. (13) declare that copeptin can be used as a marker for early detection of atherosclerosis in type 1 diabetic patients.

Extensive studies on biomarkers of psoriasis have identified some promising markers at the genome, transcriptome, proteome, and metabolome levels. These discoveries have provided new insights into the underlying molecular mechanisms and signaling pathways of psoriasis pathogenesis. There are also various abnormalities in lipid metabolism as well as oxidative stress in patients with psoriasis. In addition, decreased antioxidant enzyme activity and high lipid levels in the blood and lipid peroxidation, such as total cholesterol, triglycerides, low-density lipoprotein, and very-low-density lipoprotein, were found in psoriasis patients. This knowledge may be useful in the management of high-need patients with psoriasis. As copeptin levels do not change with age, it is beneficial for patients of any age group but not for patients with electrolyte imbalance disorders.

Different results regarding the relationship between metabolic syndrome and psoriasis have been reported (5). Our study presents independent data using inflammation indicators and metabolic function parameters. Thus, we attempted to predict which parameters are more affected in psoriasis patients, and this study compared cardiovascular disease (CVD) psoriasis with a healthy control group by evaluating metabolic functions and copeptin levels. We could not find any other studies in the literature evaluating psoriasis patients based on copeptin levels.

Materials and Methods

Compliance with Ethical Standards

All patients signed an informed consent form, and the study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Non-Drug Clinical Research Ethics Committee (382-22/06/2016).

Study Design

This study enrolled 45 patients who were admitted to the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Dermatology, between March 2016 and May 2017. All patients had had psoriasis for at least six months and had not received any therapy for at least three months before the study. The ages ranged from 18-63. Patients enrolled in the study were diagnosed by the same dermatologist, and psoriasis area and severity index (PASI) was used to determine psoriasis severity. Severe psoriasis patients (with a PASI ≥10) were studied. The control group consisted of 44 healthy individuals of the appropriate age and gender. For both groups, subjects with known coronary artery disease, hypertension, diabetes mellitus, renal failure, valvular heart disease, acute vascular involvement, malignancy, inflammatory disease, or acute or chronic infection were excluded. The demographics of the patients and the control group (name, surname, and gender) were recorded. Disease onset, age, disease duration, and medications used were recorded for patients. Arterial blood pressure, height, weight, body mass index (BMI), waist circumference, fasting blood glucose (FBG), insulin levels, lipid values, hemogram, C-reactive protein (CRP), and uric acid were measured for both groups.

Copeptin Measurement

The copeptin levels were also studied by waiting at -80° in simultaneously taken blood. The Human Copeptin ELISA test kit (Sunred Copeptin ELISA Kit, Germany) measured copeptin using a sandwich test method.

Statistical Analysis

SPSS 15.0 for Windows was used for statistical analysis. The defining statistics are presented as numbers and percentages for categorical variables, and a mean, standard deviation, and median are included for numeric variables. A comparison of numeric variables in two independent groups was carried out using Student's t-test for normal distribution and the Mann-Whitney U test for non-normal distribution. The relationships between numeric variables were examined using the Pearson correlation analysis when parametric test conditions were met, and the Spearmen correlation analysis when these conditions were not met. The statistical alpha significance level was assumed to be $p<0.05$.

Results

The general characteristics of the patient group are found in Table 1. While almost all the patients had scalp involvement, nail involvement was seen in 38 patients, and psoriatic arthritis was found in 16 patients. In addition, the patient group had more males than the control group.

As a result, the male gender rate, average height, and waist circumference were statistically significantly higher in the patient group than in the control group (p=0.044, p=0.045, and p=0.011, respectively).

Of the laboratory parameters evaluated, insulin and CRP averages were statistically significantly higher in psoriasis patients compared to the control group (p=0.001 for both). Insulin resistance was higher in patients with psoriasis (p=0.001) (Table 2). Compared with Homa-IR, the levels were average. While there was no difference between the groups regarding uric acid levels, uric acid was markedly higher in patients diagnosed for more than ten years.

There was no statistically significant correlation between the patient and control groups found between the copeptin level, general characteristics, and laboratory parameters. The neutrophil-lymphocyte rate was significantly higher in psoriasis patients (p=0.012). While thrombocytes were numerically higher in the study group, this study detected statistical significance with regard to thrombocyte/lymphocyte between patients and the control group (Table 3) (Figure 1).

Discussion

Studies have found altered CV biomarkers in patients with psoriasis. These biomarkers may help characterize a subgroup of patients who are at risk of developing CVD and/or monitor the effectiveness of therapeutic antipsoriatic strategies on concomitant diseases. This knowledge may be useful in the management of high-need patients with psoriasis. In the pathophysiology of psoriasis, inflammation of the skin is thought to lead to systemic inflammation that contributes to comorbidities. Thus, cardiac disease, metabolic syndrome, type 2 diabetes, lipid disorders, hypertension, and obesity are more frequent in these patients (14). This study evaluated metabolic function parameters in psoriasis patients and investigated their relationship with copeptin.

Although there have been many studies on psoriasis and CVD, whether these comorbidities result from inflammation, genetics, or other factors is still being debated (14,15). There have also been studies indicating no relation (16,17). Various cardiac biomarkers have

Table 1. Patient group characteristics

	Mean ± SD	Min.-Max.
Age at Diagnosis (years)	28.1±11.5	6-52
Disease Duration(years)	13.5±9.6	0.5-41.0
Smoking (years)	13.8±15.3	0-60
PASI	16.9±7.4	10-44
HBA1C	5.55±0.58	3.60-8.06
HOMA-IR	1.96±0.83	0.82-4.34
	n	%
Psoriasis family history	10	22.2
Alcohol use	5	11.1
Psoriatic arthritis	16	35.6
Nail involvement	38	84.4
Scalp involvement	44	97.8

PASI: Psoriasis area and severity index, HBA1C: HOMA-IR: Homeostatic model assessment for insulin resistance

Table 2. Comparison of laboratory values for patient and control groups

	Patients		Control		
	Mean ± SD	**Min.-Max. (Avr)**	**Mean ± SD**	**Min.-Max. (Avr)**	**p-value**
FBS	94.0±19.8	74-207 (93)	91.2±9.4	80-121 (90)	0.516
Uric acid	5.2±1.2	3.4-8.0 (5)	6.1±7.8	2.8-56.0 (4.9)	0.414
Cholesterol	191.4±37.6	104-279 (186)	181.2±47.0	22-276 (176)	0.263
Triglyceride	134.4±52.7	59-278 (123)	130.6±68.6	41-330 (117.5)	0.398
HDL	48.5±24.9	23.9-198.0 (45)	49.1±14.8	31-109 (46.35)	0.409
LDL	113.5±36.0	8.6-203.0 (113)	113.3±30.3	67-170 (108)	0.977
Insulin	9.8±11.9	1.93-81.00 (7.2)	5.8±3.5	2.3-22.4 (5.4)	0.001
WBC	8.1±2.2	4.5-15.7 (7.95)	7.3±1.9	3.8-12.2 (7.09)	0.081
PLT	258.8±65.1	142-448 (256)	258.1±57.7	167-427 (253)	0.955
NEU	58.7±17.6	3.61-90.00 (60.9)	60.0±4.4	48.4-68.1 (60.2)	0.446
LYMH	25.4±10.6	1.06-44.9 (26.2)	30.9±3.9	21.3-40.9 (31)	0.001
CRP	6.61±12.24	0.5-78.0 (3.6)	2.31±2.90	0.13-16.40 (1.45)	0.001
Copeptin	6.81±8.36	0.76-24.00 (3)	4.87±6.31	0.73-24.00 (3)	0.997

FBS: Fasting blood sugar, NEU: Neutrophil, LYMH: Lymphocyte, PLT: Platelet, SD: Standard deviation, Min.: Minimum, Max.: Maximum
Insulin and CRP averages statistically significantly higher in psoriasis patients
Insulin resistance higher in psoriasis patients
Student's t-test and Mann-Whitney U test

Table 3. Comparison of neutrophil-lymphocyte, thrombocyte-lymphocyte ratio in the patient and control groups					
	Patient		Control		
	Mean ± SD	Min.-Max.	Mean ± SD	Min.-Max.	p-value
Neutrophil number	4.79±2.35	0.23-14.09	4.40±1.22	2.12-7.56	0.385
Lymphosit number	1.97±0.85	0.11-3.85	2.26±0.68	1.17-4.27	0.208
Neutrophil-lymphocyte	2.85±2.03	0.96-13.24	1.99±0.37	1.18-3.06	0.012
Thrombocyte-lymphocyte	300.0±668.3	58.3-3780.3	121.8±39.6	57.1-262.2	0.047

The neutrophil, thrombocyte-lymphocyte rate was significantly higher in psoriasis patients
Student's t-test and Mann-Whitney U test
SD: Standard deviation, Min.: Minimum, Max.: Maximum

been used to determine the inflammation marker in psoriasis patients (18,19). There is no entirely determined biomarker. Our study investigated copeptin in addition to classical cardiac biomarkers (20).

One of the critical comorbidities of psoriasis is obesity. Obesity is a risk factor with regard to metabolic function, and it is thought to have a complex association with abdominal obesity, glucose intolerance, atherogenic lipid disorder, and hypertension (21). In our study, waist circumference in male patients was found to be high in terms of BMI. The fact that there was no difference for female patients may have been because of the low proportion of females in the group. The high incidence of central obesity in psoriasis patients and whether it triggers psoriasis are still controversial. While obesity is reported to be an outcome in a study, some studies have reported that obesity increases psoriasis (22,23). In our study, there were no characteristics found in obesity and BMI. However, insulin levels were higher in the patient group.

A high CRP level is thought to increase the risk of cardiac disease on its own. CRP is often high in psoriasis patients, and it triggers insulin resistance and adiposity (24-26). In a study of the relationship between PASI values and CRP, no ratio was determined between these two variables. However, there were regressions and decreases in normal CRP levels after treatment (27). In this study, consistent with the literature, CRP levels were higher in the study group than in the control group. As patient therapy was excluded in this study, the values after treatment are not discussed.

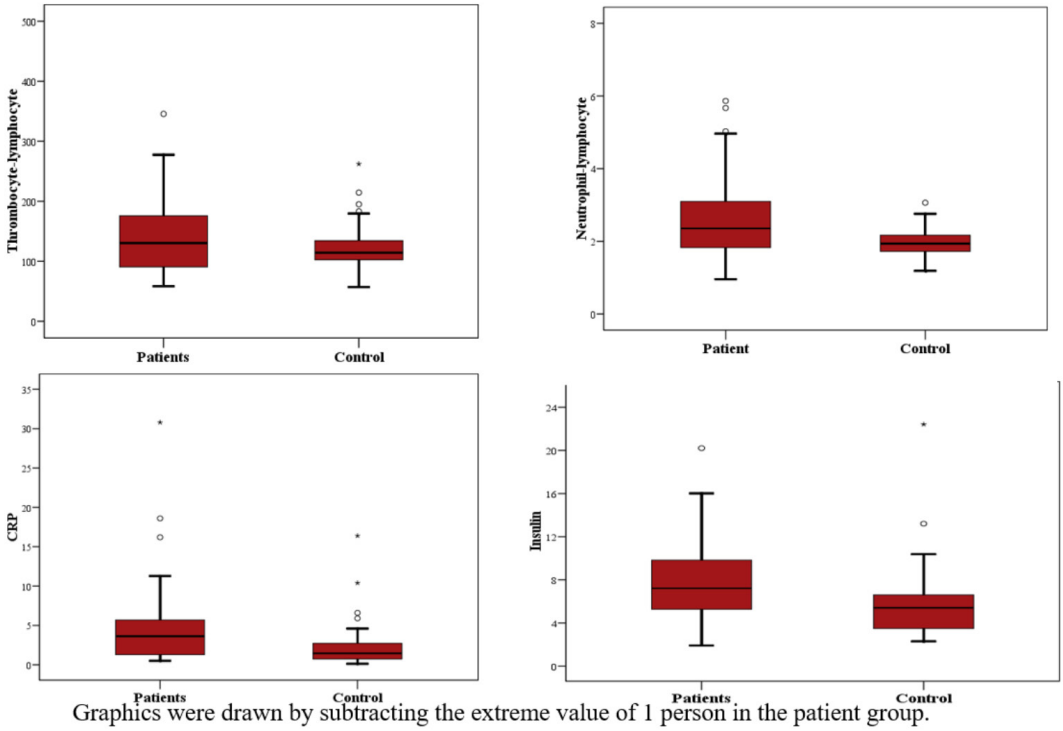

Figure 1. Neutrophil-lymphocyte rate, thrombocyte-lymphocyte rate, insulin, CRP level graphics were drawn by subtracting the extreme value of 1 person in the patient group
CRP: C-reactive protein

Neutrophil-lymphocyte and thrombocyte-lymphocyte rates are recommended as cardiac disease indicators (28). In the study by Kim et al. (29), neutrophil-lymphocyte and thrombocyte-lymphocyte ratios were evaluated and were determined to be associated with PASI scores. The authors also thought that there was an important relationship between these levels and psoriatic arthritis. This study worked with a severe patient group, and the neutrophil-lymphocyte and thrombocyte-lymphocyte rates were high in this group, in agreement with the literature.

In our study, there was no difference between the groups in terms of lipid values or hypertension. That our study did not find any difference for patients with severe psoriasis is inconsistent with the literature (30). This may be caused by the small sample size and the fact that only a single measure was evaluated.

Studies have found high levels of uric acid in psoriasis patients, especially those with psoriatic arthritis. These increased levels were related to the increase in uric acid production due to high turnover in keratinocytes (31). Uric acid levels are also high in cardiac disease and metabolic syndrome patients, as well as patients with rheumatoid arthritis and psoriatic arthritis (32). Our study found no difference between the control group and psoriasis patients in terms of uric acid levels.

The Koebner phenomenon, which is thought to be mediated by neurohormones, is also seen in patients with psoriasis (33). Copeptin is used to indicate the severity and progression of psoriasis heart failure. In several studies, copeptin was shown to be associated with insulin resistance, obesity, and metabolic disturbances (9,34). This study is the first to evaluate copeptin in psoriasis patients. Our study did not observe a statistically significant difference in copeptin levels between the two groups. This may be due to the fact that patients with CVD and acute vascular damage were excluded from our study, so the participating patients had not yet reached the level of cardiac failure.

Study Limitations

In our study, copeptin was studied in moderate-severe patients. The limited number of patients may be the lack of a statistical difference. Recently, the change in the development of cardiovascular disease with biological treatments has been the subject of frequent research. In our study, presenting the metabolic disease data of moderate-to-severe patients who did not receive treatment for three months provides data that can be used to compare new treatments.

Conclusion

Psoriasis patients are at risk of metabolic dysfunction and CVD. These patients should be monitored with easily accessible parameters such as neutrophil-lymphocyte rate, thrombocyte-lymphocyte rate, insulin level, FBG, and uric acid levels. Studies have found altered CV biomarkers in patients with psoriasis. These biomarkers may help characterize a subgroup of patients at risk of developing CVD and/or monitor the effectiveness of therapeutic antipsoriatic strategies on concomitant diseases. This knowledge may be helpful in the management of high-need patients with psoriasis. We believe that further evaluation of copeptin in patients with psoriasis will provide more information about the disease. Large-series studies are needed on this subject.

Ethics

Ethics Committee Approval: Ethical committee approval was obtained from University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Non-Drug Clinical Research Ethics Committee (382-22/06/2016)

Informed Consent: All patients signed an informed consent form.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Design: S.A., T.O.A., E.C., A.G., M.A., C.C., Data Collection and/or Processing: S.A., E.C., M.A., C.C., Analysis and/or Interpretation: M.A., Literature Research: S.A., T.O.A., F.T.D., A.G., M.A., C.C., Supervision: Z.T., Writing: S.A., T.O.A., E.C., F.T.D., A.G., M.A., Z.T., C.C.

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