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RESEARCH ARTICLE

SIGNIFICANCE OF SERUM CONCENTRATION OF HEMERINE IN THE ASSESSMENT OF CORONARY DISEASE IN DIABETES

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ABSTRACT

Background: Coronary artery disease is a major vascular complication of type 2 diabetes mellitus with a high mortality rate. Serum hemerin levels are involved in glucose and lipid metabolism and are associated with multiple cardiovascular risk factors. The aim of this study is to investigate the association and significance of serum chemerin concentration with the presence of coronary artery disease in patients with type 2 diabetes mellitus. **Methods**: The study is retrospective-prospective, clinical, comparative, descriptive. The sample of the study was patients from the internal ward of Travnik hospital (86 subjects), who had coronary angiography. One group was made up of type 2 diabetes mellitus (37 subjects) and the other group was non-diabetic subjects (49 subjects). All subjects were analyzed for serum chemerin concentration and coronarography performed. **Results of the study**: In the cohort of diabetic subjects, 57.4% had coronary disease and in the control cohort, 42.6%. The serum concentration of chemerin is significantly higher in the cohort of subjects with diabetes and coronary disease compared to the cohort of non-diabetic subjects. The serum concentration of chemerin does not depend on the severity of the coronary disease, although it does depend on its presence. Logistic regression analysis showed that serum chemerin concentration was an independent determinant of the presence of coronary artery disease in subjects with diabetes (OR = 1.037; 95% CI = 1,000 to 1,076; $p \leq 0.05$). In addition, linear regression analysis showed that the serum concentration of chemerin had a positive statistically significant association of different strengths, with the following relevant relevant parameters analyzed: waist circumference, HbA1C, cholesterol, triglycerides, BMI, and cardiovascular risk level, until statistically significant coronary disease severity was established. significant connectivity. **Conclusion**: Elevated serum chemerin levels may be considered an independent predictive marker of the presence of coronary artery disease in patients with diabetes.

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INTRODUCTION

Despite modern diagnostic methods, advances in treatment over the last three decades and the implementation of primary and secondary prevention measures, the early detection and evaluation of coronary disease in patients with diabetes has been the subject of much study and debate.Coronary disease is one of the leading clinical problems, both in terms of treatment, especially in terms of early detection and assessment of its severity, and especially in patients with diabetes mellitus (Yasushi Matsuzawa and Amir Lerman, 2014). In the US, coronary disease (CAD) is the leading cause of mortality in both sexes, responsible for 1/3 of all deaths. The mortality rate for Caucasian men aged 35-44 is 6.1 times higher than for women of the same age. For reasons not yet clear, the gender gap is not as pronounced in other races. The mortality rate in women increases after menopause, and at the age of 75 equals or even reaches that of men (Adrych, 2012). When coronary artery disease is associated with diabetes, early diagnosis of coronary artery disease is much more significant because of the higher mortality of such individuals.

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Today, around 382 million people are suffering from diabetes in the world (Figure 6), while the number will fall to nearly 592 million by 2035 (Guariguata, 2014). The global prevalence of diabetes is 8.3%, with the highest prevalence in the Middle East and North Africa region (10.9%), North America and the Caribbean islands (9.6%), Southeast Asia (8.7%), South and Central America (8.2%) and West Africa (8.1%), with the lowest incidence of registration in sub-Saharan Africa (5.7%) (Guariguata, 2013). Advances in the understanding of the pathophysiology of acute coronary syndrome (AKS) and, more recently, a growing body of studies discussing the impact of adipokine on coronary disease have led to advances in the early detection of such patients, facilitating further treatment and prevention of the disease. In the pathogenesis of diabetes, but also of coronary diseases, adipokines play a significant role in obesity. They are the products of adipose tissue that has long been thought to be an inert organ to break down this theory for the first time when Cook *et al*. 1987. god. have shown that adipose tissue secretes an active protein whose expression is reduced in obese mice. The theory of adipose tissue as an endocrine organ was confirmed in 1994. when Friedman *et al*. discovered the product of the ob / ob - leptin gene (Ohno, 2012). Today, it is known that in addition to various metabolites, fatty acids, estrogens and androgens, adipose tissue secretes and a variety of signaling proteins (cytokines) called adipokines or adipocytokines (Bragt, 2008). Adipokines regulate insulin action by affecting insulin sensitivity in target tissues, thereby affecting glucose metabolism (Rosen, 2006). Inflammation in adipose tissue increases the secretion of proinflammatory (IL-6, TNF-α, RBP-4, resistin, hemerin, etc.) and decreases the production of anti-inflammatory (ADN, visfatin, omentin, apelin, etc.) adipokines. Proinflammatory adipokines decrease and antiinflammatory increase insulin sensitivity and their relationship is an important link in the emergence of IR (Kwon, 2013).

To date, more than 600 different adipokines have been isolated that have a wide range of effects in the body. Adipokines are involved in the regulation of appetite, adipose tissue distribution, insulin sensitivity, glucose metabolism, regulation of inflammation, arterial pressure, hemostasis and endothelial function (Tang, 2011). Samaras *et al*. have shown that the profile of adipokine secretion is dependent not only on localization but also on certain metabolic disorders. Visceral adipose tissue of patients with diabetes increased expression of inflammatory mediators - tumor necrosis factor-α (TNFα), macrophage inflammatory protein (MIP), and IL-8 relative to the same tissue healthy controls (Ravussin, 2002). Studies by individual scientists Lew *et al*. 1979, Bergstrom *et al*. and later the Million Women Study show the association between high BMI and adipokine in cancer pathogenesis. In recent years, more and more attention has been paid to adipocytokines, such as chemerin. Chemerin was first identified in 1997 in studies on the pathogenesis of psoriasis as a TIG2 gene product, followed by increased expression in the skin of patients with psoriasis under the influence of tazarotene (hence the gene name: TIG2 - tazarotene-induced gene 2) (Tchoulkaova, 2010). The first paper showed that chemerin is involved in the inhibition of keratinocyte proliferation in response to the activation of the retinolic acid receptor r (RAR - retinolic acid receptor), hence the alternative name of the gene RAR-RES2 (receptor retinolic acid receptor 2) (Gimble, 2007). Chemerin is a CMKLR1 receptor ligand (also called ChemR23 or GPCR-DEZ) that is conjugated to G protein, which occurs e.g. in cells of the immune system, adipose tissue, bones, placenta, lung and heart (Gimble, 2007). The binding of active chemin to the ChemR23 receptor leads to an influx of macrophages and dendritic cells into the tissues involved in the inflammation process (Bukowiecki, 1982). This may explain the role of chemerin in psoriasis (Krassas *et al*., 2003; Grujic *et al*., 2005). Relatively little is known about the factors that regulate chemerin biosynthesis in adipose tissue. In fat reservoirs in human tissue, insulin has been shown to stimulate, metformin inhibits, and androgens (testosterone) and estrogens (17 beta-estradiol) do not affect chemerin biosynthesis (Fadini, 2014). A stimulatory effect of insulin on chemerin synthesis has also been found in rat adipocytes (Tang, 2012). However, other studies show that insulin stimulates the release of chemerin from human adipocytes but does not affect the intracellular concentration of this adipocytokine (Grujic, 2005). Increased chemerin levels and decreased adiponectin levels were also found in prediabetic conditions. Tönes and coworkers found that serum levels of chemerin and RBP4 were significantly elevated in type 2 diabetes. Chemerin induces insulin resistance in adipocytes and skeletal muscle cells in vitro. Elevated chemerin levels are associated with several components of the metabolic syndrome such as body mass index (BMI), HDL, hypertension, and triglycerides. Young and coworkers showed using multiple regression analysis that waist circumference, diastolic blood pressure, and two-hour plasma insulin after OGTT and HbA1C were independently associated with serum chemerin levels. Serum concentrations of chemerin as well as leptin are increased in non-alcoholic liver disease (NAFLD).

Physical activity is known to reduce the release of adipokines from adipokines and cytokines from skeletal muscle, endothelium and the immune system, and reduce cardiovascular risk, metabolic syndrome and type 2 diabetes (Tuomi *et al*., 1993). In type 2 diabetes, aerobic exercise has different effects on adipokines. Aerobic exercise has been found to reduce tumor necrosis factor α (TNFα) and chemerin, which significantly contribute to the reduction of type 2 diabetes in risk groups, but also to the reduction of cardiovascular risk. A decrease in the serum concentration of chemerin in obese individuals with aerobic physical activity is associated with a decrease in adipocyte size (weight loss), resulting in a decrease in inflammatory events but also in a reduction in cardiovascular risk.

MATERIALS AND METHODS

The research is retrospective-prospective, clinical, comparative, descriptive. The sample of the study was patients from the internal ward of Travnik hospital (86 subjects), who were coronary angiography according to the indications for coronary angiography. We divided the respondents into two groups. One group was made up of type 2 diabetes mellitus (37 subjects) and the other group was non-diabetic subjects (49 subjects). All respondents signed informed consent. The subjects were taken complete blood count and biochemical parameters, HbA1C, BMI, waist circumference, serum hemerin concentration analyzed, coronarography performed according to the indications for coronarography. Hemerin was determined from serum by ELISA method.The results were compared with the presence of coronary artery disease and with the extent of angiogram stenosis. We diagnosed coronary artery disease in patients who had evidence of stenosis greater than 50% in at least one major coronary artery. Patients who had cardiomyopathy, acute pericarditis, malignancy, and

advanced kidney disease were excluded from labor. Our research was approved by the ethics committee of the hospital. All subjects signed informed consent after which blood was taken for analysis.

Diagnostic criteria: Hypertension was defined as blood pressure> = 140/90 mmHg. Measurements of systolic and diastolic blood pressure were performed immediately before blood was taken for analysis. Diabetes mellitus was defined as fasting glucose levels> = 7.0 mmol / L or> = 11.0 mmol / L in any random sample or 2 hours after OGTT. Patients with a BMI of at least 25 kg / m^2 were considered obese. Hyperlipidemia was defined as total cholesterol levels> 5.0mmol / L and triglycerides> 1.7mmol / L.

Coronary angiography: Standard selective coronary angiography was performed using the Judkins technique. The coronary angiogram was evaluated by experienced cardiologists. The presence of CAD was defined as a 50% narrowing of the lumen in at least one of the three major coronary arteries. The extent of CAD was evaluated using the weight of angiographic findings. First, lesion severity was classified into coronary disease free, single-vessel coronary disease , two-vessel coronary disease, and three-vessel coronary disease.

Biochemical measurements: Samples were centrifuged and serum separated immediately analyzed in the laboratory. Serum triglycerides, total cholesterol, differential blood count, were tested with an automatic biochemistry instrument. Serum chemerin levels were measured using an enzyme-linked immunosorbent assay (Phoenix Pharmaceuticals Inc., Burlingame, California, USA). BMI was calculated as the mass in kilograms divided by the square height in meters (kg / m^2).

Statistical analysis: The collected data will be entered into a specially created database created in Microsoft Excel 2010. In multivariate analysis we will use multiple regression (when the dependent variable was continuous) and logistic regression (when the dependent variable was dichotomous). To show predictive performance, we will use Receiver Operating Characteristic (ROC) curve analysis and size and statistical significance of area under a curve (AUC). Statistical data processing will be performed using IBM SPSS Statistics 22. The statistical significance level threshold will be $p < 0.05$ and the results will be presented in tables and graphs.

RESULTS

The study included 86 subjects, 73.3% male and 26.7% female. 38 male and 16 female subjects had coronary disease. All subjects had an elevated BMI (> 24.9 kg / m2), with 65.11% being overweight (BMI 25.0-29.9 kg / m2) and 34.89% obese (BMI> 29.9kg / m2). HbA1C> 6.4% had 40.69% of subjects, 65.11% had cholesterol> 5mmol / l, and 32.55% triglycerides> 3mmol / l. 43.02% of the subjects had type 2 diabetes. 64.0% of the subjects had a waist circumference that was greater than 88cm for women and 102cm for men. There were a total of 62.79% of subjects who had coronary disease, although there was an equal representation of subjects with single-vessel coronary disease compared to two-vessel and three-vessel coronary disease. Hemerin values were increased in 82.55% of the subjects, but in the coronary cohort of patients the increased hemerin values were in 59.30% of the subjects, while in the coronary cohort there were 23.25% of the subjects but these values were significantly lower in relation to patients with coronary disease. The serum concentration of hemerin is significantly higher in the cohort of subjects with diabetes and coronary disease compared to the cohort of non-diabetic subjects. The serum concentration of hemerin does not depend on the severity of the coronary disease, although it does depend on its presence. Logistic regression analysis showed that serum hemerin concentration was an independent determinant of the presence of coronary artery disease in subjects with diabetes (OR = 1.037; 95% CI = 1,000 to 1,076; $p \leq 0.05$). In addition, linear regression analysis showed that the serum concentration of hemerin had a positive statistical association of varying strength, with waist circumference, HbA1C, cholesterol, triglycerides, BMI, and cardiovascular risk level, whereas no statistically significant association was found with coronary disease severity. The sensitivity for the optimal cut-off for the serum concentration of hemerin for the presence of diabetes is 78.4% and the specificity is 73.5%.

DISCUSSION

The study included middle-aged adults of both sexes with diabetes in one group of patients and another group of patients those who did not have diabetes. All subjects were coronary angiography, of which 37.2% had a neat coronary angiography, and 62.8% had the presence of coronary artery disease in equal proportions compared to the presence of single, two-vessel and three-vessel coronary disease. In the group of subjects with diabetes, 57.6% had coronary disease and significantly higher values of chemerin than in the group of patients who did not have diabetes and had coronary disease 42.6%. According to the literary works of Samaras *et al*. have shown that the chemerin secretion profile is dependent not only on the localization of adipose tissue but also on certain metabolic disorders such as diabetes, metabolic syndrome and others, as confirmed by this study. Tönes *et al*. found serum chemerin and retinol 4 binding protein (RBP4) elevated in type 2 diabetes, as shown by our research. Yang *et al* showed that multiple regression analysis yielded abundant structure, diagnostic blood pressure, and double plasma insulin after OGTT and HbA1C were independently associated with serum chemerin levels. Our study showed a linear regression analysis for serum chemerin concentration having a positive statistically significant association of different strengths, with structure, HbA1C, cholesterol, triglycerides, BMI and cardiovascular risk level, while no statistically significant stability was found.

At the beginning of human studies on chemerin, the expression and circulation of the chemerin gene were shown to be positively correlated with the association of BMI and obesity-related biomergers (Bozaoglu *et al*. 2007, 2009; Sell *et al*. 2009; Chakaroun *et al*. 2012). Sledzinski T. *et al*. have confirmed the stimulating effect of insulin on the synthesis of chemerin prondered in rat adipocytes, which confirms the theory of higher chemerin values in the diabetic group. However, other studies have shown that insulin stimulates release from human adipocytes but does not utilize the intracellular concentration of this adipocytokine. Other researchers' findings also indicate serum chemerin levels in men in the elderly and in the general population and a positive correlation with BMI and waist-to-hip ratio (WHR) as an indicator of central obesity in overweight and obese

Table 1. Description statistics

Variable		Patients without coronary disease (N=32; 37,2%)		Patients with coronary disease (N=54; 62,8%)		Total (N=86; 100%)	
		N	%	N	%	N	%
Sex	male	25	78,1	38	70,4	63	73,3
	female	7	21,9	16	29,6	23	26,7
Waist circumference (cm)	< 88 (f) or 102 (m)	14	43,8	17	31,5	31	36,0
	over 88 (f) or 102 (m)	18	56,3	37	68,5	55	64,0
Arrangement of fat deposit	under 0,8 (f) or 1,0 (m)	16	50,0	29	53,7	45	52,3
	over 0,8 (f) or 1,0 (m)	16	50,0	25	46,3	41	47,7
Chemerin concentration	0 - 59,42 ng/ml	12	37,5	3	5,6	15	17,4
	> 59,42 ng/ml	20	62,5	51	94,4	71	82,6
Dijabetes melitus	ne	26	81,3	23	42,6	49	57,0
	da	6	18,7	31	57,4	37	43,0
HbA1C (%)	< 5,70	22	68,8	20	37,0	42	48,8
	5,71 - 6,40	4	12,5	5	9,3	9	10,4
	> 6,40	6	18,7	29	53,7	35	40,7
Cholesterol	< 5 mmol/l	16	50,0	14	25,9	30	34,9
	> 5 mmol/l	16	50,0	40	74,1	56	65,1
Triglycerids	< 3 mmol/l	23	71,9	35	64,8	58	67,4
	≥ 3 mmol/l	9	28,1	19	35,2	28	32,6
Coronarography findings	bez koronarne bolesti	32	100,0	0	0,0	32	37,2
	JKB	0	0,0	18	33,3	18	20,9
	DKB	0	0,0	18	33,3	18	20,9
	TKB	0	0,0	18	33,3	18	20,9
BMI (kg/m^2)	25 - 29,9	31	96,9	25	46,3	56	65,1
	> 29,9	1	3,1	29	53,7	30	34,9
Cardiovascular risk (%)	< 20	26	81,3	31	57,4	57	66,3
	≥ 20	6	18,7	23	42,6	29	33,7

Table 2. Concentration of hemerin relative to the presence or absence of coronary artery disease

Group of respondents		Concentration of chemerina (ng/ml)		Total	χ^2	*p*
		reference values	elevated values			
Patients without coronary disease	N	12	20	32	14,239	0,001
	%	37,5	62,5	100,0		
Patients withcoronary disease	N	3	51	54		
	%	5,6	94,4	100,0		
Total	N	15	71	86		
	%	17,4	82,6	100,0		

Table 3. Serum concentration of hemerin for groups of subjects with different degrees of coronary disease compared to those who are not ill

Variable	Group of patients	Median (Interquartile range)
Chemerin concentration (ng/ml)	Patients withoutcoronarydisease	63,79 (23,45)
	Patientswithone vessel CD	91,92 (47,66)
	Patientswithtwo vessel CD	123,78 (57,91)
	Patientswith three vessel	108,34 (66,63)

Table 4. Analysis of serum chemerin concentration for groups of subjects with different degrees of coronary artery disease

Group of patients		Chemerin concentration		Total	Median	Correlation coefficient	*p*
		≤ medijana	> medijana				
Patients with one vessel CD	N	12	6	18	103,47	0,181	0,189
	%	66,7	33,3	100,0			
Patientswith two vesselCD	N	7	11	18			
	%	38,9	61,1	100,0			
Patientswith three vesselCD	N	8	10	18			
	%	44,4	55,6	100,0			
Total	N	27	27	54			
	%	50,0	50,0	100,0			

Table 5. Serum concentration of hemerin for cohort patients, depending on the presence of diabetes

Variable	Group of patients	Median (Interquartile range)
Chemerin concentration (ng/ml)	Non-diabetic patients with coronary disease	86,77 (48,87)
	Patients with diabetes and coronary disease	124,43 (66,65)

Table 6. Serum concentration of chemerin for patients with coronary artery disease depending on the presence of diabetes

Group of patients		Chemerin concentration		Total	Median	Correlation coefficient	*p*
		≤ median	> median				
Non-diabetic patients with coronary disease	N	15	8	23	103,47	0,262	0,055
	%	65,2	34,8	100,0			
Patients with diabetes and coronary disease	N	12	19	31			
	%	38,7	61,3	100,0			
Total	N	27	27	54			
	%	50,0	50,0	100,0			

Table 7. Serum concentration of chemerin for groups of patients with respect to the presence of diabetes

Variable	Group of patients	Median (Interquartile range)
Chemerin concentration (ng/ml)	Non-diabetic patients	75,65 (32,43)
	Patients with diabetes	115,69 (59,29)

Table 8. Analysis of serum chemerin concentration for non-diabetic patients relative to diabetic patients

Group of patients		Concetration ofchemerin		Total	Median	Correlation coefficient	*p*
		≤ median	> median				
Non-diabetes patients	N	35	14	49	86,26	0,493	0,001
	%	71,4	28,6	100,0			
Patients with diabetes	N	8	29	37			
	%	21,6	78,4	100,0			
Total	N	43	43	86			
	%	50,0	50,0	100,0			

Table 9. Correlation of serum chemerin concentration with relevant parameters

Correlation			Presence of CD	BMI	Dijabetes melitus	HbA1C	Cholesterol	Triglycerids	Waist circumference	Level of cardiovascular risk
Spearman	Concetration ofchemerina	Correlation coefficient	0,566	0,756	0,506	0,465	0,242	0,252	0,271	0,293
		Significance	0,001	0,001	0,001	0,001	0,025	0,019	0,012	0,006
		N	86	86	86	86	86	86	86	86

Table 10. Logistic regression analysis of serum chemerin concentration as a determinant of the presence of coronary artery disease in patients with diabetes

Omnibus test χ^2	p	coefficient of determination R^2 (interval)	probability of accuracy	ratio of coefficient OR	95% CI confidence interval		p
					the lower limit	The upper limit	
6,284	0,012	15,6% - 26,6%	81,1%	1,037	1,000	1,076	0,050

Logistic regression analysis showed that serum hemerin concentration was an independent determinant of the presence of coronary artery disease in subjects with diabetes (OR = 1.037; 95% CI = 1.000 to 1.076; p≤0.05).

individuals and those with the immune system (Goralski *et al*. 2007, Bozaoglu *et al*. 2007). A fundamental shift in understanding of chemerin occurred in 2007 when chemerin was found to be highly expressed in WAT (Goralski *et al*. 2007). Data on hemerin expression in patients with coronary artery disease are different. The study by Yan *et al*. found that in patients with coronary artery disease who underwent a therapeutic procedure, compared with those with normal coronary angiography, serum chemerin levels were elevated and correlated with the severity of the disease.

Our study has confirmed the theory that chemerin levels correlate with the presence of coronary disease but not with severity. Similar results were obtained by Xiaotao *et al*. (2012). On the other hand, Hah *et al*., comparing a group of patients with single-vessel coronary disease and multi-vessel coronary disease, found that serum chemerin, although higher in the group of patients with multiple-vessel coronary disease, was an independent risk factor for coronary heart disease severity after considering the lipid profile . However, the authors did not investigate patients without coronary heart disease.

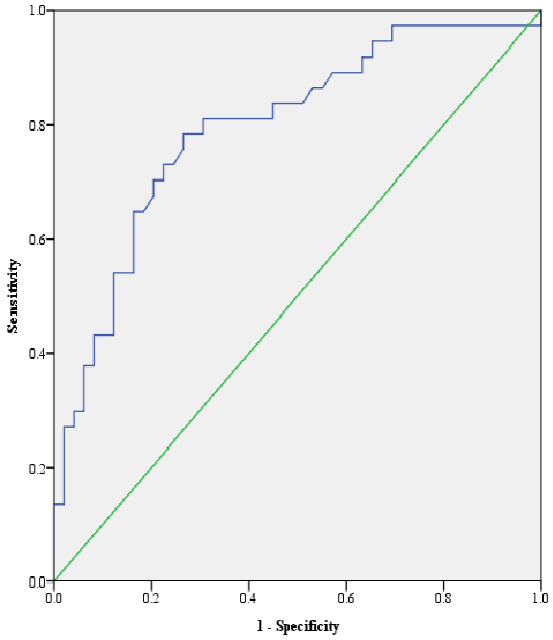

Chart 1. Chemerin is a highly sensitive test, that is, it is highly likely to distinguish patients with coronary disease from those who did not. Area = 0.795 p = 0.001

Gao *et al*. have investigated the epicardial and subcutaneous adipose tissue of individuals undergoing elective cardiac surgery. In the adipose tissue of individuals with coronary diseases, the expression of the gene encoding chemerin is increased compared with individuals without coronary disease. A 2002 study by Dandone and Sardine, which examined the anti-inflammatory and potential anti-atherogenic effect of insulin, stated that hyperinsulinemia was associated with an increase in coronary disease and atherosclerosis. Adipokines secreted by adipose tissue have been implicated in the pathogenesis of metabolic syndrome (Lehr *et al*. 2012), which is confirmed by our study (Lehr *et al*., 2012). Supporting the important roles of chemerin in the metabolism of systemic lipids and glucose, accumulated clinical data show that local or circulating chemerin levels are increased in patients with obesity, diabetes, and cardiovascular disease (Perumalsamy *et al*. 2017).

Conclusion

Logistic regression analysis showed that serum chemerin concentration was an independent determinant of the presence of coronary artery disease in subjects with diabetes (OR = 1.037; 95% CI = 1.000 to 1.076; p≤0.05). Linear regression analysis showed that serum chemerin concentration had a positive statistical association of varying strength, with waist circumference, HbA1C, cholesterol, triglycerides, BMI, and cardiovascular risk level, whereas no statistically significant association was found with coronary disease severity.

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