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Is Sortilin an Indicator of Subclinical Atherosclerosis in Patients with Psoriasis?

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ABSTRACT

Objective: Atherosclerosis and related cardiovascular events are quite common in patients with psoriasis. We aimed to evaluate the role of serum sortilin as a potential marker for subclinical atherosclerosis in psoriasis patients.

Materials and Methods: Serum levels of sortilin were measured by Enzyme-Linked Immunosorbent Assay (ELISA) in 33 psoriasis patients and 33 healthy controls. Waist circumference and body mass index were recorded for both groups; fasting plasma glucose (FPG), Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), serum lipid levels, and sortilin levels were also measured. Carotid and femoral intima-media thicknesses (CIMT, FIMT) were measured by ultrasonography (USG). Additionally, demographic characteristics, Psoriasis Area and Severity Index (PASI), age of onset, total duration, and presence of nail involvement were documented for patients in the study.

Results: The mean serum sortilin level was 6.20±3.11 ng/mL in the patient group and 7.82±4.97 ng/mL in the control group. No statistically significant difference was found between serum sortilin levels in both groups (p=0.729). There was no statistically significant relationship between serum sortilin levels and disease severity (p=0.597). The right and left CIMT values of the patients were significantly higher than those of the controls (p=0.012, p=0.020, respectively). There was no significant difference in FIMT values between the two groups. A statistically significant relationship was found between serum sortilin levels and right CIMT in patients (p=0.031).

Conclusion: The positive correlation between the level of sortilin and right CIMT in our patient group supports the notion that sortilin may be an indicator of subclinical atherosclerosis in psoriasis patients.

Keywords: Psoriasis, sortilin, atherosclerosis.

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INTRODUCTION

Psoriasis is a systemic inflammatory disease, and the associated inflammatory process contributes to the development of psoriatic comorbidities. It is suggested that psoriasis independently

increases the risk of atherosclerosis and cardiovascular diseases (CVD).[1] While psoriasis itself is a risk factor for atherosclerosis, additional factors such as smoking, metabolic syndrome (MS), high body mass index (BMI), alcohol consumption, and an atherogenic lipoprotein profile may further elevate CVD risk in patients with psoriasis.[2]

Sortilin is a 95 kDa protein encoded by the SORT1 gene on chromosome 13. It functions as both the receptor for neurotensin (NTR-3) and the coreceptor for pro-nerve growth factor (pro-NGF).[3] Initially identified in brain tissue, sortilin is also present in the spinal cord, skeletal muscle, testis, heart, liver, thyroid gland, adipose tissue, placenta, pancreas, prostate, small intestines, and immune system. It has been detected in skin cells such as melanocytes and keratinocytes. Although primarily known as a neurotensin receptor, sortilin also binds to lipoprotein lipase, pro-NGF, and pro-brain-derived neurotrophic factor (pro-BDGF). Its roles vary depending on the region of production, the receptors it binds to, and the extracellular environment in which it is released.[4–8]

Sortilin serves as a low-density lipoprotein (LDL) receptor in macrophages and plays a crucial role in foam cell formation, a key indicator of atherosclerotic plaque development.[3] It is a high-affinity receptor for the proinflammatory cytokines interleukin-6 (IL-6) and interferon-gamma (IFN-γ), influencing the inflammatory process by elevating levels of these cytokines. Furthermore, sortilin supports microcalcification in smooth muscle cells, compromising plaque stability. Therefore, sortilin is involved in both inflammatory and non-inflammatory mechanisms during the formation and progression of atherosclerotic plaque.[3,9,10]

Sortilin also contributes to the pathogenesis of vascular and metabolic diseases by causing atherosclerosis through mechanisms such as insulin resistance in type 2 diabetes mellitus (DM), arterial wall inflammation, calcification, and altered lipoprotein metabolism.[9] There are studies indicating that serum sortilin levels are associated with the severity of atherosclerosis in type 2 DM, cardiovascular system diseases, and metabolic syndrome.[3,9] Increased sortilin levels have been observed in the psoriatic epithelium.[11,12] However, another study found no significant differences in serum sortilin levels between psoriasis patients and control groups.[13]

In healthy skin, cell proliferation and apoptosis are balanced. Sortilin, acting as a co-receptor with pro-NGF and binding to the p75NTR receptor, directs cells towards apoptosis and plays a role in this regulatory mechanism. A mutation in the SORT1 gene, which leads to reduced protein levels, causes an upregulation of p75NTR. This upregulation affects the regulatory mechanisms of apoptosis in neurons and keratinocytes, emphasizing the critical role of the SORT1 gene mutation in these cellular processes, especially in neurons and keratinocytes.[12,14] In psoriatic skin, reduced expression of p75NTR, along with elevated levels of NGF and Tropomyosin receptor kinase (Trk), leads to increased keratinocyte proliferation and a corresponding decrease in apoptosis. This imbalance between cell growth and cell death is characteristic of psoriasis, contributing to rapid turnover and excessive buildup of skin cells typical of the condition.[11,12]

Studies have also highlighted the role of sortilin in apoptotic processes through other mechanisms. Suppression of sortilin expression has been shown to increase apoptosis, as evidenced by elevated levels of active caspase 3 and the Bcl-2-associated X protein/B-cell lymphoma 2 (Bax/Bcl-2) ratio, which are involved in apoptotic mechanisms. Furthermore, decreased expression of sortilin contributes to anti-proliferative processes by inhibiting the phosphatidylinositol 3-kinase (PI3K) and protein kinase B (AKT) pathway, which is crucial for cell proliferation.[11–15]

Endothelial function and carotid intima-media thickness are key indicators of subclinical atherosclerosis. Early detection of subclinical coronary atherosclerosis and the implementation of preventive measures can reduce the risk of coronary artery disease (CAD) in psoriasis patients.[16]

In our study, we aimed to evaluate the relationship between serum sortilin levels and disease severity, and to assess the potential of serum sortilin levels to indicate subclinical atherosclerosis.

MATERIALS AND METHODS

Our study was designed as a prospective case-control study. The study protocol was approved by the Diskapi Yildirim Beyazit Training and Research Hospital ethics committee and adhered to the International Ethical Guidelines of the Declaration of Helsinki (26/08/2019, 70/06). Informed consent was obtained from all participants before the study began.

Thirty-three plaque psoriasis patients (18 men and 15 women; average age 37.55±13.41 years) who visitied the Dermatology Department of Diskapi Yildirim Beyazit Training and Research Hospital between May 2019 and January 2020, and 33 sex- and age-matched healthy volunteers (18 men and 15 women; mean age 35.97±12.35 years) without skin diseases, were included in the study. The diagnosis of psoriasis was confirmed both clinically and histopathologically. Participants were included if they had moderate (Psoriasis Area and Severity Index (PASI) 5-10) or severe (PASI >10) psoriasis and were not currently receiving treatment for psoriasis.

The exclusion criteria included individuals younger than 18 or older than 65 years, pregnant or lactating women, patients diagnosed with chronic inflammatory or immunological disorders, conditions associated with endothelial dysfunction, infections, and individuals who had received systemic psoriasis treatment within the previous 3 months or were using medications known to affect endothelial function (Table 1). Importantly, none of the participants, including both patients and controls, were subject to any dietary restrictions.

A detailed medical history was obtained from all patients, and physical examinations were conducted. The duration and treatments of the patients' psoriasis were documented, and the type of psoriasis was determined. The PASI was used to evaluate the severity of the disease in patients with psoriasis.

The body weight, height, Body Mass Index (BMI), and waist circumference measurements were obtained for all subjects. BMI was calculated as the weight in kilograms divided by the square of the height in meters. Accordingly, patients were categorized into normal weight (BMI 20 to <25 kg/m^2), overweight (BMI ≥25 to <30 kg/m^2), and obese (BMI ≥30 kg/m^2).

Intima-Media Thickness Assessment

Images were obtained using the Esaote MyLab60 platform (Esaote Medical Systems, Italy) Ultrasonography (USG) device with a high-resolution 12 MHz linear array transducer (LA523) located in the Radiology outpatient clinic USG unit.

Measurements of the main carotid artery were taken from the distal 10 mm segment, and those of the main femoral artery were taken 1–2 cm proximal to the bifurcation by the same specialist radiologist.

Laboratory Tests

Peripheral venous blood samples were taken from all participants after a minimum of 12 hours of overnight fast. Tests for fasting plasma glucose (FPG), Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), high-density lipoprotein (HDL), total cholesterol, and triglyceride levels were conducted using routine techniques in our hospital's biochemistry laboratory.

Serum sortilin levels were measured by enzyme-linked immunosorbent assay (ELISA) using commercial kits (Sandwich-ELISA, Sunred Bio, Catalog Number: 201-12-4967, Shanghai, China) at Diskapi Yildirim Beyazit Training and Research Hospital Laboratories. The sortilin concentration of the samples was interpolated from the standard curve, with a detection range of 0.08–22 ng/mL for sortilin.

Table 1. Patient inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Active, untreated, moderate (Psoriasis Area and Severity Index (PASI) 5–10) or severe (PASI >10) psoriasis	Arterial hypertension Diabetes mellitus Metabolic syndrome Chronic renal disease Chronic hepatic disease Active malignancy or history of malignant disease Active local or systemic infection, or previous history of infection (<3 months) Body Mass Index (BMI) ≥30 Hyperlipidemia in patients receiving statin therapy Inflammatory disorders (e.g. Crohn's disease, ulcerative colitis) Patients who received treatment for psoriasis up to 3 months prior to the start of the study Cardiac disease and history of stent placement

Statistical Analysis

The minimum sample size required for each group was determined to be 30 individuals, based on a margin of error of 5% (α), a 95% confidence interval, an effect size of 0.35, and a test power of 80%.

Data were transferred to a computer and analyzed using the Statistical Package for the Social Sciences (SPSS) version 15.0. Results were considered statistically significant at $p<0.05$. Quantitative data were described using ranges (minimum and maximum), mean, standard deviation, and median. After testing the normal distribution and suitability of the data, appropriate tests were selected for intergroup comparisons. The Kolmogorov-Smirnov test assessed the data's adherence to normal distribution. Analysis of data not conforming to normal distribution was performed using the Mann-Whitney U and Spearman Correlation tests; analysis of data adhering to normal distribution was conducted using the Student t-test. Chi-square analysis was utilized to evaluate categorical variables in the study.

Table 2. Serum sortilin levels of study participants

	Cases (n=33)		Control (n=33)		p
	Min–Max	Median (IQR)	Min–Max	Median (IQR)	
Serum sortilin (mg/dl)	3.52–15.22	4.89 (4.39–6.40)	3.18–16.88	4.67 (4.25–12.78)	0.729

Mann-Whitney U Test. IQR: Interquartile range.

RESULTS

The study included 66 participants, with 33 patients and 33 controls. Each group comprised 15 (45.5%) women and 18 (54.4%) men. There was no statistically significant difference in gender distribution between the patient and control groups. The mean age in the patient group was 37.55±13.41 years (range 18-61 years), and in the control group, it was 35.97±12.35 years (range 18-57 years). There were no statistically significant differences in the mean ages between the groups.

The PASI scores for the patient group ranged from 5.0 to 21.6, with a mean of 9.12±4.20. There were no differences between the patient and control groups regarding smoking habits, alcohol consumption, BMI, and abdominal obesity. Similarly, no significant differences were observed in LDL, HDL, VLDL, cholesterol levels, triglyceride (TG) levels, HOMA-IR values, waist circumference, or BMI between the groups.

There was no significant difference in serum sortilin levels between the patient and control groups (p>0.05) (Table 2).

No correlations were found between lipid profile, waist circumference, BMI, and sortilin levels; however, a positive correlation existed between insulin resistance and sortilin levels in the study group (p=0.046) (Table 3).

Insulin resistance was identified in 3 (9.1%) individuals in the patient group and 4 (12.1%) in the control group. Individuals with insulin resistance in the study group exhibited higher sortilin levels (p<0.05). In the patient group, sortilin levels were higher in individuals with insulin resistance compared to those without (p=0.045). In the control group, there was no relationship between insulin resistance and sortilin levels (p=0.348).

In terms of right and left femoral intima-media thickness (FIMT), there was no significant difference between the patient and control groups (p>0.05). However, a significant difference was observed in right and left carotid intima-media thickness (CIMT) between the groups (p<0.05). The patient group showed significantly higher right and left CIMTs compared to the control group (Table 4).

Table 3. Serum sortilin and its correlations with clinical and laboratory characteristics

Study group (n=66)	Sortilin
	rho; p
LDL	-0.120; 0.339
HDL	0.101; 0.420
VLDL	-0.064; 0.612
Cholesterol	-0.135; 0.278
TG	-0.064; 0.612
HOMA-IR	**0.246; 0.046**
Waist circumference	-0.073; 0.558
BMI	0.166; 0.183

Spearman Correlation. LDL: Low-density lipoprotein; LDH: Lactate dehydrogenase; VLDL: Very-low-density lipoprotein; TG: Triglyceride; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; BMI: Body mass index.

There was no significant relationship between serum sortilin levels and right-left FIMT or left CIMT in the patient and control groups (p>0.05). However, a significant relationship was observed between right CIMT and sortilin level in the patient group (p=0.031) (Table 4).

No correlation was found between disease duration and PASI score with sortilin, CIMT, and FIMT values in the patient group (Table 5).

DISCUSSION

Atherosclerosis may manifest clinically as peripheral artery disease, CAD, and cerebrovascular events. One of the most significant consequences is reduced life expectancy.[17] Psoriasis is now recognized as an independent risk factor for atherosclerosis and CVD.[1]

An increase in CIMT is associated with cardiovascular outcomes, such as an increased risk of stroke and a higher frequency of CAD.[18] One study found that the prevalence of femoral atherosclerotic plaques in patients with psoriasis was significantly higher than in the control group. The frequency of femoral atherosclerotic plaques in patients was twice that of carotid plaques.[19] Consistent with much of the literature, our

Table 4. Carotid and femoral arteries intima-media thickness measurements in study participants

intima-media thickness	Cases (n=33)		Control (n=33)		p
	Min–Max	Median (IQR)	Min–Max	Median (IQR)	
Right femoral artery	0.322–1.500	0.557 (0.482–0.878)	0.319–0.769	0.539 (0.423–0.575)	0.064
Left femoral artery	0.325–1.300	0.611 (0.416–0.870)	0.347–0.934	0.562 (0.470–0.673)	0.573
Right carotid artery	0.382–1.520	0.587 (0.536–0.800)	0.403–0.891	0.542 (0.455–0.637)	**0.012**
Left carotid artery	0.408–1.400	0.626 (0.550–0.760)	0.386–0.798	0.566 (0.489–0.641)	**0.020**

Mann-Whitney U Test. IQR: Interquartile range.

Table 5. Correlations between serum sortilin levels and carotid and femoral intima-media thicknesses (CIMT-FIMT)

Mean intima-media thickness	Sortilin	
	Cases (n=33) rho; p	Control (n=33 rho; p
Right femoral artery	0.280; 0.114	-0.256, 0.150
Left femoral artery	0.278; 0.118	-0.142; 0.432
Right carotid artery	**0.377; 0.031**	-0.359; 0.055
Left carotid artery	0.182; 0.310	-0.149; 0.408

Spearman Correlation.

Table 6. Correlations between serum sortilin levels, CIMT-FIMT, and disease characteristics

Cases (n=33)	Sortilin rho; p	CIMT rho; p	FIMT rho; p
Disease duration	0.278; 0.117	0.089; 0.622	0.113; 0.532
PASI	0.097; 0.597	0.161; 0.365	0.77; 0.671

Spearman Correlation. CIMT: Carotid intima-media thickness; FIMT: Femoral intima-media thickness; PASI: Psoriasis Area and Severity Index.

study found that the right (p=0.012) and left CIMT (p=0.020) values of the patient group were significantly higher than those of the control group. However, no significant difference was found between the two groups in terms of right and left FIMT values, suggesting that carotid artery thickening precedes femoral artery thickening in patients with psoriasis, similar to other inflammatory diseases.[20,21]

Sortilin is believed to influence atherosclerosis independently of the hepatic lipoprotein mechanism.[22] In our study, there was no significant relationship between serum sortilin levels and LDL, HDL, VLDL, cholesterol, and TG levels in either the patient or control groups. Our findings also support the role of sortilin in the lipid mechanism, which is not yet fully understood.

The source of circulating sortilin, which contributes to cardiovascular risk, remains poorly understood.[9,23,24] Numerous studies have linked sortilin levels with CAD and peripheral artery disease (PAD).[3,25,26] Japanese researchers found a statistically significant decrease in serum sortilin levels (12±27%) in 90 patients with CAD after eight months of treatment with statin group antihyperlipidemics.[27] Statin group antihyperlipidemics are also known to stabilize atherosclerotic plaque, though their mechanisms are not fully understood. Furthermore, sortilin increases vascular calcification on smooth muscle cells. While statins are thought to affect sortilin, further research is necessary to explore their relationship with arterial microcalcification.

In our study, similar to the findings of Nowowiejska et al.,[13] serum sortilin levels in psoriasis patients were compared with those in a control group, revealing no significant difference (p=0.749). In the same study, it was demonstrated that sortilin levels significantly decreased in psoriasis patients following methotrexate treatment. These findings suggest that sortilin is not involved in pathogenesis. The small sample size and the mean PASI score of 9.12±4.20, which is below the threshold for moderate to severe psoriasis (PASI>10), could explain the absence of observed differences. Additionally, sortilin activity may be limited to psoriatic tissue.

In our study, a significant positive correlation was found between serum sortilin levels and right CIMT in the patient group (p=0.031). Anatomically, left-CIMT typically develops earlier than right-CIMT, as the left carotid artery branches directly from the aortic arch. Interestingly, one study found that left-CIMT was associated with biochemical parameters such as TG, LDL, and fasting blood glucose, while right-CIMT correlated with hemodynamic factors.[28] Our findings indicate that sortilin levels correlate with right-CIMT in the patient group, suggesting that sortilin could be used to indicate right-CIMT before clinical signs of systemic inflammation become apparent.

In the patient group, there was no significant relationship between serum sortilin levels and HOMA-IR, waist circumference, or BMI. The absence of a relationship with insulin resistance in this patient group may be attributed to the low number of patients with insulin resistance (n=3, 9.1%). However, when evaluating both the patient and control groups together, a significant positive correlation was observed between sortilin levels and insulin resistance (p=0.046). Literature shows both positive and negative relationships between insulin resistance and sortilin,[5,9,25] with most studies indicating a positive relationship. Our research aligns with these findings.

Sortilin is a protein influenced by comorbid conditions such as DM, hypertension, obesity, and MS.[3] In our study, we selected a patient group in which the systemic complications of psoriasis had not yet manifested clinically. We assessed whether sortilin levels could indicate subclinical atherosclerosis. The detection of a positive correlation between sortilin levels and right-CIMT confirmed that sortilin could be a marker for subclinical atherosclerosis and can also indicate insulin resistance. Additionally, we investigated the correlation between the presence and severity of psoriasis and serum sortilin levels, finding no significant relationship.

Further studies with larger patient populations, including those with and without comorbid conditions, will enable a more comprehensive evaluation of sortilin's role in the risk of developing atherosclerosis in patients with psoriasis. Drugs like statin, which can target sortilin, may offer new therapeutic options to prevent the development of atherosclerosis in these patients.

CONCLUSION

In recent years, the role of sortilin in the pathogenesis of psoriasis has been extensively researched. Our study contributes valuable insights into the potential for assessing atherosclerosis—an important comorbidity in psoriasis patients—through the biochemical parameter, sortilin. We found a statistically significant correlation between serum sortilin levels and right CIMT in the patient group (p=0.031). The detection of this positive correlation confirms that sortilin could serve as an indicator of subclinical atherosclerosis.

Ethics Committee Approval: The Diskapi Yildirim Beyazit Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 26.08.2019, number: 70/06).

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