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Diagnostic accuracy of angiopoietin-like protein 2 and atherosclerotic variables in psoriasis vulgaris using ROC analysis

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Abstract

Aim: Psoriasis vulgaris is a chronic inflammatory skin disease associated with various comorbidities such as metabolic syndrome and cardiovascular disease. The disease is affected by many variables. Angiopoietin-like protein 2 (ANGPTL2) is a proinflammatory cytokine, and increased serum levels are associated with inflammation, obesity, dyslipidemia, metabolic syndrome, and atherosclerosis. The aim of this study was to determine the diagnostic accuracy of the new variable ANGPTL2 and other atherosclerotic variables for psoriasis, using Receiver Operating Characteristic (ROC) analysis.

Material and Methods: The study included 41 psoriasis patients and 43 healthy volunteers. Ultrasound examination of the carotids and carotid intima-media thickness (CIMT) measurements were performed in all participants. Serum ANGPTL2 levels, lipid levels/ratios and anthropometric measurements were recorded. A ROC curve of multivariate statistical methods was used for statistical evaluation.

Results: According to the results of the ROC curves, seven diagnostic variables (ANGPTL2, BMI, weight, systolic blood pressure, waist circumference for females, uric acid and LDL-cholesterol) were found to be significant. The highest Area Under the Curve (AUC) value was found for ANGPTL2; AUC=0.721, 95% CI: 0.595-0.847, p=0.002. There was no significant difference in the lipid ratios and CIMT measurements between psoriasis patients and healthy controls.

Discussion: This study revealed that increased ANGPTL2 levels in psoriasis patients are evidence of the strong relationship between the disease and atherosclerosis. Therefore, the measurement of serum ANGPTL2 level may be a new marker that can be used to determine the risk of early atherosclerosis and metabolic complications in psoriasis patients.

Keywords

ANGPTL2; Psoriasis vulgaris; Atherosclerosis; ROC analysis

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Introduction

Psoriasis vulgaris is an inflammatory skin disease, in the etiopathogenesis of which genetic, autoimmune, and immunological factors act. It has been reported to be more frequent in patients with metabolic syndrome, cardiovascular disease (CVD), obesity, type 2 diabetes mellitus, and hypertension, and is related to many comorbidities [1, 2]. Various pro-inflammatory, prothrombotic markers increase in psoriasis disease. Atherosclerosis is considered an inflammatory disease like psoriasis. Proinflammatory cytokine production in the formation of atherosclerotic lesions is similar to that of psoriasis. All biologically active cytokines, chemokines, adipokines, and adhesion molecules have been determined to be related to the pathogenesis of both psoriasis and atherosclerosis [3, 4].

Angiopoietin-like protein (ANGPTL) is a protein with structural resemblance to angiopoietin, which is responsible for angiogenesis. Eight types of ANGPTL protein with different structures and functions have been detected. The recently identified ANGPTL2 is a proinflammatory cytokine secreted primarily from adipose tissue. ANGPTL2 has autocrine, paracrine, proinflammatory, and pro-oxidative characteristics. It is secreted from various cells such as adipocytes, macrophages, endothelial cells, cardiomyocytes, cancer cells, kidney, liver, and skeletal muscle cells, triggered by genetic susceptibility, environmental stress and risk factors, increasing the ANGPTL2 level in circulation. It has been reported that an increased serum ANGPTL2 level may be positively correlated with inflammation, atherosclerosis, insulin resistance, obesity, dyslipidemia, metabolic syndrome and cancer progression [5-7].

Carotid intima-media thickness (CIMT) measurement is a non-invasive ultrasonographic parameter, which provides information about subclinical atherosclerosis [8]. The total cholesterol/HDL (TC/HDL) ratio, low-density lipoprotein/high-density lipoprotein (LDL/HDL) ratio, and triglyceride/HDL (TG/HDL) ratio are also accepted as parameters showing the risk of CVD progression risk [9]. Body mass index (BMI), waist circumference, and waist-to-hip ratio (WHR) are body fat distribution and accumulation parameters, which are known to be related to coronary artery disease, cardiovascular mortality, and metabolic complication risk (Waist Circumference and Waist-Hip Ratio: Report of a WHO Expert Consultation, Geneva, 8-11 December 2008) [10].

When the results of current studies are examined, it can be seen that the data have generally been analyzed using a univariate method. However, multivariate statistical methods consider variations in all of the variables as a whole and therefore provide more sensitive and powerful results than univariate statistical methods. When the univariate analysis is used for multivariate data, the validity and reliability of the results decrease because of the shortcomings of the test and loss of information. This can be prevented by using multivariate statistical methods [11]. The aim of this study was to determine the Area Under Curve (AUC) diagnostic value of the new biomarker serum ANGPTL2, newly studied in psoriasis vulgaris, and other atherosclerotic variables that were included using Receiver Operating Characteristic (ROC) analysis. With the determination of asymptomatic atherosclerosis burden, the power of these diagnostic markers can be revealed.

Material and Methods

This study was conducted in the Department of Dermatology, Faculty of Medicine, Hatay Mustafa Kemal University between September 2017 and June 2019. The study included 41 patients with psoriasis vulgaris who presented at the Dermatology Outpatient Clinic and 43 age and gender-matched healthy volunteers as the control group. Adult patients with plaque type psoriasis who had not received any systemic treatment recently were included in the study. Patients with psoriatic arthritis and patients receiving immunosuppressive therapy were excluded from the study, considering that it might affect inflammation. Pregnant women, disabled individuals, aged <18 years, other dermatological diseases and those with chronic diseases such as hypertension, CVD, diabetes mellitus were excluded from the study. Informed consent was obtained from all study participants. The disease severity score in the patient group was evaluated with the psoriasis area severity index (PASI). BMI, waist circumference, WHR values, current smoking, alcohol consumption, regular daily activity, disease duration, and demographic data were recorded. The serum ANGPTL2 level measurement was made using a Human (ANGPT2) Elisa Kit (Sunredbio-Shanghai). Blood lipid levels were measured spectrophotometrically using an autoanalyzer (Abbot Architect C-8000) in a biochemistry laboratory. Lipid ratios (TC/HDL, LDL/HDL and TG/HDL) were calculated. The bilateral intima-media thickness of the common carotid arteries (carotid intima-media thickness, CIMT) measurement and the presence of carotid plaque lesion were recorded ultrasonographically via a superficial transducer (5-13 MHz).

Ethical approval was obtained for the study from the Hatay Mustafa Kemal University, Faculty of Medicine (06.16.2016/164). All procedures were applied in compliance with the Helsinki Declaration. Patient confidentiality was ensured.

Statistical analysis

The current study was planned from the outset with the aim of increasing validity and reliability. It was planned to use multivariate statistical methods instead of univariate statistical methods to increase the internal validity and accuracy of the analysis in the evaluation of the data. Mean and standard deviation (SD) values were calculated for continuous variables. The conformity of the variables to normal distribution was analyzed using the Kolmogorov-Smirnov test. Student's t-test was used to compare the mean values between the two groups. The Chi-Square test was used to analyze the interaction between categorical variables. The Mann Whitney U-test was applied to determine the relationship between ANGPTL2 and PASI.

ROC curve analysis was applied to calculate the diagnostic accuracy, as defined by the AUC, with a 95% Confidence Interval (CI). The advantage of ROC analysis for quantitative diagnostic variables is to determine the optimal cut-off points in ROC space. Therefore, optimal cut-off points were also determined.

Sample size: Based on literature information [12], the rate of psoriasis is given as 0.013. Taking the expected rate as 0.055, it was calculated with the R program that at least 57 participants should be included in the study to provide 80% power.

Two-sided p-values were considered statistically significant at p≤0.05. All statistical analyses were made using R software (version 3.6.2 (2019-12-12) – CRAN).

Results

The demographic, clinical and laboratory findings of the patients and control group were calculated as mean ± standard deviation values and analyzed with the Student's t- test. The results are presented in Table 1. ANGPTL2, BMI, weight, systolic pressure, waist circumference for females, uric acid and LDL-cholesterol were determined to be statistically significantly higher in the patient group compared to the control group (p <0.05). The demographic characteristics, symptoms, and comorbidity findings were analyzed with the Chi-Square test and the results are presented in Table 2. No statistically significant difference was determined between the groups in respect of all the categorical variables presented in Table 2 when analyzed with the Fisher Exact Test (p>0.05). The mean disease duration was 12.17±7.20 years. The mean PASI score was 8.39±5.78 (range 2 to 20). Serum ANGPTL2 level was compared with the PASI value in psoriasis patients, and no statistically significant difference was found (p> 0.05).

The ROC curve and the AUC were calculated to define the diagnostic effect of ANGPTL2, systolic blood pressure, LDL, uric acid as shown in Figure 1. ROC curves for the diagnostic accuracy of the anthropometric variables of BMI, weight and waist circumference for females are shown in Figure 2.

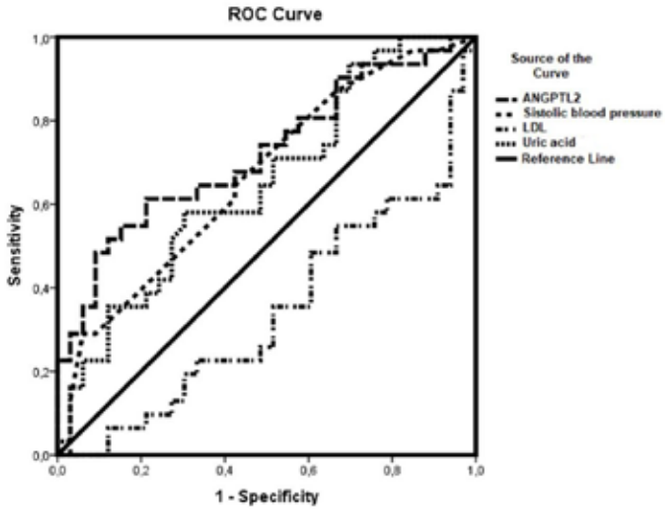

Figure 1. ROC curves for the diagnostic value of blood variables

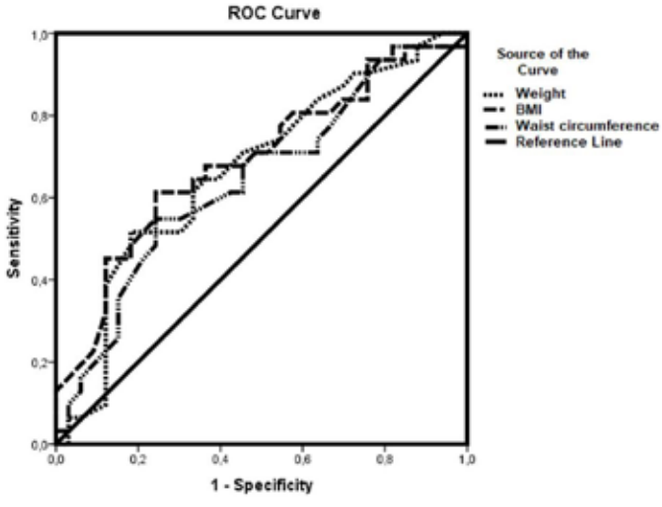

Figure 2. ROC curves for the diagnostic value of anthropometric values

Table 1. Demographic, clinical and laboratory findings of the study groups

Variables	Control	Patient	t	p
	Mean ± SD	Mean ± SD		
ANGPTL2 (ng/ml)	10.93 ± 6.400	19.42 ± 11.13	3.771	<0.001
Age (years)	37.03 ± 8.820	37.77 ± 9.820	0.319	0.751
Height (cm)	167.6 ± 7.570	168.1 ± 7.890	0.223	0.825
Weight (kg)	69.09 ± 12.03	75.19 ± 10.59	2.148	0.036
BMI (kg/m²)	24.50 ± 3.190	26.63 ± 3.390	2.588	0.012
Waist circumference for male (cm)	90,88 ± 10.88	93.88 ± 13.08	0.716	0.479
Waist circumference for female (cm)	82.75 ± 9.644	91.13 ± 9.501	2.436	0.021
Hip circumference (cm)	100.9 ± 7.420	104.2 ± 8.980	1.600	0.115
WHR	0.860 ± 0.080	0.890 ± 0.080	1.406	0.165
Systolic BP (mmHg)	110.9 ± 12.71	118.8 ± 12.76	2.499	0.015
Diastolic BP (mmHg)	70.45 ± 9.630	74.84 ± 10.29	1.761	0.083
Fasting blood glucose (mg/dL)	91.98 ± 10.24	90.74 ± 8.370	0.527	0.600
Total cholesterol (mg/dL)	198.2 ± 37.19	183.0 ± 41.91	1.539	0.129
Triglyceride (mg/dL)	103.9 ± 46.66	121.9 ± 53.77	1.434	0.157
LDL cholesterol (mg/dL)	134.7 ± 33.69	116.3 ± 34.53	2.162	0.034
HDL cholesterol (mg/dL)	43.85 ± 11.52	42.05 ± 11.41	0.625	0.534
TC / HDL ratio	4.770 ± 1.320	4.550 ± 1.250	0.689	0.493
LDL / HDL ratio	3.260 ± 1.070	2.920 ± 1.050	1.276	0.207
TG / HDL ratio	2.670 ± 1.790	3.110 ± 1.570	1.026	0.309
Uric acid (mg/dL)	4.570 ± 1.290	5.320 ± 1.320	2.326	0.023
Creatinine (mg/dL)	0.750 ± 0.100	0.740 ± 0.160	0.161	0.872
CRP (mg/dL)	4.780 ± 6.490	4.960 ± 3.680	0.133	0.895
Right carotid plaque	0.030 ± 0.170	0.060 ± 0.250	0.639	0.525
Left carotid plaque	0.000 ± 0.000	0.060 ± 0.250	1.485	0.143
Mean right CIMT (mm)	0.480 ± 0.110	0.510 ± 0.130	1.028	0.308
Mean left CIMT (mm)	0.490 ± 0.110	0.520 ± 0.110	1.062	0.292

ANGPTL2, Angiopoietin-like protein 2; BMI, body mass index; BP, blood pressure; CIMT, carotid intima media thickness; CRP, c-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, Triglyceride; WHR, waist- to- hip ratio.

Table 2. Selected characteristics of the study findings and of Chi-Square Test results

	Control	Patients	Test (x^2)	p
Current smoker (%)	13 (30.2)	16 (39.0)	0.501	>0.05
Alcohol (%)	5 (11.6)	4 (9.75)		>0.05*
Physical activity (%)	10 (23,3)	13 (31.7)	0.508	>0.05
Family history of CVD (%)	14 (32.5)	12 (29.3)	0.138	>0.05
Right carotid plaque (%)	1 (2.32)	3 (7.31)		>0.05*
Left carotid plaque (%)	0 (0.0)	3 (7.31)		>0.05*
Gender				
Male (%)	22 (51.2)	21 (51.2)	0.000	>0.05
Female (%)	21 (48.8)	20 (48.8)		

*Fisher Exact Test

Table 3. Area under curve, 95% confidence interval, cut-offs and sensitivity-specificity obtained from ROC curve analysis

Variables	AUC	SE	p	Asymptotic 95% Confidence Interval		Cut-off	Sensitivity-Specificity
				Lower Bound	Upper Bound		
ANGPTL2 (ng/ml)	0.721	0.064	0.002	0.595	0.847	9.522	0.645-0.636
BMI (kg/m2)	0.689	0.067	0.009	0.558	0.820	25.75	0.677-0.636
Weight (kg)	0.667	0.069	0.022	0.533	0.802	71.50	0.645-0.636
Systolic blood pressure (mmHg)	0.665	0.068	0.024	0.532	0.797	112.5	0.613-0.576
Waist circumference for female (cm)	0.659	0.069	0.031	0.507	0.790	85.50	0.677-0.545
Uric acid (mg/dL)	0.650	0.069	0.040	0.515	0.784	4.545	0.645-0.515
LDL cholesterol (mg/dL)	0.342	0.068	0.030	0.208	0.476	131.7	0.355-0.485

ANGPTL2, Angiopoietin-like protein 2; AUC, area under curve; BMI, body mass index; CRP, c-reactive protein; LDL, low-density lipoprotein; SE, standard error.

The AUC, Standard Error (SE) of AUC values, 95% CI, cut-off values of the diagnostic variables that were considered and the sensitivity and specificity values of the cutoff values obtained from the ROC curve analysis are shown in Table 3.

The AUC values of seven variables in the ROC analysis were found to be statistically significant ($p<0.05$) as follows: ANGPTL2 (AUC=0.721 at a cut-off value of ≥9.522 ng/ml), BMI (AUC=0.689 at a cut-off value of ≥ 25.75 kg/m2), weight (AUC=0.667 at a cut-off value of ≥71.50 kg), systolic blood pressure (AUC=0.665 at a cut-off value of ≥112.5 mmHg), waist circumference for females (AUC=0.659 at a cut-off value of ≥ 85.50 cm), uric acid (AUC=0.650 at a cut-off value of ≥4.545 mg/dL) and LDL-cholesterol (AUC=0.342 at a cut-off value of ≥131.7 mg/dL).

Discussion

The results of this study demonstrated the highest statistically significant AUC value (0.721, p=0.002) for the serum ANGPTL2 level, therefore this could be accepted as a strong diagnostic variable in psoriasis. BMI, weight, systolic blood pressure, waist circumference for females, uric acid and LDL-cholesterol levels were also found to be significant diagnostic markers for the disease. The increase of these markers in patients with psoriasis may be a significant indicator of inflammation associated with CVD risk and atherosclerosis. This study demonstrates the diagnostic power of these biomarkers.

In the literature, there is only one study, which has evaluated the ANGPTL2 level in psoriasis vulgaris and the relationship with metabolic syndrome. Kenawy et al. reported that serum ANGPTL2 levels were statistically significantly increased in patients with psoriasis compared to the healthy control group, and the serum ANGPTL2 level correlated with PASI [13]. In the current study, no statistically significant difference was found between the increase in serum ANGPTL2 levels and PASI values in the psoriasis patient group.

Hata et al. suggested that high serum ANGPTL2 levels are also a new risk factor for CVD progression in the general population and that this marker is partially mediated for metabolic disorders and inflammation [14]. Wang et al. reported that high serum ANGPTL2 levels are a new biomarker for determining acute coronary syndrome risk [15]. In another study, high serum ANGPTL2 levels were seen to be related to an increased risk of CVD in patients with type-2 diabetes [16]. In patients with coronary artery disease and in males with post-acute coronary syndrome, ANGPTL2 levels have been found to decrease with exercise [17, 18]. These data affirm the relationship between ANGPLT2 and CVD. In another study, it was suggested that high ANGPTL2 levels in circulation were clinical markers of systemic inflammation [7]. Current research suggests high serum ANGPTL2 level in psoriasis patients may be associated with an increased risk of inflammation, CVD and atherosclerosis.

BMI, waist circumference, and WHR are parameters of the distribution and accumulation of body fat, which have been shown to be associated with coronary artery disease, cardiovascular mortality, and metabolic complication risk [10]. The risk of metabolic complications has been shown to be increased in patients with waist circumference >94 cm in males, and >80 cm in females, and significantly increased when waist circumference is >102 cm in males and >88 cm in females (Waist Circumference and Waist-Hip Ratio: Report of a WHO Expert Consultation, Geneva, 8-11 December 2008). Tabata et al. reported that high serum ANGPTL2 levels indicated chronic adipose tissue inflammation and obesity related to systemic insulin resistance [19]. Park et al. reported that through diet modifications, the ANGPTL2 levels in circulation could be decreased in overweight and obese males and arterial stiffness was also seen to decrease [20]. Kenawy et al. evaluated anthropometric measurements, lipid profile, fasting blood glucose, and ANGPTL2 levels in patients with psoriasis and a control group. In addition to elevated serum ANGPTL2 levels in the psoriatic patients, fasting blood glucose, body mass index, waist circumference and mean blood pressure were also determined to be higher than in the control group [13]. Similarly, in the current study, BMI, weight, systolic blood pressure, waist circumference for females, uric acid and LDL-cholesterol levels were found to be higher in patients with psoriasis compared to healthy individuals.

TC/HDL, LDL/HDL, and TG/HDL ratios and the CIMT measurement are accepted as parameters showing CVD progression risk [8, 9]. Warnecke et al. reported that the LDL/HDL ratio was a pro-atherogenic cholesterol profile that has been seen to be increased in patients with psoriasis. It was also reported that smoking, obesity, diabetes, insulin resistance, and myocardial infarction prevalence increased significantly and cardioprotective adiponectin decreased significantly in patients with psoriasis [21]. Pietrzak et al. demonstrated that lipid metabolism anomalies and oxidative imbalance may be related to chronic inflammation in patients with psoriasis and psoriatic arthritis. The results of that study showed that HDL concentrations were higher in healthy individuals, and

TC/HDL and LDL/HDL ratios were increased in patients with psoriatic arthritis [22]. Ciccone et al. reported that central fat accumulation can accelerate the development of clinically silent early atherosclerosis and that the prevalence of CVD is higher in patients with abdominal obesity. The CIMT value was also seen to be higher in obese patients than in non-obese patients [23]. In the study conducted in patients with psoriasis, CIMT values, which are known early atherosclerosis markers, have been shown to be higher in the patient group than in the control group [24]. In the current study, no significant difference was found between the groups in terms of CIMT measurement and lipid ratios. However, it was determined that the LDL-cholesterol level was statistically significantly higher in the patient group. The increase in ANGPTL2 is thought to occur at an earlier stage than the early CVD marker of CIMT and the increase in blood lipid ratios.

The greater the AUC, the greater the diagnostic power of the variable for psoriasis vulgaris. Therefore, ANGPTL2, BMI, weight, systolic blood pressure, waist circumference for females, uric acid and LDL-cholesterol were proven to be the most powerful diagnostic variables, with high AUC values obtained in ROC analysis, as a modern multivariate statistical analysis. The evidence-based optimal cut-off points obtained in the ROC curves and their sensitivity-specificity values will provide important insights for the clinician in clinical practice.

The strengths of this study were the statistical comparison of many variables including serum ANGPTL2, which determines the risk of atherosclerosis and CVD, in patients with psoriasis and healthy individuals, and the use of ROC curve analysis with higher sensitivity and specificity as a multivariate statistical method for statistical evaluation. However, as this study was cross-sectional in design, a limitation of the study was the lack of a cohort for long-term follow-up of patients with psoriasis.

Conclusion

In conclusion, the AUC values of the variables, including ANGPTL2, defined in this study provide a new approach to the clinical diagnosis of psoriasis vulgaris. The variables of ANGPTL2, BMI, weight, systolic blood pressure, waist circumference for females, uric acid and LDL-cholesterol were determined to be significant for psoriasis vulgaris, and also constituted a risk for atherosclerosis and CVD. The data obtained in this study revealed that increased ANGPTL2 levels in patients with psoriasis are evidence of the strong relationship between the disease and atherosclerosis. Therefore, the measurement of serum ANGPTL2 level may be a new marker that can be used to determine the risk of early atherosclerosis and metabolic complications in psoriasis patients.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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