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WNT Signaling Cascade Proteins and LRP6 in the Formation of Various Types of Coronary Lesions in Patients With Coronary Artery Disease

Aim	Assessment of WNT1, WNT3a, and LRP6 concentrations in patients with ischemic heart disease (IHD) and obstructive and non-obstructive coronary artery (CA) disease.
Material and methods	This cross-sectional observational study included 50 IHD patients (verified by coronary angiography, CAG), of which 25 (50%) were men, mean age 64.9±8.1 years; 20 patients had non-obstructive CA disease (stenosis <50%), and 30 patients had hemodynamically significant stenosis. Concentrations of WNT1, WNT3a and LRP6 were measured in all patients.
Results	The concentrations of WNT1 and WNT3a proteins were significantly higher in patients with IHD and obstructive CA disease (p<0.001), while the concentration of LRP6 was higher in the group with non-obstructive CA disease (p=0.016). Data analysis of the group with obstructive CA disease showed a moderate correlation between WNT1 and LRP6 (ρ=0.374; p=0.042). Correlation analysis of all groups of patients with CA disease revealed a moderate association between the concentrations of WNT1 and uric acid (ρ=0.416; p=0.007). Regression analysis showed that risk factors for the development of IHD, such as increased body mass index, age, smoking, dyslipidemia, and hypertension, did not significantly influence the type of CA disease in IHD patients. According to ROC analysis, the obstructive form of IHD was predicted by a WNT3a concentration higher than 0.155 ng/ml and a LRP6 concentration lower than 12.94 ng/ml.
Conclusion	IHD patients with non-obstructive CA disease had the greatest increase in LRP6, while patients with obstructive CA disease had significantly higher concentrations of the canonical WNT cascade proteins, WNT1 and WNT3a. According to the ROC analysis, a WNT3a concentration >0.155 ng/ml can serve as a predictor for the presence of hemodynamically significant CA stenosis in IHD patients (sensitivity 96.7%; specificity 70%), whereas a LRP6 concentration >12.94 ng/ml can predict the development of non-obstructive CA disease (sensitivity 76.7%; specificity 65%).

Keywords	Ischemic heart disease; non-obstructive coronary artery disease; WNT1; WNT3a; LRP6
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Introduction

According to the World Health Organization (WHO), coronary artery disease (CAD) is the leading cause of mortality worldwide, ranking first among the top 10 causes of death [1]. In addition to the decline in population size, cardiovascular diseases (CVDs) and CAD in particular result in a considerable increase in financial costs. The total annual expenditure of 27 EU countries on the examination, hospitalization, revascularization, and other treatments of patients with CVDs is estimated to be 282 billion euros. Of this amount, 27 % (77 billion euros) is allocated to the treatment of CAD [2]. Coronary angiography (CAG) shows that approximately 70 % of patients presenting with anginal pain exhibit ischemia with no obstructive coronary arteries (INOCA). Non-obstructive coronary artery lesions are more common in women (50–70 %) than in men (30–50 %) [3].

It is important to note that the prognosis for patients with CAD and no hemodynamically significant stenosis is not favorable. In a large retrospective study (12,814 patients with chronic heart failure with reduced ejection fraction), non-obstructive CAD (2,254 (17.6 %) patients) was associated with an increased risk of cardiovascular mortality (hazard ratio (HR) 1.82; 95 % confidence interval (CI) [1.27; 2.62], p=0.001) and all-cause mortality (OR 1.18; 95 % CI [1.05; 1.33], p=0.005) compared with those in patients without coronary artery stenosis (2,656 (20.7 %) patients) [4]. Consequently,

INOCA is not a benign condition and is associated with impaired quality of life and the development of adverse outcomes, the incidence of which may be comparable to that of obstructive CAD. It should be recognized as an essential disease in routine clinical practice.

Despite the significant advances in modern medicine, the pathogenesis of coronary atherosclerosis development and progression, including non-obstructive or obstructive lesions, remains poorly understood.

The WNT cascade is one of the major signaling pathways regulating endothelial function. It is hypothesized that disruption of WNT signaling by oxidative stress and/or inflammation may be a common molecular mechanism contributing to atherosclerosis, insulin resistance, and hyperlipidemia. The incidence of these conditions increases with age. In vivo studies established a role for the WNT pathway at all stages of atherosclerosis development. However, much of the pathogenesis remains unexplored or controversial [5].

The WNT signaling pathway was first identified over 30 years ago as a result of a concurrent investigation into the genes regulating pattern formation in the Drosophila wingless and the preferred integration sites of the mammary tumor virus in mice (int1). A comparison of the results of these works revealed that homologous genes are involved in this process, which led to the above family being given the common name WNT [6].

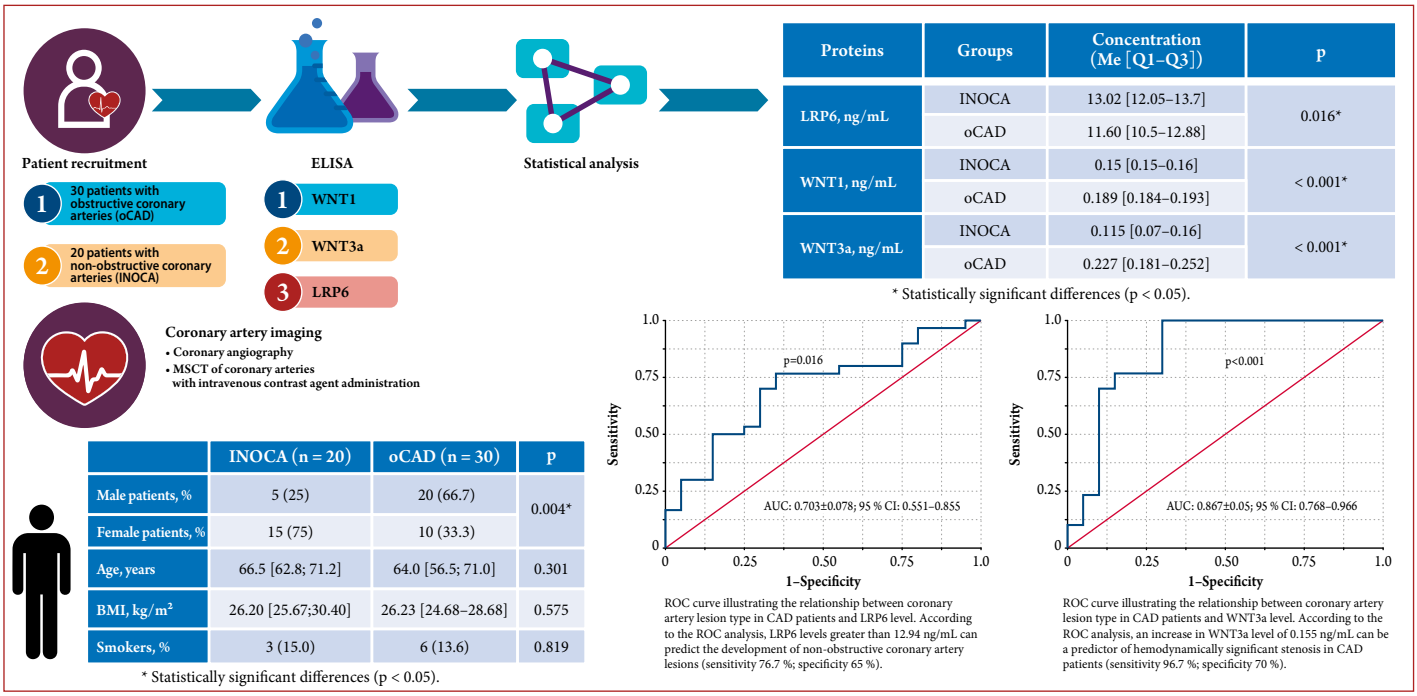
WNTs are cysteine-rich extracellular signaling molecules highly conserved glycoproteins that are involved in the regulation of cell cycle, growth, and differentiation. A total of 19 WNT proteins have been identified that act as ligands for Frizzled (FZD) family receptors [7, 8].

The WNT family of proteins can be divided into two distinct groups: the canonical and non-canonical. The canonical WNT cascade comprises WNT1, WNT2, WNT3, WNT8, and WNT10, while the non-canonical cascade includes WNT4, WNT5, WNT6, WNT7, and WNT11. Both canonical and non-canonical WNT pathways are capable of activating unrelated co-receptors through a common mechanism [9].

The WNT receptor is a protein with seven FZD transmembrane segments and an LRP6 co-receptor (lipoprotein receptor protein-6, which is a member of the low-density lipoprotein receptor (LDLR) family) consisting of structurally related cell surface receptors. LRP6 functions in conjunction with FZD receptors to mediate the WNT/β-catenin canonical signaling pathway [10, 11].

LRP6 dysregulation is closely associated with the development of atherosclerosis and CAD. Based on limited experimental data (WNT models of the LRP6 co-receptor in heterozygous mice), it was concluded that altered WNT cascade signaling may be involved in the pathogenesis of atherosclerotic plaque erosion [12]. The role of LRP6 in regulating lipid and glucose metabolism was established by full genomic analysis of CAD patients. It was shown that mutations in the LRP6 co-receptor, including R473Q, R360H, N433S, and R611C, are associated with high blood levels

Central illustration. WNT Signaling Cascade Proteins and LRP6 in the Formation of Various Types of Coronary Lesions in Patients With Coronary Artery Disease



Proteins	Groups	Concentration (Me [Q1–Q3])	p
LRP6, ng/mL	INOCA	13.02 [12.05–13.7]	0.016*
	oCAD	11.60 [10.5–12.88]	
WNT1, ng/mL	INOCA	0.15 [0.15–0.16]	< 0.001*
	oCAD	0.189 [0.184–0.193]	
WNT3a, ng/mL	INOCA	0.115 [0.07–0.16]	< 0.001*
	oCAD	0.227 [0.181–0.252]	

* Statistically significant differences ($p < 0.05$).

	INOCA (n = 20)	oCAD (n = 30)	p
Male patients, %	5 (25)	20 (66.7)	0.004*
Female patients, %	15 (75)	10 (33.3)	
Age, years	66.5 [62.8; 71.2]	64.0 [56.5; 71.0]	0.301
BMI, kg/m^2	26.20 [25.67;30.40]	26.23 [24.68–28.68]	0.575
Smokers, %	3 (15.0)	6 (13.6)	0.819

* Statistically significant differences ($p < 0.05$).

ROC curve illustrating the relationship between coronary artery lesion type in CAD patients and LRP6 level. According to the ROC analysis, LRP6 levels greater than 12.94 ng/mL can predict the development of non-obstructive coronary artery lesions (sensitivity 76.7 %; specificity 65 %).

ROC curve illustrating the relationship between coronary artery lesion type in CAD patients and WNT3a level. According to the ROC analysis, an increase in WNT3a level of 0.155 ng/mL can be a predictor of hemodynamically significant stenosis in CAD patients (sensitivity 96.7 %; specificity 70 %).

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of glucose and low-density lipoprotein cholesterol (LDL-C) [13]. Furthermore, the LRP6R611C mutation is associated with reduced LDL uptake by macrophages, increased vascular smooth muscle cell (VSMC) proliferation, and the suppression of WNT/β-catenin signaling and stimulation of the non-canonical WNT pathway [14]. Consequently, the proliferation and migration of VSMCs, accompanied by their accelerated accumulation in the arterial wall, are further enhanced [15]. The aforementioned data allows for the reasonable assumption that LRP6 is the primary modulator of receptor-mediated LDL endocytosis [16]. Insulin resistance and dyslipidemia contribute significantly to the development of CVDs. Consequently, LRP6 dependent regulation of the WNT cascade reduces the risk of cardiometabolic abnormalities [17]. The disruption of LRP6 activity is associated with the development of coronary artery atherosclerosis, which is mediated by platelet-derived growth factor (PDGF) signaling. The activation of PDGF results in the abnormal proliferation of VSMCs, which contributes to the development of atherosclerosis [18].

It is therefore relevant to compare the expression of individual WNT proteins and LRP6 in CAD patients with hemodynamically significant and insignificant coronary artery stenosis.

Objective

Evaluate the levels of WNT1, WNT3a, and LRP6 in patients with CAD who had obstructive or non-obstructive coronary arteries.

Material and Methods

Study population

The cross-sectional observational study was conducted at the University Clinical Hospital No. 1 of the Sechenov University Clinical Center. The study included 50 (male and female) patients aged 45-75 years with a verified diagnosis of stable CAD (according to the Clinical Guidelines for Stable Coronary Artery Disease of the Ministry of Health of the Russian Federation, 2020) who signed informed consent. The study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki. Myocardial ischemia in hospitalized patients presenting with the clinical picture of stable angina pectoris or its equivalent was confirmed by stress echocardiogram or single-photon emission computed tomography (myocardial scintigraphy) during exercise stress testing. Patients were divided into two groups based on the findings of coronary artery angiography or multislice computed tomography. The first group consisted of 20 patients with non-obstructive CAD (stenosis<50 % or normal coronary arteries), while the second group included 30 patients with obstructive CAD (hemodynamically significant coronary artery stenosis).

Diabetes mellitus, ACS, myocardial infarction and stroke, chronic heart failure NYHA class III-IV, autoimmune diseases and cancer, severe liver and kidney dysfunction were the exclusion criteria.

Blood collection and enzyme-linked immunosorbent assay (ELISA)

Blood plasma samples were frozen in cryotubes at –80 °C after centrifugation. The samples were centrifuged for 20 minutes with EDTA K3 as anticoagulant. ELISA was conducted on an Adaltis Personal Lab ELISA analyzer (Italy) using Cloud-Clone Corp. kits (USA) in order to estimate the concentration of WNT proteins and LRP6. The coefficient of variation (CV) of the kits was found to be 10 % and 12 %, respectively.

All patients underwent routine laboratory investigations: clinical blood and urine tests, biochemical tests including lipid profile, glucose and uric acid levels.

Statistical analysis

Statistical analysis of the data obtained was carried out in StatTech v. 3.1.10 (StatTech, Russia) using the free Python computing environment (v. 3.11). The normal distribution of the parameters was evaluated using the Shapiro-Wilk test (n<50) or the Kolmogorov-Smirnov test (n > 50). Arithmetic mean (M) and standard deviation (SD), 95 % confidence interval (CI) were used to describe normally distributed quantitative variables. Non-normally distributed quantitative data were described using the median (Me) and the lower and upper quartiles [Q1–Q3]. Non-normally distributed quantitative variables were compared between two groups using the Mann-Whitney U-test. Three or more groups were compared by non-normally distributed quantitative indicators using the Kruskal-Wallis test; post hoc comparisons were made using the Bonferroni test. ROC curve analysis was conducted to ascertain the diagnostic value of quantitative indicators in predicting a specific outcome. The quantitative sign cutoff was determined by the highest value of the Youden index.

Results

Clinical characteristics of patients

The study groups were comparable in terms of the main clinical and demographic parameters, including age and body mass index (BMI). There were more women among patients with no obstructive coronary arteries, with 75 % of female patients and 25 % of male patients. A statistical analysis of the patients included in the study revealed that 12 patients in the INOCA group were overweight, while 5 patients had obesity grade 1. In the obstructive CAD group, 10 patients

Table 1. Key clinical and demographic characteristics of patients

Parameter	INOCA (n=20)	oCAD (n=30)	p
Male patients, n (%)	5 (25)	20 (66.7)	0.004*
Female patients, n (%)	15 (75)	10 (33.3)	
Age, years	66.5 [62.8; 71.2]	64.0 [56.5; 71.0]	0.301
BMI, kg/m2	26.20 [25.67; 30.40]	26.23 [24.68; 28.68]	0.575
Smoking, n (%)	3 (15.0)	6 (13.6)	0.819
Hemoglobin, g/L	142 [134; 151]	144 [133; 152]	0.446
Glucose, mmol/L	5.60 [5.2; 6.21]	5.40 [5.1; 5.63]	0.121
Creatinine, μmol/L	83.4 [74.8; 96.3]	89.80 [81; 101.8]	0.462
Total cholesterol, mmol/L	5.11±1.51	3.85±0.95	< 0.001*
LDL-C, mmol/L	2.89 [4.34; 3.62]	2.12 [1.79; 2.48]	0.005*
HDL-C, mmol/L	1.27 [1.06; 1.37]	1.11 [1.02; 1.33]	0.014*
Uric acid, mmol/L	292.9±62.1	347.7±62.8	0.003*

* Statistically significant differences (p<0.05). oCAD, coronary artery disease with obstructive coronary arteries; INOCA, ischemia and non-obstructive coronary arteries; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

were overweight and 6 had obesity grade 1. All patients were administered the recommended therapy in accordance with the national and international clinical guidelines. The general clinical and demographic characteristics of the subjects are summarized in Table 1.

Uric acid levels in patients with hemodynamically significant coronary artery stenosis were significantly elevated compared to the INOCA group (p=0.003). Patients with obstructive CAD exhibited significantly lower levels of total cholesterol and LDL-C. The observed differences could be attributed to the administration of higher doses of statins (p=0.02). The blood lipid profile values are provided at the time of patient inclusion in the study, prior to any adjustments to the statin dosage. These values reflect the general population level. There were no other differences between the groups with regard to the drug therapy received.

The results of the study showed statistically significant differences in LRP6, WNT1 and WNT3a levels between patients with obstructive and non-obstructive CAD. The levels of WNT1 and WNT3a proteins were found to be higher in patients with CAD and obstructive coronary arteries, whereas the concentration of LRP6 was higher in the INOCA group (Table 2).

A moderate correlation was observed between WNT1 and LRP6 levels in patients with obstructive CAD (ρ=0.374; p=0.042). Correlation analysis of all groups of patients with CAD demonstrated a moderate correlation between WNT1 and uric acid levels (ρ=0.416; p=0.007).

The results of the regression analysis indicated that the risk factors for CAD development, including increased BMI, advanced age, smoking, dyslipidemia, and hypertensive heart disease, did not significantly affect the type of coronary artery lesions. According to the univariate logistic regression analysis, the concentrations of LRP6 and WNT3a were significant predictors of the type of coronary artery lesion.

Table 2. Plasma levels of WNT cascade proteins in examined patients

Protein	Group	Concentration, ng/mL (Me [Q1; Q3])	p
LRP6	INOCA	13.02 [12.05; 13.7]	0.016
	oCAD	11.60 [10.5; 12.88]	
WNT1	INOCA	0.15 [0.15; 0.16]	< 0.001
	oCAD	0.189 [0.184; 0.193]	
WNT3a	INOCA	0.115 [0.07; 0.16]	< 0.001
	oCAD	0.227 [0.181; 0.252]	

oCAD, coronary artery disease with obstructive coronary arteries; INOCA, ischemia and non-obstructive coronary arteries; BMI, body mass index.

The results of the univariate logistic regression are presented in Table 3.

ROC curves were constructed to assess the diagnostic significance of the WNT proteins (Figures 1 and 2).

The cutoff value for LRP6, which corresponded to the highest value of the Youden index, was 12.94 ng/mL. The presence of obstructive coronary arteries was predicted when the LRP6 value fell below this threshold. Sensitivity and specificity were 76.7 % and 65.0 %, respectively.

The cutoff value for WNT3a, which corresponded to the highest value of the Youden index, was 0.155 ng/mL. The presence of obstructive CAD was indicated when the WNT3a value was found to be equal to or greater than the aforementioned value. Sensitivity and specificity were 96.7 % and 70 %, respectively.

Discussion

The analysis of patient groups with different variants of coronary artery lesions revealed that INOCA was more frequently identified in female patients (75 %). The largest American registry, the NCDR (National Cardiovascular Data Registry, 375,886 patients with CAD, 2000–2002),

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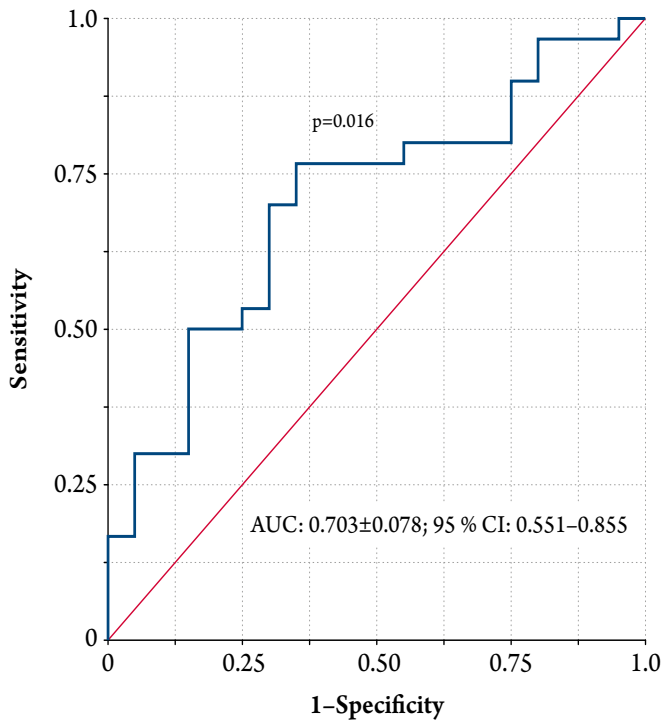
Table 3. Univariate logistic regression analysis between groups of patients with obstructive and non-obstructive CAD

Factor / Predictor	B	OR (95 % CI) Exp (B) (95 % CI)	p	Pseudo R-squ
LRP6	0.475	1.608 (1.037–2.494)	0.034*	0.094
WNT1	–1808.16	0.0 (0.0 – infinity)	0.999	1.000
WNT3a	–30.917	0.0 (0.0–0.0005)	0.001*	0.426
Age	0.036	1.037 (0.969–1.11)	0.297	0.014
Smoking	0.111	1.117 (0.25–5.005)	0.884	0.000
Sex	–1.658	0.191 (0.058–0.622)	0.006*	0.107
BMI	0.041	1.042 (0.891–1.218)	0.605	0.004
Hypertensive heart disease	0.329	1.39 (0.136–14.255)	0.781	0.001
Dyslipidemia	0.329	1.39 (0.136–14.255)	0.781	0.001
Anginal pain	0.542	1.719 (0.417–7.084)	0.454	0.008
Myocardial infarction	–1.923	0.146 (0.03–0.708)	0.017*	0.098
ACE inhibitors	–0.724	0.485 (0.165–1.422)	0.187	0.022
Angiotensin II receptor blockers	0.347	1.415 (0.43–4.647)	0.568	0.004
Beta-blockers	0.405	1.499 (0.359–6.271)	0.579	0.004
Calcium channel blockers	0.529	1.697 (0.583–4.945)	0.332	0.012
Antiplatelet drugs	–1.204	0.3 (0.06–1.494)	0.142	0.028
Statins	–21.683	0.0 (0.0 – infinity)	0.999	0.029
Glucose	–0.021	0.979 (0.898–1.067)	0.635	0.005

CAD, coronary artery disease; OR, odds ratio; CI, confidence interval; BMI, body mass index; ACE, angiotensin-converting enzyme. * Statistically significant differences ($p<0.05$).

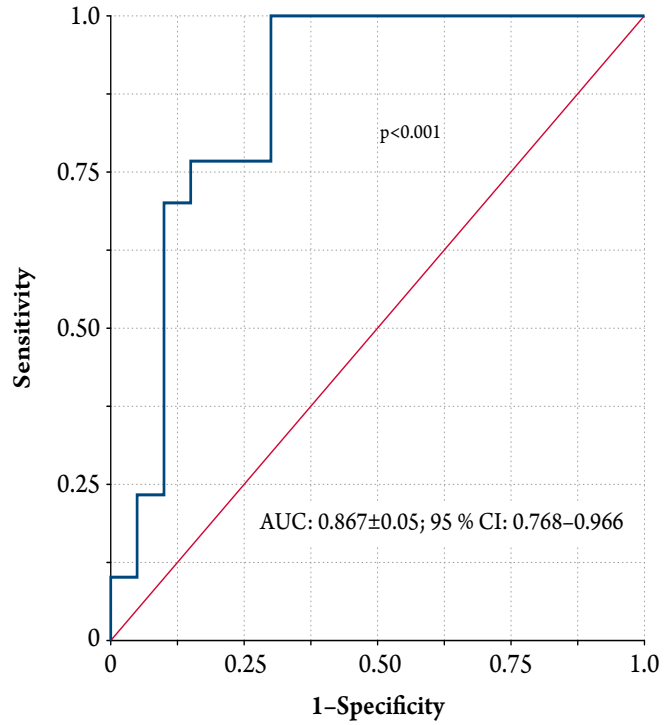
demonstrated a comparable trend: non-obstructive heart arteries were more prevalent in women (51 %), whereas their detection in men was less frequent (32 %) [19]. The higher prevalence of INOCA in women was also confirmed in the WISE study, in which 62 % of female patients did not demonstrate coronary artery stenosis [20]. Coronary artery atherosclerosis is a multifactorial disease. Among the various epigenetic factors that regulate the development and progression of coronary atherosclerosis, those regulated by the WNT signaling pathway play a

Figure 1. ROC curve illustrating the dependence of coronary artery lesion type in CAD patients on LRP6 level



CI, confidence interval; CAD, coronary artery disease.

Figure 2. ROC curve illustrating the dependence of coronary artery lesion type in CAD patients on WNT3a level



CI, confidence interval; CAD, coronary artery disease.

significant role. The involvement of the WNT signaling cascade in the pathogenesis of all stages of atherosclerosis development has been established. It is hypothesized that disruption of WNT signaling by oxidative stress and/or inflammation may be a common molecular mechanism contributing to atherosclerosis, insulin resistance, and hyperlipidemia. The incidence of these conditions increases with age [21].

The canonical WNT pathway (e.g., WNT1 and WNT3a) is primarily responsible for regulating cell proliferation, whereas non-canonical WNT pathways (e.g., WNT4 and WNT5a) are involved in controlling cell polarity and migration [22]. In this study, the highest concentrations of WNT1 and WNT3a proteins were observed in the group of patients with obstructive CAD. The findings of Wang et al. [23] suggest that inhibition of WNT1 signaling by SIRT6 promotes lipophagy and increases the stability of atherosclerotic plaques. At the same time, Brown et al. [24] demonstrated that WNT3a is expressed in human coronary artery plaques and actively participates in the inhibition of oxidative stress-induced VSMC apoptosis. Consequently, elevated levels of WNT1 and WNT3a may be associated with the development of significant coronary stenosis.

Correlation analysis of the results from all CAD patients showed a moderate association between WNT1 and uric acid levels. The results of current research suggest that uric acid may be considered a risk factor for cardiovascular disease. Hyperuricemia was demonstrated to result in the development of endothelial dysfunction [25], vascular remodeling, and coronary atherosclerosis [26].

LRP6 was demonstrated to play a key role in the protection against dyslipidemia and atherosclerosis [27]. However, immunohistochemical analysis revealed that LRP6 was expressed at very low concentrations in the intima of normal coronary arteries, whereas the level of LRP6 was significantly elevated in atherosclerotic plaques [14]. This may account for the moderate correlation observed between WNT1 and LRP6 levels in patients with obstructive CAD.

The results of the ROC analysis indicate that a WNT3a level of greater than 0.155 ng/mL is a predictor of the presence of obstructive coronary arteries.

Conclusion

In patients with coronary artery disease and non-obstructive coronary arteries, the maximum increase in the level of LRP6 was observed. Whereas, in the group with obstructive coronary artery disease, the levels of the canonical WNT cascade proteins, WNT1 and WNT3a, were found to be elevated.

The results of the ROC analysis suggest that elevated levels of WNT3a and LRP6 may serve as potential biomarkers for the presence of obstructive or non-obstructive coronary arteries in patients with coronary artery disease. The pathogenesis of non-obstructive lesions is complex and involves a combination of functional and structural changes that result in impaired coronary blood flow and myocardial ischemia. The observed differences serve to reinforce the hypothesis that the processes occurring in the coronary arteries differ between the two variants of coronary artery disease. Further investigation into the mechanisms of coronary insufficiency is required in order to identify potential points of action for drugs that could be used in targeted therapy of coronary artery disease with non-obstructive coronary arteries.

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No conflict of interest is reported.

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