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Association between coronary artery lesion severity in coronary computed tomography angiography and hemoglobin A1c in nondiabetic patients with chronic coronary syndrome

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ABSTRACT

Objectives: In this study, we aimed to investigate whether there is a relationship between coronary artery lesion severity detected on coronary computed tomography angiography (CTA) and the hemoglobin A1c (HbA1c) value in nondiabetic patients with chronic coronary syndrome (CCS).

Patients and methods: The retrospective observational study included 125 patients (64 males, 61 females; median age: 55 years; IQR, 46.5-63.0) who underwent coronary CTA with the diagnosis of CCS and applied between March 2020 and July 2022. Two groups were formed according to the severity of coronary artery lesion by coronary CTA: Group 1 (n=71), with <70% coronary lesion severity, and Group 2 (n=54), with >70% coronary lesion severity.

Results: The two groups were similar in terms of median age, (p=0.09) and male sex ratios (47% *vs.* 55%, p=0.47). The HbA1c value in Group 2 was statistically significantly higher than in Group 1 [5.89 (5.43-6.15) *vs.* 5.42 (5.1-5.8), p=0.001]. The HbA1c cut-off value was determined as 5.66. The ideal HbA1c cut-off value, calculated by the Youden index, had a sensitivity of 64% and a specificity of 63% in predicting the severity of coronary artery lesions in nondiabetic patients with CCS.

Conclusion: In nondiabetic patients with CCS, HbA1c is associated with the presence of severe CAD lesions detected in coronary CTA.

Keywords: Chronic coronary syndrome, coronary computed tomography angiography, HbA1c.

Coronary artery disease (CAD), characterized by atherosclerotic plaque accumulation in the epicardial arteries, is one of the leading causes of morbidity and mortality worldwide.[1] In the 2019 European Society of Cardiology (ESC) guidelines for chronic coronary syndrome (CCS), patients with stable angina pectoris or angina-equivalent symptoms/signs were defined as CCS (nonacute coronary syndrome), and diagnosis and treatment protocols were established for these patients.

During the diagnosis stage, noninvasive tests are recommended, and it is emphasized to decide on the pretest probability by evaluating cardiovascular risk factors (age, sex, hypertension, diabetes mellitus [DM], hyperlipidemia, smoking, and family history). Coronary computed tomography angiography (CTA), a noninvasive test, is the first recommended test when CAD cannot be excluded in symptomatic patients with clinical evaluation (ESC 2019 CCS guideline: Class I recommendation).[1]

Hemoglobin A1c (HbA1c) is one of the endogenous advanced glycation end products. In addition, HbA1c indicates the long-term average glycemic index. Hemoglobin A1c measurement does not require the fasting state of the patient or glucose loading to the patient; therefore, it is a parameter that provides higher reproducibility than fasting glucose and measurement of glycemia with a single sampling.[2] Known as an indicator of uncontrolled type 2 DM, HbA1c has been associated with echocardiographic left ventricular functions and with the frequency of infection after coronary

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artery bypass grafting in some studies.[3,4] It has been demonstrated that HbA1c is strongly associated with CAD and the diagnosis of DM and can be used as a biomarker of CAD.[2,5,6] The relationship between HbA1c and CAD severity in patients with DM is well understood, but the relationship between HbA1c levels and CAD severity in patients without DM is still controversial.[7,8] Hence, we aimed to investigate the relationship between HbA1c and CAD lesion severity in the nondiabetic adult population. We also tried to find the HbA1c cut-off value for risk stratification in nondiabetic patients with CCS.

PATIENTS AND METHODS

The retrospective study included 125 patients (64 males, 61 females; median age: 55 years; IQR, 46.5-63.0) who applied to the cardiology clinic of the Izmir Bakırçay University Çiğli Training and Research Hospital between March 2020 and July 2022. Demographic characteristics, such as age, sex, and comorbid diseases were recorded. Coronary CTA (256 multislice computed tomography) reports, which were reported by experienced specialists and taken under appropriate technical conditions, were reviewed, and information about the coronary artery lesion severity was recorded in the case report form. There were two groups formed according to the coronary CTA lesion severity: Group 1 (n=71), with a lesion severity <70%, and Group 2 (n=54), with a lesion severity >70%.

Patients younger than 18 years, patients with a history of DM or an HbA1c level above 6.5%, patients with a history of coronary artery bypass grafting, patients not in sinus rhythm, patients with severe liver failure, and patients with active malignancy were excluded from the study. Anemic patients (hemoglobin <10 g/dL) were excluded from the study. Therefore, it cannot be thought that it will affect the HbA1c value.

The blood pressures measured by manual sphygmomanometer at the outpatient admissions of the patients included in the study and the heart rates from the electrocardiograms taken at the outpatient admissions were noted from the hospital records. The body mass index was calculated as weight/height.[2]

Smoking and alcohol use of the patients were accepted if they were active users according to their verbal expressions. For the definition of hypertension, which is one of the comorbid diseases, a blood pressure >140/90 mmHg with repeated measurements or the use of oral antihypertensive drugs was taken as criteria. A glomerular filtration rate <60 mL/min was considered chronic renal failure, and total cholesterol >200 mg/dL, low-density lipoprotein cholesterol >130 mg/dL or triglyceride >150 mg/dL was considered hyperlipidemia.

Statistical analysis

Data were analyzed using IBM SPSS version 24.0 software (IBM Corp., Armonk, NY, USA). Normal distribution of numerical variables was examined using the Kolmogorov-Smirnov test. Numerical variables were expressed as median and interquartile range (IQR) and evaluated using Student's t-test. Categorical variables were reported as numbers and frequencies and evaluated using the Pearson chi-square test and Fisher exact test. If there was no normal distribution among the numerical variables, the Mann-Whitney U test was used. The HbA1c cut-off value was found by performing receiver operating characteristic (ROC) curve analysis. The cut-off value was determined according to the Youden index. A p value <0.05 was considered statistically significant.

RESULTS

The male sex ratio of the patients was 51%. The median body mass index was 25.5 (23.10-28.85) kg/m^2. No statistically significant difference was found between the two groups in demographic data, except for hypertension (Table 1). The rate of hypertension was higher in Group 2 compared to Group 1 (33% *vs.* 53%, p=0.03). The most common comorbid conditions (hypertension not included) were CAD (25%) and hyperlipidemia (24%). The rate of active smokers was similar between Group 1 and Group 2 (16% *vs.* 18%, p=0.81, Table 1).

One of the biochemical parameters, the high-density lipoprotein value was higher in Group 1 than in Group 2, but there was no statistically significant difference between groups (44 [38.15-51.32] *vs.* 40.5 [35-46.3], p=0.054). The median left ventricular ejection fraction (LVEF) value of the patients in the echocardiography was 60% (50-60%). The LVEF was higher in Group 1 than in Group 2 (60 [55-60] *vs.* 50 [45-60], p<0.001).

Table 1
Baseline characteristics and comorbid diseases of the study population

	Coronary lesion <70% (n=71)				Coronary lesion >70% (n=54)				Total (n=125)				
Variables	n	%	Median	IQR	n	%	Median	IQR	n	%	Median	IQR	*p*
Age (year)			54	43-61			56	50-63.25			55	46.5-63.0	0.09
BMI (kg/m^2)			25.8	23.5-28.7			25.4	22.92-29.02			25.5	23.10-28.85	0.51
Sex Male	34	47			30	55			64	51			0.47
SBP (mmHg)			130	120-143			140	129.75-155			135	125-149	0.1
DBP (mmHg)			75	65-85			80	70-90			80	70-90	0.09
Heart rate (min)			75	65-87			74	65-80			74	65-84	0.52
Smoking	12	16			10	18			22	17			0.81
Alcohol use	3	4			1	1			4	3			0.63
Hypertension	24	33			29	53			53	42			0.03
CAD	15	21			17	31			32	25			0.21
Hyperlipidemia	15	21			16	29			31	24			0.3
COPD	2	2			4	7			6	4			0.4
Asthma	5	7			2	3			7	5			0.69
CKD	4	5			7	12			11	8			0.2
PAD	2	2			5	9			7	5			0.23

IQR: Interquartile range; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; PAD: Peripheral artery disease.

Table 2
Biochemical and imaging findings

	Coronary lesion <70% (n=71)		Coronary lesion >70% (n=54)		Total (n=125)		
Parameters	Median	IQR	Median	IQR	Median	IQR	*p*
Urea (mg/dL)	18	11-27	17.25	12.75-32.1	18	11.45-28	0.14
Creatinine (mg/dL)	0.85	0.77-1.13	0.9	0.69-1.2	0.87	0.74-1.14	0.13
Na (mEq/L)	139	137-141	139	136.75-140	139	137-140	0.28
K (mEq/L)	4.2	3.9-4.53	4.22	4-4.6	4.2	3.96-4.60	0.28
Ca (mg/dL)	9	8.7-9.2	9	8.55-9.3	9	8.7-9.2	0.24
Fasting glucose (mg/dL)	96	90-106	100.53	88.25-115	96	88-108.5	0.39
TSH (mU/L)	1.13	0.88-1.77	1.52	0.76-2.02	1.13	0.84-1.83	0.4
Total cholesterol (mg/dL)	183.5	163.75-216.25	195	156-216	185	160-216	0.75
Triglyceride (mg/dL)	163.5	128.5-207.75	166	120.75-203	165	123.75-204.25	0.89
HDL (mg/dL)	44	38.15-51.32	40.5	35-45.65	42	36-48	0.054
LDL (mg/dL)	97.5	80.22-135	112	90.05-131.12	103	84-132	0.39
WBC (k/mm^3)	9.35	7.7-10.67	8.48	7.22-10.24	8.91	7.57-10.5	0.1
Hb (g/dL)	13.4	12.4-14.6	13.6	12.45-14.72	13.6	12.4-14.65	0.93
Platelet	276	225-298	264	215.75-313.5	272	220-302.5	0.64
HbA1c	5.42	5.1-5.8	5.89	5.43-6.15	5.6	5.18-6	0.001
LVEF (%)	60	55-60	50	40-60	60	50-60	<0.001

IQR: Interquartile range; Na: Sodium; K: Potassium; Ca: Calcium; TSH: Thyroid stimulating hormone; HDL: High density lipoprotein; LDL: Low density lipoprotein; WBC: White blood cell; Hb: Hemoglobin; HbA1c: Hemoglobin A1c; LVEF: Left ventricular ejection fraction.

Table 3
Medications used by patients

	Coronary lesion <70% (n=71)		Coronary lesion >70% (n=54)		Total (n=125)		
	n	%	n	%	n	%	*p*
Beta-blockers	17	23	18	33	35	28	0.31
ACEi	16	22	18	33	34	27	0.22
ARBs	7	9	5	9	12	9	1
Dhp CCBs	8	11	13	24	21	16	0.08
Non-Dhp CCBs	7	9	4	7	11	8	0.75
Antiplatelet	21	29	20	37	51	40	0.44
Anticoagulant	6	8	2	3	8	6	0.46
Statin	15	21	17	31	32	25	0.21

ACEi: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; Dhp CCB: Dihydropyridine calcium channel blockers.

There was no difference between the groups in terms of drug use. The laboratory findings of the patients and the drugs they used are summarized in Tables 2 and 3.

The median HbA1c value in Group 2 was statistically higher than in Group 1 [5.89 (5.43-6.15) *vs.* 5.42 (5.1-5.8), p=0.001]. In the ROC analysis, a HbA1c >5.66 had 64% sensitivity

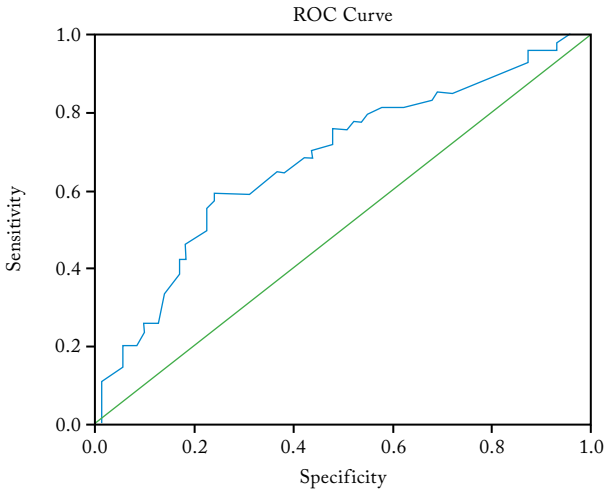

Figure 1. The sensitivity and specificity of HbA1c associated with coronary artery lesion severity in the ROC curve.
ROC: Receiver operating characteristic; HbA1c: Hemoglobin A1c.

and 63% specificity (area under the curve: 0.68, 95% confidence interval: 0.585-0.776, p=0.001) for determining the coronary artery lesion severity (Figure 1).

DISCUSSION

This is a rare study in the literature that aimed to determine the correlation between coronary artery lesion severity determined by coronary CTA and HbA1c value in nondiabetic patients. In our study, the median HbA1c levels were significantly higher in the patient group with significant coronary artery stenosis compared to the group with nonsignificant coronary artery stenosis (p<0.001), and there was a strong correlation between coronary artery lesion severity and the HbA1c value in nondiabetic patients with CCS.

One of the confounding factors affecting HbA1c is the hemoglobin value, as it changes HbA1c. A low hemoglobin value may lower the HbA1c level. Therefore, low hemoglobin status may show an inaccurate relationship between CAD severity and low HbA1c levels.[9] One of the advantages of our study is that the median hemoglobin values were within normal limits in both groups.

Garg et al.,[10] Ayhan et al.,[11] and Kis and Guzel[12] found the cut-off values of HbA1c as 5.7, 6.52, and 5.5, respectively, and concluded that it was an independent predictor of the severity of CAD in nondiabetic patients. In our study, the HbA1c cut-off value was determined as 5.66 as a predictor of a severe coronary artery lesion in coronary CTA.

Hemoglobin A1c is a parameter that is used in the diagnosis and follow-up of DM and quantitatively shows the three-month glycemic control. It is possible to establish a relationship between HbA1c and coronary atherosclerosis, considering that exposure to high blood sugar causes vascular complications. Unregulated blood sugar induces oxidative stress, and the developing glycation end products and lipid peroxidation products initiate endothelial damage. As a result, an inflammatory process develops, and atherogenesis becomes active.[13] Hemoglobin A1c is also an advanced glycation end product.

In a study by Haring et al.[14] in 1798 nondiabetic patients, it was shown that the carotid intima-media diameter increased by 0.02 mm for each 1% increase in HbA1c. The study of Kayalı and Ozder[15] hypothesized that HbA1c predicts CAD in nondiabetic patients. In the study, 247 patients were recruited and classified according to the coronary arteries lesion severity, and a close relationship was found between HbA1c and coronary stenosis. When the recent prospective studies were examined, it was observed that although some claimed the opposite between HbA1c and CAD, most of them contributed to the literature. It has been shown that each percentage increase in HbA1c in nondiabetic patients increases the risk of CAD 1.2 times.[16] In a study that included 93 patients investigating the relationship between the severity of coronary atherosclerosis and HbA1c, HbA1c values were found to be higher in the group with severe atherosclerosis.[17] In the study of Dutta et al.,[18] it was concluded that as the HbA1c level increased, the number of affected vessels in the coronary arteries also significantly increased.

Ashraf et al.[19] investigated whether HbA1c was an independent predictor of CAD in their study of 382 patients with suspected coronary ischemia without a known history of DM. However, while age and sex were statistically significantly higher at first, among the cardiovascular risk factors (for example, sex, hypertension, dyslipidemia, and smoking), no statistically significant difference was observed after additional analysis. We can believe that these risk factors that may cause CAD may have affected the outcome of the current study. However, a significant

difference was found between the two groups only in terms of hypertension, which is one of the etiological factors that may cause coronary atherosclerosis. In this study, LVEF was found to be lower in the group with more severe coronary lesions. This result was thought to be due to the negative effect of coronary ischemia on left ventricular systolic function. In our study, the hypertension rate was higher and the median LVEF value was lower in the group with higher coronary lesion severity.

There are several limitations to this study. First, the HbA1c values of the patients were calculated when the patients were admitted to the hospital. The HbA1c value is based on a single measurement; thus, it may underestimate any relationship between HbA1c and coronary artery lesion severity. Second, coronary CTA calcium score was not included in the analysis as the selected patient population differed according to whether severe lesions were detected. Although the study population was relatively small, the patient group was found to be sufficient in the power analysis performed before the study. However, studies involving more patients are needed, and we believe that our study may be a pioneer for further studies on this subject. Since we do not have long-term follow-up results, we do not know the prognostic value of HbA1c in the long-term follow-up of patients with CCS.

In conclusion, in nondiabetic patients with CCS, HbA1c, which shows the long-term glycemic index, is associated with severe coronary artery lesions detected in CTA. Controlling the HbA1c values of patients while planning diagnostic coronary CTA may be a guide in patients with suspected nondiabetic CAD.

Ethics Committee Approval: The study protocol was approved by the Bakırçay University Medicine Faculty Ethics Committee (date: 03.08.2022, no: 684). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, design, control/supervision, critical review: M.K., Data collection and/or processing, analysis and/or interpretation, references and fundings, materials: F.S.Y.; Literature review, writing the article: F.S.Y., M.K.

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