Kardiologia Polska 2017; 75, 4: 351–359; DOI: 10.5603/KP.a2016.0185 ISSN 0022–9032

ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

# Galectin-3 is associated with coronary plaque burden and obstructive sleep apnoea syndrome severity

Hamdi Pusuroglu[1], Umut Somuncu[1], Ismail Bolat[2], Ozgur Akgul[1], Vesile Ornek[1], Hayriye Ak Yıldırım[1], Emre Akkaya[1], Huseyin Karakurt[1], Aydin Yıldırım[1], Ayfer Utku Savaş[1]

[1]Department of Cardiology, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Centre, Training and Research Hospital, Istanbul, Turkey
[2]Department of Cardiology, Fethiye Government Hospital, Fethiye, Turkey

## Abstract

**Background:** Obstructive sleep apnoea syndrome (OSAS) is reported to be associated with hypertension, coronary artery disease, atrial fibrillation, and heart failure. Galectin-3 plays an important role in the regulation of inflammation, development of cardiac fibrosis, and remodelling. A significant relationship between galectin-3 and the total number of coronary plaques and the macrocalcified plaque structures of patients with type 2 diabetes mellitus has been reported.

**Aim:** The aim of this study was to investigate the association between galectin-3 level and coronary plaque burden as well as OSAS severity in patients with OSAS.

**Methods:** A total of 87 consecutive patients with a diagnosis of OSAS and 21 age- and gender-matched control subjects were recruited for the present study. The patients with OSAS were also categorised according to their apnoea hypopnoea index (AHI) as follows: mild (AHI = 5–15), moderate (AHI = 15–30), and severe (AHI > 30). All study subjects underwent coronary computed tomography angiography to detect coronary atherosclerosis. Also, all participants of serum galectin-3 concentrations were measured.

**Results:** Mean galectin-3 level was significantly higher in patients with OSAS compared to control subjects ($p < 0.001$) and in the severe OSAS group, compared to the moderate and mild OSAS groups ($p < 0.001$). Correlation analysis indicated significant positive relationships between galectin-3 concentrations and the total number of coronary plaques ($p < 0.001$), high-sensitivity C-reactive protein ($p = 0.001$), and severity of OSAS ($p < 0.001$). In multivariate analysis, galectin-3 ($p = 0.01$) and age ($p = 0.025$) were significant independent predictors of coronary atherosclerosis, after adjusting for other risk factors. Also, it has been found that galectin-3 concentration is a predictor of OSAS severity ($p = 0.001$).

**Conclusions:** Galectin-3 is associated with coronary atherosclerosis and OSAS severity in OSAS patients.

**Key words:** galectin-3, obstructive sleep apnoea syndrome, coronary atherosclerosis

Kardiol Pol 2017; 75, 4: 351–359

## INTRODUCTION

Obstructive sleep apnoea syndrome (OSAS) is a condition characterised by repetitive episodes of complete or partial obstruction of the upper airway during sleep [1]. The crucial role of OSAS in the initiation and progression of atherosclerosis and increased arterial stiffness has been reported in recent studies [2, 3]. OSAS is reported to be associated with various cardiovascular diseases including hypertension, coronary artery disease (CAD), atrial fibrillation, cerebrovascular disease, and heart failure [4, 5].

Galectin-3 is a carbohydrate-binding protein that plays an important role in the regulation of inflammation, tissue fibrosis, development of cardiac hypertrophy and fibrosis, and cardiac remodelling [6, 7]. Many studies have demonstrated an important relation between galectin-3 concentrations and atherosclerosis-related risk factors such as age, smoking, diabetes, hypertension, chronic renal failure, hyperlipidaemia, and high sensitive-C-reactive protein (hs-CRP) [8, 9].

Ozturk et al. [10] reported a significant relationship between serum galectin-3 concentrations and the total number

**Address for correspondence:**
Dr. Hamdi Pusuroglu, Department of Cardiology, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Turkey, e-mail: hpusts@gmail.com

**Received:** 05.08.2016 **Accepted:** 14.11.2016 **Available as AoP:** 27.12.2016

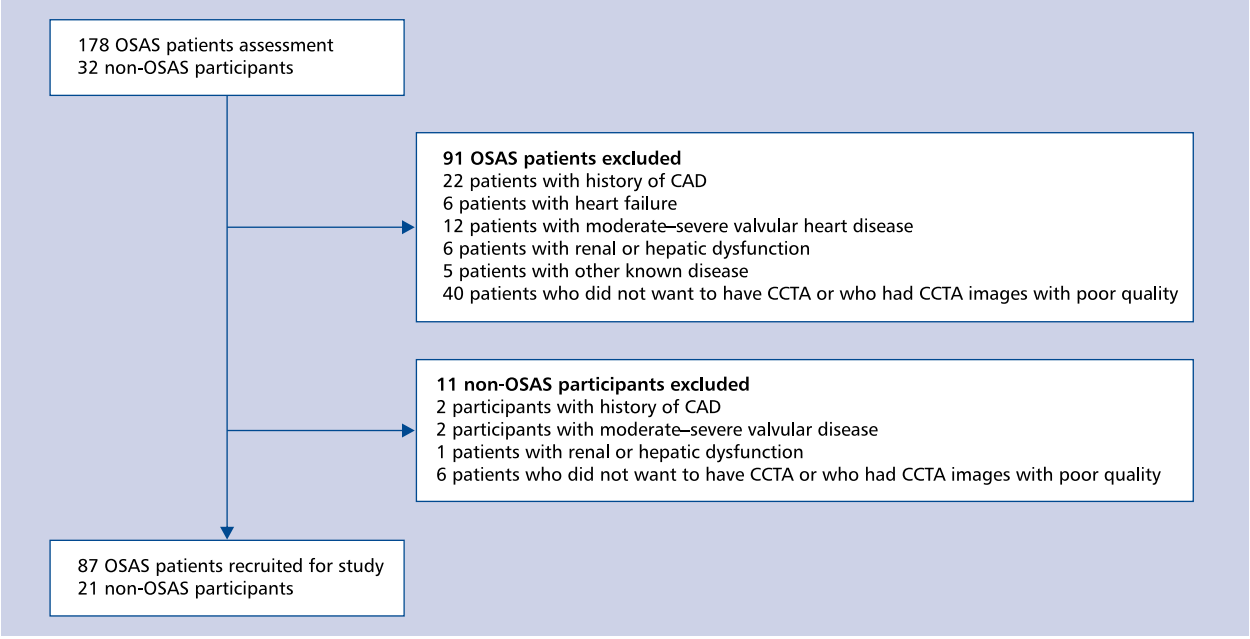


Figure 1. Study flow chart; CAD — coronary artery disease; CCTA — coronary computed tomography angiography; OSAS — obstructive sleep apnoea syndrome

of coronary plaques and the macrocalcified plaque structures, as detected by coronary computed tomography angiography (CCTA), of patients with type 2 diabetes mellitus (DM).

To the best of our knowledge, there is no information in the literature about the relationship between galectin-3 concentrations and coronary atherosclerosis indicated by the presence of coronary plaque detected by CCTA in patients with OSAS. We hypothesised that galectin-3 may be related with the presence and burden of coronary plaque and severity of disease in OSAS.

## METHODS

### *Patient selection*

This single-centre observational case-control study was conducted at a high-volume training and research hospital. A total of 178 consecutive patients, who were admitted to outpatient clinics with a diagnosis of OSAS, and 32 age- and gender-matched control subjects were recruited for the present study.

The diagnosis of OSAS was based on the defined criteria [11]. The control group composed of consecutive subjects, based on a clinical referral, suspected of having obstructive sleep apnoea admitted to the sleep laboratory at the high-volume training and research hospital, for overnight sleep studies (polysomnography). All study subjects underwent CCTA imaging.

The indications for CCTA in the study population were 97 patients with atypical chest pain, but at low-intermediate risk for CAD according to Heart Risk Score; eight inconclusive or uninterpretable stress test results; one evaluation of suspected coronary anomalies; and two exclusion of significant CAD before non-coronary cardiac surgery.

The exclusion criteria were: history of symptomatic CAD, history of coronary revascularisation procedure (percutaneous or coronary artery bypass graft surgery), heart failure, moderate–severe valvular heart disease, aortic aneurysm, renal or hepatic dysfunction, hepatitis B and C infection, other known liver diseases, patients who did not want to have CCTA or who have CCTA images with poor quality, haemolytic disorders, acute/chronic inflammatory conditions, and neoplastic diseases.

After applying the exclusion criteria, 87 patient with OSAS and 21 control subjects were enrolled into the study (Fig. 1). The patients with OSAS were also categorised according to their apnoea–hypopnoea index (AHI) as follows: mild (AHI = 5–15), moderate (AHI = 15–30), or severe obstructive sleep apnoea (AHI > 30).

Demographic information and cardiovascular risk factors of the study groups including age, gender, body mass index (BMI), and medical histories for well-known risk factors of atherosclerosis such as hypertension, DM, smoking habit, and family history were recorded following a systematic review of the patient's hospital records. Epworth sleepiness scale scores and medical histories regarding sleep habits were collected from patient records. Posteroanterior chest X-ray, respiratory function test, and electrocardiography, which were performed before polysomnography, were assessed. Furthermore, all study participants underwent a transthoracic echocardiographic examination using a Vivid S6 device with

a 3.5-MHz phased array transducer (GE Medical Systems, Horten, Norway) to evaluate left ventricular dimensions and function. Recordings were performed with the patients in the left lateral decubitus position.

Eligible patients were between 18 and 80 years of age, and all were able to provide written informed consent, which was a prerequisite for enrolment. The study complies with the Declaration of Helsinki, and the trial protocol was approved by the local Ethics Committee.

### Polysomnography

An overnight polysomnography procedure was performed with 16-channel Embla (Medcare Inc., Iceland) and continuous sleep technician monitoring. The system includes two channels of electroculogram, four channels of electroencephalography (with electrode placements at C4-A1, C3-A2, O2-A1, and O1-A2), submental electromyography (EMG), tibial EMG, oronasal air flow, pulse oximeter oxygen saturation, thoracic and abdominal movements, body position detector, tracheal sound, and electrocardiogram. Apnoea was defined as complete cessation of airflow lasting more than 10 s. Hypopnoea was defined as a reduction > 30% in airflow lasting more than 10 s accompanied by > 4% desaturation and/or arousal. The average number of episodes of apnoea and hypopnoea per hour of sleep were measured according to the AHI. The OSAS diagnosis was made on the basis of AHI > 5. Sleep stages were scored following standard criteria with 30-s epochs and were reviewed and verified by a certified sleep physician.

### Definitions

Hypertension was defined as an office blood pressure of ≥ 140/90 mm Hg or active use of antihypertensive drugs [12]. Diabetes mellitus was defined based on the American Diabetes Association criteria (fasting serum glucose ≥ 126 mg/dL [7 mmol/L], or non-fasting glucose ≥ 200 mg/dL [11.1 mmol/L], or active use of anti-diabetic treatment) [13]. The heights and weights of the study participants were measured, and BMI was calculated as body weight in kilograms divided by the square of the height in metres [kg/m$^2$]. Smokers included current and past smokers. Daily smoking habits of current smokers were obtained. Past smokers were defined as those who had abstained from smoking for a period of > 3 months at the time of the examination. Hyperlipidaemia was defined as total serum cholesterol levels greater than 240 mg/dL, low-density lipoprotein (LDL) cholesterol more than 130 mg/dL, or serum triglycerides exceeding 180 mg/dL, or if the patient used lipid-lowering agents.

### Coronary computed angiography examination

Coronary computed tomography angiography images were obtained using the dual-source CT system (Definition Flash, Siemens Medical Solution, Forchheim, Germany) with 280 ms of rotation time, 2 × 128 slices, a pitch of 3.4, and triggering at 60% of the R-R interval. The tube current was set at 180–300 mAs. A 0.6 mm slice collimation was achieved. Nonionic contrast material (Iomero 400 mgI/mL; Bracco, Milan, Italy) at a dose of 80–100 mL was administered at a rate of 5 mL/s with a dual-head power injector attached to an 18-gauge needle positioned in an antecubital vein. The bolus tracking technique was used and images were obtained during a single breath-hold of 6 s.

### Image analysis

Two experienced radiologists, blinded to the clinical data of the patients, analysed the scans on a three-dimensional workstation (Syngo; Siemens Healthcare, Erlangen, Germany); a consensus diagnosis was achieved using multi-detector CT. The radiologists analysed the presence of coronary plaques/segments on the basis of the modified American Heart Association classification [14]. Plaques were defined as 1 mm$^2$ structures within or adjacent to a vessel lumen that could be clearly distinguished from the lumen and the surrounding pericardial tissue. Coronary plaques were classified as non-calcified, calcified, and mixed according to their structure. Plaques without any calcification were defined as non-calcified, plaques with > 50% of the plaque area occupied by calcified tissue (density ≥ 130 Hounsfield in native scans) were defined as calcified, and plaques with < 50% calcium were defined as mixed type [14].

### Blood sampling

After they had undergone a 12-h fast, venous blood samples were drawn from the patients to determine levels of hs-CRP, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, and serum creatinine (Cobas C501 Autoanalyzer; Roche Diagnostics, Mannheim, Germany). Serum creatinine levels were measured using the alkaline picrate (Jaffe) method and hs-CRP levels were analysed turbidimetrically.

LDL-cholesterol measurement was performed with the indirect method, using the Friedewald formula, but when triglyceride levels of patients were above 400 mg/dL then the direct method (homogeneous calorimetric enzyme test) was used.

Serum galectin-3 concentrations were measured with a commercially available kit using an enzyme-linked immunosorbent assay method (Human Galectin-3 ELISA kit, Catalogue No. SK00199-01; Aviscera Bioscience Inc., Santa Clara, California, USA) with a lower sensitivity limit of 100 pg/mL. Samples were measured in duplicate in a single experiment. The intra- and inter-assay coefficients of variance of this kit are 4–6% and 8–10%, respectively. The detection range of galectin-3 was 156–10,000 pg/mL.

### Statistical analysis

Descriptive statistics were expressed as numbers (%) for categorical variables and as means ± standard deviation for numerical variables. The variables were investigated using

Table 1. Baseline demographic, clinical, and laboratory characteristics of the obstructive sleep apnoea syndrome (OSAS) and control groups

| | Non-OSAS (n = 21) | OSAS (n = 87) | p |
|---|---|---|---|
| Age [years] | 51.8 ± 7.3 | 53.1 ± 7 | 0.415 |
| Gender (male) | 18 (85.7%) | 62 (71.3%) | 0.175 |
| Body mass index [kg/m$^2$] | 35.2 ± 4.7 | 35.1 ± 5.8 | 0.942 |
| Smoking | 7 (33.3%) | 47 (54%) | 0.244 |
| Diabetes | 6 (28.6%) | 19 (21.8%) | 0.511 |
| Family history | 1 (4.8%) | 6 (6.9%) | 0.711 |
| Hypertension | 9 (42.9%) | 36 (41.4%) | 0.902 |
| Hyperlipidaemia | 10 (47.6%) | 57 (65,6%) | 0.129 |
| Creatinine [mg/dL] | 0.76 ± 023 | 0.81 ± 0.37 | 0.583 |
| LDL-cholesterol [mg/dL] | 135.3 ± 39.8 | 138 ± 37.6 | 0.771 |
| Haematocrit [(%] | 42.8 ± 3.9 | 42.3 ± 4.3 | 0.666 |
| Glucose [mg/dL] | 112.1 ± 26 | 118.2 ± 38.7 | 0.5 |
| hs-CRP [mg/dL] | 3.6 ± 4.1 | 5.2 ± 5.9 | 0.2 |
| Leukocyte count [10$^9$ cell/L] | 6.6 ± 1.2 | 7.2 ± 1.8 | 0.133 |
| LVEF [%] | 62.3 ± 2.97 | 63.0 ± 2.6 | 0.247 |
| Plaques | 3 (14.3%) | 54 (62.1%) | **< 0.001** |
| Number of plaque | 0.23 ± 0.7 | 2.8 ± 3.4 | **0.002** |
| Distribution of plaques: | | | 0.622 |
| Calcified | 1 (33.3%) | 16 (29.7%) | |
| Non-calcified | 0 (0%) | 22 (40.6%) | |
| Mixed | 2 (66.6%) | 16 (29.7%) | |
| AHI score | 5.4 ± 3.8 | 28.5 ± 25.7 | **< 0.001** |
| Galectin-3 [ng/mL] | 3.600 ± 850 | 5.200 ± 1600 | **< 0.001** |

AHI — apnoea-hypopnea index; hs-CRP — high-sensitivity C-reactive protein; LDL — low-density lipoprotein; LVEF — left ventricular ejection fraction

visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov) to determine if they were normally distributed. Differences between continuous and categorical variables among the groups were assessed using one-way ANOVA, Kruskal-Wallis, and $\chi^2$ test. A Mann-Whitney U or Tukey test was performed to test the significance of pairwise differences, using the Bonferroni correction to adjust for multiple comparisons. Spearman correlation analysis was performed to determine the association of galectin-3 with the examined variables In addition, stepwise multivariate logistic regression analyses, which included variables with p-values less than 0.10 in the univariate analysis, were carried out to identify the independent predictors of coronary plaque burden and OSAS severity. An overall 5% type-I error level was used to infer statistical significance, and a p-value less than 0.05 was considered significant. Statistical analyses were performed using the Statistical Package for Social Sciences version 20 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY, USA).

## RESULTS

The present study included 87 patients with OSAS (mean age 53.1 ± 7 years; 71.3% male) and 21 control subjects (mean age 51.8±7.3 years; 85.7% male). Baseline demographic, clinical, and laboratory characteristics of the OSAS and control groups are summarised in Table 1. There was no difference between two groups except for the presence and number of coronary plaques ($p < 0.001$ and $p = 0.002$) and AHI score ($p < 0.001$), which were found to be higher in the OSAS group than in the controls.

Baseline demographic, clinical, and laboratory characteristics of the mild, moderate, and severe OSAS groups are summarised in Table 2. There was no difference between the three groups except BMI, which was higher in the severe OSAS group compared to the other groups ($p = 0.011$). Furthermore, glucose ($p = 0.023$), hs-CRP ($p = 0.037$), presence ($p = 0.019$) and number of coronary plaques ($p < 0.001$), and AHI score ($p < 0.001$) were significantly higher in the severe OSAS group than in the mild and moderate groups.

Table 2. Baseline demographic, clinical, and laboratory characteristics of the mild, moderate, and severe obstructive sleep apnoea syndrome (OSAS) groups

| | Mild OSAS (n = 34) | Moderate OSAS (n = 27) | Severe OSAS (n = 26) | p |
|---|---|---|---|---|
| Age [years] | 51.6 ± 6.5 | 53.6 ± 6.7 | 55 ± 7.5 | 0.119 |
| Gender (male) | 22 (64.7%) | 20 (74.1%) | 20 (76.9%) | 0.542 |
| Body mass index [kg/m$^2$] | 32.9 ± 4.2 | 35.5 ± 5.5 | 37.3 ± 6.9 | **0.011** |
| Smoking | 16 (47.1%) | 15 (55.6%) | 16 (61.5%) | 0.527 |
| Diabetes | 2 (5.9%) | 6 (22.2%) | 12 (46.2%) | 0.105 |
| Family history | 2 (5.9%) | 3 (11.1%) | 1 (3.8%) | 0.711 |
| Hypertension | 11 (32.4%) | 12 (44.4%) | 13 (50%) | 0.360 |
| Hyperlipidaemia | 23 (67.7%) | 17 (62.9%) | 17 (65,3%) | 0.487 |
| Creatinine [mg/dL] | 0.76 ± 0.18 | 0.87 ± 0.61 | 0.81 ± 0.22 | 0.473 |
| LDL-cholesterol [mg/dL] | 138.2 ± 35.5 | 145.9 ± 41.7 | 130 ± 34.5 | 0.309 |
| Haematocrit [%] | 42.2 ± 4.2 | 41.6 ± 4.9 | 43.3 ± 4.1 | 0.347 |
| Glucose [mg/dL] | 104.2 ± 15 | 127.7 ± 48.4 | 128.7 ± 46 | **0.023** |
| hs-CRP [mg/dL] | 3.7 ± 3.1 | 4.9 ± 4.7 | 7.6 ± 8.8 | **0.037** |
| Leukocyte count [10$^9$ cell/L] | 6.8 ± 1.9 | 7.6 ± 1.9 | 7.5 ± 1.7 | 0.230 |
| LVEF [%] | 63.0 ± 2.57 | 63.0 ± 2.54 | 63.2 ± 2.58 | 0.919 |
| Plaques | 15 (44.1%) | 19 (70.4%) | 20 (76.9%) | **0.019** |
| Number of plaques | 1.1 ± 1.86 | 2.9 ± 3.5 | 5.1 ± 3.9 | **< 0.001** |
| Distribution of plaques: | | | | 0.088 |
| Calcified | 8 (53.3%) | 2 (10.6%) | 6 (30%) | |
| Non-calcified | 5 (33.3%) | 10 (52.6%) | 7 (35%) | |
| Mixed | 2 (13.3%) | 7 (36.8%) | 7 (35%) | |
| AHI score | 9.7 ± 4.7 | 25.3 ± 21.5 | 56.6 ± 21.6 | **< 0.001** |
| Galectin-3 [ng/mL] | 4.300 ± 1200 | 5.100 ± 1.400 | 6.400 ± 1700 | **< 0.001** |

AHI — apnoea-hypopnea index; hs-CRP — high sensitivity C-reactive protein; LDL — low-density lipoprotein; LVEF — left ventricular ejection fraction

In the OSAS patients, the total number of plaques was 2.8 ± 3.4. Although the rate of non-calcified plaques was highest, the rate of calcified and mixed types were similar. Moreover, when the mild, moderate, and severe OSAS groups were compared, the total number of plaques were 1.1 ± 1.86, 2.9 ± 3.5, and 5.1 ± 3.9, respectively.

Mean galectin-3 concentrations were significantly higher in patients with OSAS compared to control subjects (5.200 ± 1600 ng/mL vs. 3.600 ± 850 ng/mL, $p < 0.001$) and in the severe OSAS group compared to the moderate and mild OSAS groups (6.400 ± 1700 ng/mL, 5.100 ± 1.400 ng/mL, and 4.300 ± 1200 ng/mL, respectively, $p < 0.001$).

Correlation analysis indicated significant positive relationships between galectin-3 concentrations and the total number of coronary plaques, severity of OSAS, age, BMI, DM, hs-CRP, and AHI score (Table 3).

The discriminatory value of galectin-3 concentrations for coronary atherosclerosis was assessed by receiver operating characteristic (ROC) curve analysis and revealed the sensitivity (73.7%), specificity (77.7%), positive predictive value (74.3%), and negative predictive value (70.5%) of a cutoff value of > 4.6 ng/mL (area under the curve [AUC] 0.803; 95% confidence interval [CI] 0.720–0.887; $p < 0.001$) (Fig. 2).

In a univariate regression analysis, age, DM, hs-CRP, and galectin-3 were significantly associated with coronary atherosclerosis. Variables that were statistically significant in a univariate analysis were entered into multivariate stepwise logistic regression analysis (Table 4). In multivariate analysis, galectin-3 and age were significant independent predictors of coronary atherosclerosis, after adjusting for other risk factors in patients with OSAS. It has been shown that galectin-3 concentration is an independent predictor of OSAS severity (Table 5).

## DISCUSSION

The main findings of the present study were: (1) galectin-3 concentrations were significantly higher in patients with OSAS compared to non-OSAS subjects; (2) galectin-3 concentrations were higher as the severity of OSAS increased;

Table 3. Correlations coefficients of the relationship between galectin-3 and selected variables

| Variable | r | p |
|---|---|---|
| Age | 0.082 | **0.448** |
| Plaque | 0.438 | **< 0.001** |
| Number of plaques | 0.417 | **< 0.001** |
| Calcified plaque | 0.105 | **0.279** |
| Non-calcified plaque | 0.149 | **0.125** |
| Mixed plaque | 0.108 | **0.264** |
| Severity of OSAS | 0.473 | **< 0.001** |
| Gender | 0.084 | 0.437 |
| Body mass index | 0.239 | **0.026** |
| Total cholesterol | –0.121 | 0.266 |
| Diabetes mellitus | 0.295 | **0.006** |
| Creatinine | –0.129 | 0.235 |
| hs-CRP | 0.337 | **0.001** |
| AHI score | 0.337 | **< 0.001** |

AHI — apnoea-hypopnoea index; hs-CRP — high-sensitivity C-reactive protein; OSAS — obstructive sleep apnoea syndrome

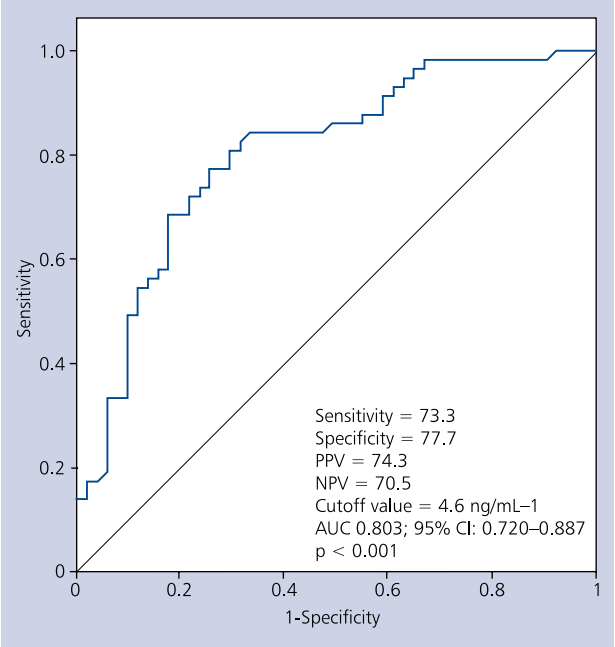


Figure 2. Receiver operator characteristic curves showing the predictive value of galectin-3 for coronary atherosclerosis in patients with obstructive sleep apnoea syndrome; AUC — area under the curve; CI — confidence interval; NPV — negative predictive value; PPV — positive predictive value

(3) galectin-3 concentrations correlated with the total number of coronary plaques; and (4) galectin-3 and age were independent significant predictors of coronary atherosclerosis in patients with OSAS. The findings of the present study indicated that elevated galectin-3 concentrations may implicate the presence of atherosclerotic changes and may suggest risk beyond that described by well-defined cardiovascular risk factors.

To the best of our knowledge, despite an association between galectin-3 and major adverse cardiovascular outcomes being shown in patients with cardiovascular disease [8], data on the relationship between galectin-3 and coronary atherosclerosis in patients with OSAS have not been published to date. We investigated this relationship using CCTA, which is a noninvasive imaging technique with a high sensitivity and specificity for the diagnosis of CAD. Galectin-3 concentration has been demonstrated to be associated with plaque burden and correlated positively with the total number of plaques in this study.

Obstructive sleep apnoea syndrome is a common condition, estimated to be prevalent in at least 5% to 15% of the adult population in developed countries. It is associated with risk factors of atherosclerosis such as smoking, obesity, age, and diabetes. Recent studies have demonstrated that OSAS is accompanied by recurrent hypoxia, arousals from sleep, and generation of exaggerated negative intrathoracic pressure that can be harmful to the cardiovascular system through several pathways, such as sympathetic activation, chronic inflammation, oxidative stress, endothelial dysfunction, and arterial stiffness [15].

The association between OSAS and atherosclerosis has been investigated in many recent studies [16–20]. Kwon et al. [16] reported a relation between OSAS and coronary calcium score (CCS) progression after adjustment for demographics, behaviours, and body mass index. However, the relation was not significant after accounting for cardiovascular risk factors. Kent et al. [18] evaluated the relationship of OSAS with occult CAD detected by CCTA and reported that severity of OSAS may predict occult coronary atherosclerosis in otherwise healthy overweight or obese male subjects. Furthermore, a significant association was revealed between OSAS and the presence of subclinical atherosclerosis assessed by tomographic CCS in patients with OSAS but with no history of known CAD. Age and AHI were also found to be independent predictors of CCS in OSAS [19]. Kepez et al. [20] investigated the direct effects of OSAS on the presence and extent of coronary atherosclerosis by using tomographic CCS on a population asymptomatic for CAD, and it was found to be higher in the severe OSAS group compared to the other OSAS groups. In addition, age was found to be a significant predictor of the presence of coronary calcification in this setting. These analyses suggest that the presence of OSAS may contribute to CAD risk of patients in association with its severity; however, association between OSAS and subclinical atherosclerosis seemed to be primarily dependent on age [20]. In our study, we investigated the relation between galectin-3 concentration and coronary atherosclerosis indicated by the presence and burden of coronary plaque detected by CCTA in patients

Table 4. Univariate and multivariate regression analysis of predictors of coronary atherosclerosis in patients with obstructive sleep apnoea syndrome (OSAS)

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR (95% CI) | p | OR (95% CI) | p |
| Smoking | 0.388 (0.124–1.214) | 0.104 | | |
| OSAS severity | 0.175 (0.076–0.405) | **0.002** | 0.393 (0.149–1.37) | 0.059 |
| Galectin-3 | 2.433 (1.653–3.582) | **0.001** | 2.175 (1.425–3.320) | **0.010** |
| Age | 1.023 (0.969–1.079) | **0.016** | 1.079 (1.009–1.153) | **0.025** |
| hs-CRP | 1.064(0.963–1.149) | 0.154 | | |
| Male gender | 0.962 (0.609–2.840) | 0.944 | | |
| NLR | 1.605 (0.837–3.075) | 0.283 | | |
| Hypertension | 0.599 (0.256–1.335) | 0.234 | | |
| Hyperlipidaemia | 1.197 (0.427–3.335) | 0.215 | | |
| Diabetes mellitus | 0.905 (0.426–2.322) | **0.005** | 0.172 (0.050–0.590) | 0.070 |
| Ejection fraction | 0.906 (0.792–1.051) | 0.193 | | |

CI — confidence interval; hs-CRP — high-sensitivity C-reactive protein; NLR — neutrophil-to-lymphocyte ratio; OR — odds ratio

Table 5. Univariate and multivariate regression analysis of predictors of obstructive sleep apnoea syndrome severity

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR (95% CI) | p | OR (95% CI) | p |
| Body mass index | 1.097 (1.016–1.184) | **0.018** | 1.110 (1.001–1.231) | 0.053 |
| Galectin-3 | 2.364 (1.624– 3.441) | **< 0.001** | 2.329 (1.558–3.480) | **0.001** |
| Age | 1.061 (1.003–1.122) | **0.040** | 1.107 (1.025–1.195) | **0.014** |
| hs-CRP | 1.117(1.106–1.227) | **0.022** | 1.091 (0.970–1.226) | 0.145 |
| Male gender | 0.867 (0.366–2.053) | 0.745 | | |
| Hypertension | 1.563 (0.724–3.374) | 0.256 | | |
| Hyperlipidaemia | 0.765 (0.163–3.593) | 0.734 | | |
| Diabetes mellitus | 1.776 (0.716–4.410) | 0.216 | | |

CI — confidence interval; hs-CRP — high-sensitivity C-reactive protein; OR — odds ratio

with OSAS. Galectin-3 and age were independent predictors of coronary atherosclerosis in OSAS patients. Furthermore, the presence and total number of coronary plaques and AHI score were found to be higher in the OSAS group than in the controls and in the severe OSAS group compared to the moderate and mild OSAS groups, which is consistent with previous studies [16–20].

Galectin-3 plays a pivotal role in the development of fibrosis and tissue remodelling in kidney and heart [6]. It has been produced by macrophages and activated myofibroblasts, and soluble galectin-3 concentrations can be measured in peripheral blood as fibrosis biomarker [21]. Galectin-3 level was reported to be a strong prognostic marker for major adverse cardiovascular events in heart failure in recent studies [22, 23]. Moreover, de Boer et al. [9] reported that galectin-3 level was an independent predictor of all-cause and cardiovascular mortality in the general population, independent of other cardiovascular risk factors. A significant relationship between serum galectin-3 concentrations and the total number of coronary plaques and the macrocalcified plaque structures, as detected by CCTA, of patients with type 2 DM was demonstrated in a study by Ozturk et al. [10]. Galectin-3 levels were correlated with BMI, hs-CRP, and the total number of plaques. Older age, smoking, high hs-CRP, and high LDL-cholesterol concentrations, in addition to galectin-3, were predictors of coronary atherosclerosis in patients with type 2 DM [10]. In our study, consistent with the findings of this study, BMI, hs-CRP, and the total number of plaques were significantly positively correlated with galectin-3. However, only age and galectin-3 were found to be significant independent predictors of coronary atherosclerosis in patients with OSAS. We also evaluated the association between galectin-3 concentrations and plaque composition. However, no association was found between galectin-3 and calcified, non-calcified, and mixed plaques.

As a result, higher galectin-3 levels in the severe OSAS group concomitant with the significant positive relation with hs-CRP, AHI, and the total number of plaques may be explained by chronic inflammation, recurrent and/or long-term hypoxia, oxidative stress, endothelial dysfunction, and arterial stiffness, which are the main pathophysiological mechanisms of OSAS.

### Limitations of the study

There are some limitations related with the present study. First, this study involved a single centre and was a non-randomised study and therefore was subject to selection bias. Second, the study population was relatively small; however, we were still able to demonstrate a strong relationship between galectin-3 concentration and subclinical atherosclerosis indicated by the presence of coronary plaque detected by CCTA in patients with OSAS. Third, a lack of follow-up data describing future cardiovascular events meant that the prognostic value of galectin-3 concentrations was not evaluated. Last, the study participants were Turkish, so the results may not be applicable to other ethnic groups or populations.

## CONCLUSIONS

We demonstrated a significant association between serum galectin-3 concentrations and coronary atherosclerosis in patients with OSAS. Also, it was found that more severe OSAS is associated with galectin-3 concentrations. It may be used for risk stratification and follow-up of OSAS patients.

***Conflict of interest:*** *none declared*

### References


1. Somers VK, Dyken ME, Clary MP, et al. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest. 1995; 96(4): 1897–1904, doi: 10.1172/JCI118235, indexed in Pubmed: 7560081.
2. Mooe T, Franklin KA, Holmström K, et al. Sleep-disordered breathing and coronary artery disease: long-term prognosis. Am J Respir Crit Care Med. 2001; 164(10 Pt 1): 1910–1913, doi: 10.1164/ajrccm.164.10.2101072, indexed in Pubmed: 11734445.
3. Ip MSM, Tse HF, Lam B, et al. Endothelial function in obstructive sleep apnea and response to treatment. Am J Respir Crit Care Med. 2004; 169(3): 348–353, doi: 10.1164/rccm.200306-767OC, indexed in Pubmed: 14551167.
4. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med. 2001; 163(1): 19–25, doi: 10.1164/ajrccm.163.1.2001008, indexed in Pubmed: 11208620.
5. Lattimore JDL, Celermajer DS, Wilcox I. Obstructive sleep apnea and cardiovascular disease. J Am Coll Cardiol. 2003; 41(9): 1429–1437, indexed in Pubmed: 12742277.
6. Sharma UC, Pokharel S, van Brakel TJ, et al. Galectin-3 marks activated macrophages in failure-prone hypertrophied hearts and contributes to cardiac dysfunction. Circulation. 2004; 110(19): 3121–3128, doi: 10.1161/01.CIR.0000147181.65298.4D, indexed in Pubmed: 15520318.
7. Gruson D, Ko G. Galectins testing: new promises for the diagnosis and risk stratification of chronic diseases? Clin Biochem. 2012; 45(10-11): 719–726, doi: 10.1016/j.clinbiochem.2012.04.009, indexed in Pubmed: 22546645.
8. Yu X, Sun Y, Zhao Y, et al. Prognostic value of plasma galectin-3 levels in patients with coronary heart disease and chronic heart failure. Int Heart J. 2015; 56(3): 314–318, doi: 10.1536/ihj.14-304, indexed in Pubmed: 25902879.
9. de Boer RA, van Veldhuisen DJ, Gansevoort RT, et al. The fibrosis marker galectin-3 and outcome in the general population. J Intern Med. 2012; 272(1): 55–64, doi: 10.1111/j.1365-2796.2011.02476.x, indexed in Pubmed: 22026577.
10. Ozturk D, Celik O, Satilmis S, et al. Association between serum galectin-3 levels and coronary atherosclerosis and plaque burden/structure in patients with type 2 diabetes mellitus. Coron Artery Dis. 2015; 26(5): 396–401, doi: 10.1097/MCA.0000000000000252, indexed in Pubmed: 25887000.
11. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep. 1999; 22(5): 667–689, indexed in Pubmed: 10450601.
12. O'Brien E, Asmar R, Beilin L, et al. Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. Journal of Hypertension. 2005; 23(4): 697–701, doi: 10.1097/01.hjh.0000163132.84890.c4.
13. Genuth S, Alberti KG, Bennett P, et al. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care. 2003; 26(11): 3160–3167, indexed in Pubmed: 14578255.
14. Austen WG, Edwards JE, Frye RL, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. Circulation. 1975; 51(4 Suppl): 5–40, indexed in Pubmed: 1116248.
15. Wolk R, Kara T, Somers VK. Sleep-disordered breathing and cardiovascular disease. Circulation. 2003; 108(1): 9–12, doi: 10.1161/01.CIR.0000072346.56728.E4, indexed in Pubmed: 12847053.
16. Kwon Y, Duprez DA, Jacobs DR, et al. Obstructive sleep apnea and progression of coronary artery calcium: the multi-ethnic study of atherosclerosis study. J Am Heart Assoc. 2014; 3(5): e001241, doi: 10.1161/JAHA.114.001241, indexed in Pubmed: 25261530.
17. Gunnarsson SI, Peppard PE, Korcarz CE, et al. Obstructive sleep apnea is associated with future subclinical carotid artery disease: thirteen-year follow-up from the Wisconsin sleep cohort. Arterioscler Thromb Vasc Biol. 2014; 34(10): 2338–2342, doi: 10.1161/ATVBAHA.114.303965, indexed in Pubmed: 25189572.
18. Kent BD, Garvey JF, Ryan S, et al. Severity of obstructive sleep apnoea predicts coronary artery plaque burden: a coronary computed tomographic angiography study. Eur Respir J. 2013; 42(5): 1263–1270, doi: 10.1183/09031936.00094812, indexed in Pubmed: 23471346.
19. Arik B, Inci MF, Gumus C, et al. Advanced age and apnea-hypopnea index predict subclinical atherosclerosis in patients with obstructive sleep apnea syndrome. Multidiscip Respir Med. 2013; 8(1): 9, doi: 10.1186/2049-6958-8-9, indexed in Pubmed: 23384202.
20. Kepez A, Niksarlıoğlu EY, Hazırolan T, et al. Evaluation of association between obstructive sleep apnea and coronary risk scores predicted by tomographic coronary calcium scoring in asymptomatic patients. Anadolu Kardiyol Derg. 2011; 11(5): 428–435, doi: 10.5152/akd.2011.106, indexed in Pubmed: 21652293.
21. Liu YH, D'Ambrosio M, Liao Td, et al. N-acetyl-seryl-aspartyl-lysyl-proline prevents cardiac remodeling and dysfunction induced by galectin-3, a mammalian adhesion/growth-regulatory lectin. Am J Physiol Heart Circ Physiol. 2009; 296(2): H404–H412, doi: 10.1152/ajpheart.00747.2008, indexed in Pubmed: 19098114.
22. van Kimmenade RR, Januzzi JL, Ellinor PT, et al. Utility of amino-terminal pro-brain natriuretic peptide, galectin-3, and apelin for the evaluation of patients with acute heart failure. J Am Coll Cardiol. 2006; 48(6): 1217–1224, doi: 10.1016/j.jacc.2006.03.061, indexed in Pubmed: 16979009.
23. Tang WH, Shrestha K, Shao Z, et al. Usefulness of plasma galectin-3 levels in systolic heart failure to predict renal insufficiency and survival. Am J Cardiol. 2011; 108(3): 385–390, doi: 10.1016/j.amjcard.2011.03.056, indexed in Pubmed: 21600537.


**Cite this article as:** Pusuroglu H, Somuncu U, Bolat I, et al. Galectin-3 is associated with coronary plaque burden and obstructive sleep apnoea syndrome severity. Kardiol Pol. 2017; 75(4): 351–359, doi: 10.5603/KP.a2016.0185.

# Związek galektyny-3 z liczbą blaszek miażdżycowych w tętnicach wieńcowych i stopniem ciężkości obturacyjnego bezdechu sennego

Hamdi Pusuroglu[1], Umut Somuncu[1], Ismail Bolat[2], Ozgur Akgul[1], Vesile Ornek[1], Hayriye Ak Yıldırım[1], Emre Akkaya[1], Huseyin Karakurt[1], Aydin Yıldırım[1], Ayfer Utku Savaş[1]

[1]Department of Cardiology, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Centre, Training and Research Hospital, Istanbul, Turcja
[2]Fethiye Government Hospital, Department of Cardiology, Fethiye, Turcja

## Streszczenie

**Wstęp:** Jak podają doniesienia, zespół obturacyjnego bezdechu sennego (OSAS) wiąże się z nadciśnieniem tętniczym, chorobą wieńcową, migotaniem przedsionków i niewydolnością serca. Galektyna-3 odgrywa istotną rolę w regulacji stanu zapalnego, rozwoju zwłóknienia serca i jego przebudowy. Opisywano istotne zależności między stężeniem galektyny-3 a całkowitą liczbą blaszek miażdżycowych w naczyniach wieńcowych i blaszek uwapnionych u chorych na cukrzycę typu 2.

**Cel:** Celem niniejszego badania była ocena związku między stężeniem galektyny-3 a liczbą blaszek miażdżycowych i stopniem ciężkości OSAS u chorych z zespołem obturacyjnego bezdechu sennego.

**Metody:** Do badania włączono 87 kolejnych pacjentów z rozpoznaniem OSAS i 21 dobranych pod względem wieku i płci osób kontrolnych. Chorych z OSAS dodatkowo podzielono na grupy ciężkości OSAS w zależności od wskaźnika stosunku bezdechów do spłyconych oddechów (AHI): łagodny (AHI = 5–15), umiarkowany (AHI = 15–30), ciężki (AHI > 30). U wszystkich uczestników badania wykonano koronarografię metodą tomografii komputerowej w celu wykrycia miażdżycy tętnic wieńcowych oraz zmierzono stężenie galektyny-3 w surowicy.

**Wyniki:** Średnie stężenie galektyny-3 było istotnie wyższe u chorych z OSAS niż u osób z grupy kontrolnej ($p < 0,001$), a u pacjentów z ciężkim OSAS było istotnie wyższe niż w grupach z umiarkowanym i łagodnym OSAS ($p < 0,001$). Wykazano istotne dodatnie korelacje między stężeniem galektyny-3 a całkowitą liczbą blaszek miażdżycowych w tętnicach wieńcowych ($p < 0,001$), stężeniem białka C-reaktywnego mierzonego metodą wysokoczułą ($p = 0,001$) i stopniem ciężkości OSAS ($p < 0,001$). W analizie wieloczynnikowej stężenie galektyny-3 ($p = 0,01$) i wiek ($p = 0,025$) były istotnymi niezależnymi czynnikami predykcyjnymi miażdżycy tętnic wieńcowych po skorygowaniu względem innych czynników ryzyka. Stwierdzono również, że stężenie galektyny-3 jest czynnikiem predykcyjnym stopnia ciężkości OSAS ($p = 0,001$).

**Wnioski:** U chorych z OSAS stężenie galektyny-3 wiąże się z nasileniem zmian miażdżycowych i stopniem ciężkości OSAS.

**Słowa kluczowe:** galektyna-3, zespół obturacyjnego bezdechu sennego, miażdżyca tętnic wieńcowych

Kardiol Pol 2017; 75, 4: 351–359

**Adres do korespondencji:**
Dr. Hamdi Pusuroglu, Department of Cardiology, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Turkey, e-mail: hpusts@gmail.com

**Praca wpłynęła:** 05.08.2016 r. **Zaakceptowana do druku:** 14.11.2016 r. **Data publikacji AoP:** 27.12.2016 r.