Sakarya Tıp Dergisi
Sakarya Med J

E-ISSN: 2146-409X
Publisher: Sakarya University

Vol. 15, No. 1, 40-46, 2025
DOI: http://doi.org/10.31832/smj.1614604

Research Article

Galectin-3 Level in Carotid Artery Stenosis

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Objective: Carotid atherosclerosis is an important cause of cerebral ischaemic events and asymptomatic diagnosis of patients with advanced carotid artery stenosis is important in preventing stroke-related mortality and morbidity. Galectin-3 is known to increase inflammation by inducing the expression of a number of proinflammatory molecules in plaque pathophysiology. In this study, we aimed to evaluate the utility of serum galectin-3 level as a potential assessment tool for the severity of carotid artery disease.

Material and Methods: This prospective cross-sectional study was conducted between 06.12.2024 and 26.12.2024 in the stroke outpatient clinic of the department of neurology, Health Sciences University Adana City Training and Research Hospital. A total of 109 patients were included in the study, including 69 consecutive patients admitted with advanced (70-99% stenosis) carotid artery stenosis (CAS) and 40 patients without CAS in carotid imaging were included in the control group. An interventional neurologist and an additional neurologist determined the degree of CAS by examining carotid computed tomography angiography or carotid magnetic resonance angiography. The lipid profile (total cholesterol, high molecular weight lipoprotein, low molecular weight lipoprotein, triglycerides, apolipoprotein A1, apolipoprotein B), CRP and albumin levels were recorded. Galectin-3 levels were analysed in serum centrifuged blood.

Results: Age, hypertension incidence rate, triglycerides and Gal-3 values were found to be statistically significantly higher in the advanced CAS group compared to controls. For advanced CAS in ROC analysis; Gal-3 value was found to have a moderate discrimination ability (70-80%).

Conclusion: Our study suggests that Gal-3 levels may be used as a potential marker for the severity of carotid artery disease in CAS patients. Since advanced CAS patients are associated with a high stroke risk in follow-up, it is important that this condition is diagnosed early and treatment is directed.

Keywords: Carotid artery stenosis, Galectin-3, CRP, Albumin, Stroke

Received: 06.01.2025
Accepted: 25.02.2025
Available Online: 23.03.2025

1. INTRODUCTION

Stroke is one of the leading causes of mortality and morbidity worldwide. Carotid atherosclerosis contributes significantly to cerebral ischaemic events and increasing evidence suggests that it is associated with the stability of carotid plaque tissue. Rupture of atherosclerotic plaque can lead to thrombus formation and embolisation of the thrombus to distantly located intracranial arteries.[1,2,3]

Galectin-3 (Gal-3), a member of the galectins, a family of b-galactoside-specific lectins, is predominantly found in the cytoplasm, migrates to the nucleus and is secreted to the cell surface and biological fluids such as serum and urine. It plays important functions in numerous biological activities including cell growth, apoptosis, pre-mRNA splicing, differentiation, transformation, angiogenesis, inflammation, fibrosis and host defence. Different studies have shown that Gal-3 can be used as a diagnostic or prognostic biomarker for heart disease, kidney disease and types of cancer. Gal-3 has been recognised to be extremely useful in the detection of many of these diseases, especially at an early stage.[4]

The mechanisms by which Galectin-3 may increase the risk of atherosclerotic events are not fully understood. In the literature, Gal-3 has been reported to increase inflammation by inducing the expression of a number of proinflammatory molecules well known in plaque pathophysiology and has been found to be abundant not only in advanced lesions but also at both mRNA and

Cite as: Söker EB, Özdoğru D, Erdem M. Galectin-3 level in carotid artery stenosis. *Sakarya Med J*. 2025;15(1):40-46. doi:10.31832/smj.1614604

protein levels. Gal-3 has been shown to be involved in experimental animal models of atherosclerosis, possibly mediated by the proinflammatory effects of galectin-3, suggesting that Gal-3 levels could potentially be used as a novel biomarker of advanced plaques. In studies further implicating galectin-3 in atherosclerosis, galectin-3 inhibition in experimental mouse models of atherosclerosis reduced atherosclerotic plaque progression and inflammation. [5,6] Two studies by Zhuang et al. and Han et al. showed that higher serum Gal-3 levels were associated with stroke severity at hospitalisation and stroke prognosis at discharge.[7,8]

C-Reactive Protein (CRP) is a proinflammatory protein produced by the liver under proinflammatory cytokine induction in the acute phase response. Elevated levels of highly sensitive CRP have been associated with both increased risk of ischaemic stroke and poor functional outcome and recurrent stroke prediction in patients with minor stroke or transient ischaemic attack (TIA).[9] It has been reported in the literature that the combination of ultrasound-detected intraplaque neovascularisation and CRP levels may allow more accurate assessment of plaque stability.[10] However, carotid artery stenosis (CAS) resulting from atherosclerosis of the carotid artery is associated with ischaemic stroke, and in patients undergoing carotid angiography the ratio of CRP to albumin ratio (CAR) has been shown to be an independent risk factor for severe CAS in relation to increased severity of carotid stenosis.[11]

There is a lack of strong clinically relevant biomarkers that can predict adverse outcomes in the CAS population. CAS is often asymptomatic and difficult to detect before adverse outcomes occur; therefore, having the ability to predict patients at higher risk of an adverse event is vital in developing targeted and effective preventive strategies. In this study, we aimed to investigate the association of serum galectin-3, an inflammatory protein, and CAR with CAS and their ability to predict adverse outcomes including TIA, cerebrovascular accident (CVA) and death, suggesting that the association of Gal-3 and CAR may be considered as a potential index of the severity of carotid artery disease.

2. MATERIALS AND METHODS

2.1. The population and sample of the research

This prospective cross-sectional study was conducted between 06.12.2024 and 26.12.2024 in the stroke outpatient clinic of the Department of Neurology, Health Sciences University Adana Şehir Training and Research Hospital. A total of 109 patients were included in the study, including 69 consecutive patients admitted with asymptomatic advanced CAS (70-99% stenosis) and as a control group, 40 patients who presented to the outpatient clinic with dizziness, vertigo and no CAS was detected on carotid imaging. An interventional neurologist and an additional neurologist determined the grade of CAS by carotid computed tomography angiography or carotid magnetic resonance angiography. Patients with a history of total carotid stenosis, myocardial infarction within the last six months, TIASVO were excluded. Patients with severe hepatic or renal insufficiency, heart failure, atrial fibrillation and valvular abnormalities commonly associated with possible sources of cardioembolism were excluded. Also excluded were patients with concurrent diseases affecting the expression of inflammatory mediators, such as those with a history of major surgery in the past month, a history of malignancy, chronic inflammatory autoimmune diseases, and patients with acute infection.

2.2. Data collection tools

Past medical history including hypertension, hypercholesterolaemia, diabetes mellitus (DM), history of stroke, coronary artery disease, obesity, smoking, alcohol habits and medications were collected.

Patients with systolic blood pressure of 140 mmHg and/or diastolic blood pressure of 90 mmHg were considered hypertensive. Patients with a diagnosis of DM were recorded. A body mass index above 30 kg/m^2 was considered obesity. Patients receiving lipid-lowering therapy or patients with total cholesterol (TC) levels higher than 200 mg/dL, low molecular weight lipoprotein (LMWL) cholesterol or triglyceride (TG) levels higher than 150 mg/dL were considered hyperlipidaemic. Routine lipid profile

(total cholesterol, high molecular weight lipoprotein, LDL, triglyceride, apolipoprotein A1, apolipoprotein B, CRP and albumin levels were in patients and control group. Gal-3 levels were analysed in serum centrifuged blood

2.3. Enzyme-linked immunosorbent assay (ELISA)

Blood samples from the patient and control groups were collected in a serum separator tube. After coagulation for 2 hours at room temperature, they were centrifuged at 1000 x g for 20 minutes. Test samples were aliquoted and stored at -80°C for later use.

Galectin-3 concentration in serum samples was determined by Human GAL3 (galectin-3) ELK2790 ELISA Kit (ELK biotechnology, USA). All kit contents were stored at -20°C, and the kit was placed at 4°C one day before the study day. Serum samples were also placed at 4°C one day before the study day. The test procedure was applied to DS2 (DYNEX, USA) Enzyme-Linked Immunosorbent Assay (ELISA) Automated Processing System according to the manufacturer's instructions and galectin-3 levels in serum samples were measured. Measurement range: 0.16-10 ng/mL. Absorbance was read at 450 ± 10 nm.

2.4. Statistical method

Patient data collected within the scope of the study were analysed with IBM Statistical Package for the Social Sciences (SPSS) for Macos 29.0 (IBM Corp., Armonk, NY). Frequency and percentage for categorical data, mean, standard deviation, median, minimum and maximum for continuous data were given as descriptive values. Normality test of the variables was evaluated by Kolmogorov Smirnov test. "Mann Whitney U-Test" was used for comparisons between groups and "Chi-Square or Fisher's Exact Test" was used for comparisons of categorical variables. ROC analysis was performed for serum galectin C value, which was thought to have a discriminative effect for being sick, and the ROC curve was drawn. The results were considered statistically significant when the p value was less than 0.05.

3. FINDINGS

A total of 109 participants (69 patients and 40 controls) were included in the study. The ages of the participants ranged between 26-83 years with a median age of 65 years, 36.7% (n=40) were female and 63.3% (n=69) were male. The distribution of demographic and clinical findings of the patient and control groups is shown in Table 1. The age and the rate of HT in the advanced CAS group were found to be statistically significantly higher than in the control group (p=0.008, p=0.010).

Table 1.

Distribution of demographic and clinical findings

Variables (N=109)	Total	Advanced CAS (n=69)	Control (n=40)	p-value
	n (%) or Median (Min-Max)	n (%) or Median (Min-Max)	n (%) or Median (Min-Max)	
Age	65 (26-83)	**68 (44-83)**	**63 (26-81)**	**0.008**[a]
Gender				1.000[b]
Woman	40 (36.7)	25 (36.2)	15 (37.5)	
Male	69 (63.3)	44 (63.8)	25 (62.5)	
Comorbidities				
HT	75 (68.8)	**54 (78.3)**	**21 (52.5)**	**0.010**[b]
DM	44 (40.4)	32 (46.4)	12 (30)	0.140[b]
KAH	52 (47.7)	35 (50.7)	17 (42.5)	0.529[b]
SVO	16 (14.7)	10 (14.5)	6 (15)	1.000[b]
Migraine	4 (3.7)	2 (2.9)	2 (5)	0.623[b]

Table 1. (Continued)

Hyperlipidaemia	41 (37.6)	27 (39.1)	14 (35)	0.823[b]
Obesity	16 (14.7)	7 (10.1)	9 (22.5)	0.140[b]
Smoking	52 (47.7)	35 (50.7)	17 (42.5)	0.529[b]
Alcohol use	6 (5.5)	3 (4.3)	3 (7.5)	0.667[b]

* Patient group only. [a]Mann Whitney U-Test [b]Chi-square or Fisher's Exact Test.
CAS: Carotid artery stenosis, HT: Hypertension, DM: Diabetes Mellitus, CAD: Coronary Artery Disease, CVO: Cerebrovascular event

In the advanced CAS group, TG and Gal-3 values were statistically significantly higher than controls (p= 0.012, p=< 0.001) (Table 2).

Table 2.

Distribution of laboratory measurements

Laboratory (N=109)	Total	Advanced CAS (n=69)	Control (n=40)	p-value
	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	
Total cholesterol	171 (77-344)	166 (80-344)	171 (77-302)	0.910[a]
HDL	46 (23-96)	46 (23-96)	47.5 (31-68)	0.242[a]
LDL	105 (32-234)	105 (32-234)	109.5 (44-202)	0.338[a]
Triglyceride	128 (35-844)	**134 (53-844)**	**105.5 (35-352)**	**0.012**[a]
Apolipoprotein-b	89 (35-155)	87 (47-155)	90 (35-151)	0.456[a]
Apolipoprotein-a1	136 (49-225)	135 (49-225)	139 (105-179)	0.591[a]
Albumin	41 (32-52)	40 (32-52)	42 (32-46)	0.111[a]
CRP	3 (0.1-15.1)	2.8 (0.1-15.1)	3.8 (0.7-9.1)	0.358[a]
CRP/Albumin ratio	0.1 (0-0.4)	0.1 (0-0.4)	0.1 (0-0.2)	0.540[a]
Gal-3	0.5 (0-2.9)	**0.5 (0.3-2.9)**	**0.2 (0-1.5)**	**<0.001**[a]

[a]Mann Whitney U-Test.
CAS: Carotid artery stenosis, HDL: High density lipoprotein, LDL: Low density lipoprotein, CRP: C-Reactive protein, Gal-3: Galectin-3

In the ROC analysis, the area under the curve for alpha was 75.6% and the cut-off value was 0.37. The area under the curve shows the statistical significance of the discrimination ability of the diagnostic test. The diagnostic test evaluated in our study determined that the Gal-3 value had a moderate discrimination ability (70-80%) for advanced CAS (Table 3) (Figure 1).

Table 3.

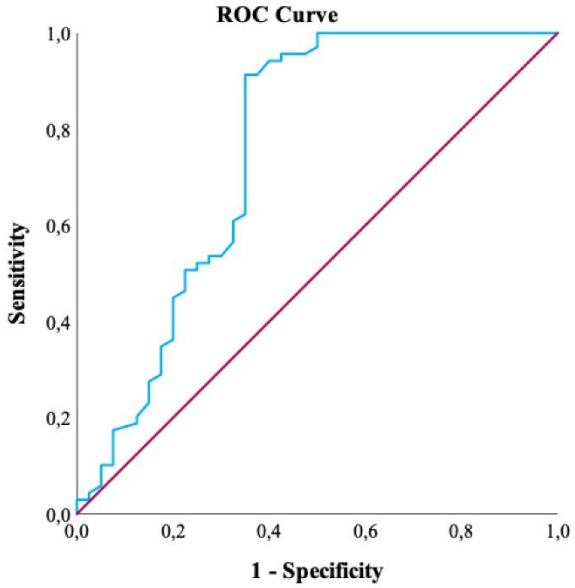
ROC analysis result for serum Gal-3 measurement parameter in advanced CAS patients

Risk Factor	AUC (95% CI)	Border	p-value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Gal-3	0.756 (0.647-0.865)	>0.37	<0.001	91.3	70.3	85.1	81.2

AUC: Area Under Curve; PPV: Positive Predictive Value; NPV: Negative Predictive Value.
CAS Carotid artery stenosis Gal-3: Galectin

Figure 1.

Serum Gal-3 ROC Curve



Gal-3: Galectin-3

4. DISCUSSION

In our study, Gal-3 value was found to be statistically significantly higher for advanced CAS and it was determined that this value had a moderate discrimination ability (70-80%). The hypothesis that atherosclerosis-related agents such as Gal-3 may enter the circulation and reflect the ongoing activity within atherosclerotic plaques is still a matter of debate.[12] In the literature, there are studies indicating that Gal-3 may be a marker of advanced plaques and may indicate stroke prognosis.[4,5,6,7] Similarly, another study found that intra-plaque Gal-3 expression levels increased proportionally as plaque width and degree of inflammation increased.[13] In another study, serum Gal-3 levels did not correlate with Gal-3 concentration in carotid plaques, suggesting that circulating Gal-3 may not be a marker of carotid plaque vulnerability. In a study, Gal-3 was found to be a predictive marker for cerebrovascular events in female patients undergoing CEA for atherosclerotic carotid stenosis. Thus, it was thought that Gal-3 could be used to select patients at high risk for the development of atherothrombotic cerebrovascular events and to prevent the occurrence of ischaemic events by intensifying their medical treatment.[14]

Studies describing the role and mechanism of Gal-3 in vascular calcification under different pathological conditions, including atherosclerosis, DM and chronic kidney disease, are summarised in the literature.[15]

However, limited data have previously documented the relationship between coronary plaque destabilisation and plasma Gal-3 levels.[16] In another study, Gal-3 levels were found to be a marker of inflammatory and metabolic distress, reflecting coronary atherosclerotic plaque instability and has been shown to be associated with long-term mortality.[17] In our study, Gal-3 levels increased in patients with advanced CAS compared to the healthy group, and we think that Gal-3 levels can be monitored in patients with CAS and used in CAS grade follow-up. However, long-term follow-up was not performed in our patient group, the relationship between Gal-3 levels and the frequency of cerebrovascular disease development in patients with advanced CAS may be revealed in future studies.

Gal-3 is a stable biomarker that is not associated with age, BMI org ender and does not exhibit circadien variation.[18]

TG elevation, whose exact role in atherosclerosis and potential benefits as a therapeutic target are still a matter of debate, was found to be statistically significantly higher than other lipid values in our study. Studies have shown that hypertriglyceridemia is common and is a significant contributor to the risk of atherosclerosis. Certain hypertriglyceridemia treatments have shown variable success in reducing the risk of atherosclerosis. [19,20]

Unlike the literature, CRP/ albumin (CAR) ratio was not found to be associated with the severity of carotid stenosis in our study. In contrast, elevated CAR was found to be an effective marker for the assessment of adverse outcomes in stroke patients and those who underwent mechanical thrombectomy.[21,22]

5. CONCLUSION

Our study suggests that Gal-3 levels may be used as a potential marker for the severity of carotid artery disease in CAS patients. Since advanced CAS

patients are associated with a high risk of stroke in follow-up, it is important that this condition is diagnosed early and treatment is directed.

Limitations

Our study has some limitations. Firstly, our sample size is relatively small and confirmatory studies in larger and diverse populations are required. Second, because our study has a cross-sectional design, we cannot assess the dynamics of changes in galectin-3 levels over time. Finally, our study did not examine the effects of genetic variations on galectin-3 levels, which may lead to deficiencies in understanding individual differences and genetic predisposition. More extensive studies are needed in the future to address these limitations.

Article Information Form

Funding

No financial support was received from any institution for the study.

The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by authors.

Ethical Statement

In our cross-sectional study, which was conducted in strict adherence to the Declaration of Helsinki, the study protocol was approved by the local ethics committee, at its meeting on 05.12.2024 (decision no:247) and written informed consent was provided by all participants.

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