Relationship between Hemoglobin A1c and Fractional Flow Reserve Lesion Severity in Non-diabetic Patients

Mehmet Kis[1] and Tuncay Guzel[2]

[1]*Department of Cardiology, Silopi State Hospital, Sirnak, Turkey*
[2]*Department of Cardiology, Health Science University, Gazi Yaşargil Training and Research Hospital, Diyarbakır, Turkey*

ABSTRACT

Objective: To find out whether there is any correlation between the fractional flow reserve (FFR) that indicates the severity of coronary artery disease (CAD), and the HbA1c value in non-diabetic patients.

Study Design: Observational study.

Place and Duration of Study: Department of Cardiology, Dicle University, Turkey, from September 2015 to November 2019.

Methodology: Patients who underwent elective FFR procedure were included in the study. There were two groups formed according to FFR lesion severity: FFR <0.8 group (75 patients), FFR >0.8 group (39 patients). HbA1c was compared between the two groups. The relationship between categorical variables was examined with Pearson Chi-square and Fisher's Exact test. ROC (Receiver operating characteristic) analysis was performed for the HbA1c the cut-off value.

Results: The two groups were similar in terms of mean age and male gender ratios (58.4±9.6 *vs*. 57.9 ± 10.8 years, p=0.794; 64% *vs.* 74.4%, respectively, p=0.262). HbA1c value was statistically higher in the group with FFR value <0.8 [(5.8 (IQR: 5.7-6.0)] compared to the group with FFR value ≥0.8 [(5.5 (IQR: 5.2-6.0, p = 0.002)]. The HbA1c cut-off value was determined as 5.55. The ideal HbA1c threshold value calculated by the Youden index had 88% sensitivity, and 53.85% specificity.

Conclusion: HbA1c, which shows the long-term glycemic index in non-diabetic individuals, is associated with the severity of CAD determined by the fractional flow reserve.

Key Words: *Coronary artery disease, fractional flow reserve, HbA1c.*

How to cite this article: Kis M, Guzel T. Relationship between Hemoglobin A1c and Fractional Flow Reserve Lesion Severity in Non-diabetic Patients. *J Coll Physicians Surg Pak* 2022; **32(01)**:4-8.

INTRODUCTION

Coronary artery disease (CAD), characterised by atherosclerotic plaque accumulation in the epicardial arteries, is one of the leading causes of morbidity and mortality worldwide.[1] Although coronary angiography (CAG) is the gold standard in the diagnosis of CAD, it cannot show whether the lesion causes ischemia, and cannot show arterial vessel wall, or plaque burden in patients with moderate stenosis.[2] Therefore, fractional flow reserve (FFR) is an important interventional diagnostic method to determine the functional significance of moderate epicardial artery stenosis (between 40-70%) and to detect the lesion that requires intervention in CAG.[3] As a result of the measurement, the cut-off FFR value for stenosis to requiring intervention is <0.80. If the FFR was >0.80, it should be considered that the lesion was not hemodynamically serious.[4] FFR is being increasingly utilised in many centres to evaluate coronary artery stenosis. In addition, FFR-guided coronary revascularisation is a safe and long-term effective method.[4,5]

Correspondence to: Dr. Mehmet Kis, Department of Cardiology, Silopi State Hospital, Sirnak, Turkey
E-mail: drmehmet.kis@hotmail.com

Received: July 03, 2021; Revised: October 20, 2021;
Accepted: November 15, 2021
DOI: https://doi.org/10.29271/jcpsp.2022.01.4

Hemoglobin A1c (HbA1c), is one of the endogenous advanced glycation-end products (AGE), and it is a parameter that shows the long-term mean glycemic index. Determination of HbA1c does not require fasting state or glucose loading; and it is a parameter that provides a single-sample glycemia determination with higher reproducibility than fasting glucose.[6] It was stated that besides the diagnosis of diabetes mellitus, HbA1c was strongly associated with CAD and can be used as a marker of CAD, and also predicts cardiovascular disease and mortality in patients without diabetes mellitus.[6-8]

The correlation between CAD severity and HbA1c levels in patients with diabetes mellitus is well understood. However, the relationship between HbA1c levels and CAD severity in patients without diabetes mellitus is still controversial.[9,10]

The aim of this study was to investigate whether there is any correlation between the FFR, which indicates CAD severity, and HbA1c in the non-diabetic adult population; and find the ideal cut-off value of HbA1c for better risk stratification and prediction of CAD occurrence in non-diabetic patients.

METHODOLOGY

This observational study was conducted at Department of Cardiology, Medical Faculty, Dicle University from September 2015 to November 2019. Patients, who underwent elective FFR proce-

dure, were included in this study. Ethics Committee approval was obtained from Faculty of Medicine, Bakırçay University (Decision No. 263). Demographic characteristics, such as age, gender, blood pressure, and heart rate were recorded. There were two groups, according to FFR lesion severity as FFR <0.8 group (75 patients), FFR >0.8 group (39 patients).

Patients with no previous history of diabetes mellitus, fasting blood glucose <126 mg / dl, and HbA1c <6.5% were included in the study. Patients younger than the age of 18 and older than the age of 90 years, those with a history of diabetes or HbA1c level above 6.5%, or a history of previous revascularisation, who had severe renal failure and severe liver failure, anemic patients (Hb values below 10mg/dl), and active malignancy, were excluded from the study.

IBM SPSS Statistics version 21.0 programme was used. The suitability of numerical variables to normal distribution was examined, using the Shapiro–Wilk and Kolmogorov-Smirnov tests. Numerical variables are given as mean and standard deviation. For a comparison between the two groups in terms of numerical variables, if normal distribution was achieved independent samples t-test was used; if not, Mann-Whitney U-test was used. Categorical variables were shown as numbers (n) and proportions (%). Median and interquartile range (IQR) 25^{th}- 75^{th} percentiles values were given for non-parametric findings. The relationship between categorical variables was examined with Pearson Chi-square and Fisher's Exact test. ROC (Receiver operating characteristic) analysis was performed for the HbA1c cut-off value. The cut-off was determined, according to Youden index. The significance level was accepted as <0.05 for all hypotheses.

G Power 3.0.8 programme was done for the sample size calculation. Estimated sample size was calculated using Student's-t test with 80% power, α=0.05 error level and Cohen (d) effect size = 0.8. Accordingly, it was found appropriate to complete the study with at least 52 patients. G Power 3.1.9.7 programme was used for post hoc power. Difference between two independent means test was applied. The power (1-β err probe) was determined as 0.986 with alpha 0.05 error level, Cohen (d) effect size = 0.8.

RESULTS

The mean age of the 114 patients included in the study, who had a moderate coronary lesion documented by CAG (coronary angiography) and had FFR to determine the severity of the lesion, was 58.2 ± 9.3 years, and 68% of the patients were males. The group with FFR lesion severity <0.8 consisted of 75 (65.8%) patients, and the group with FFR lesion severity ≥0.8 consisted of 39 (34.2%) patients. The groups were similar in terms of mean age and male gender ratios (58.4 ± 9.6 *vs.* 57.9 ± 10.8, p=0.794; 64% vs. 74.4%, respectively, p=0.262, Table I).

When both groups were compared in terms of comorbidities, no significant difference was found for hypertension (42.7% *vs.* 48.7%, p=0.538), previous CAD (49.3% *vs.* 43.6%, p=0.560), and hyperlipidemia (54.7% vs. 59.0%, p=0.660). The comorbid conditions of the study population is summarised in Table I. Biochemical and echocardiographic parameters were similar in both groups. This result shows that the patient groups are homogeneously distributed. The laboratory and imaging findings of the patients are summarised in Table II.

The HbA1c median value in the group with FFR value <0.8 (5.8 (IQR: 5.7-6.0)) was statistically higher than the group with FFR value ≥0.8 [(5.5 (IQR: 5.2-6.0, p=0.002)]. The mean HbA1c value is 5.73 ± 0.36. In the ROC analysis applied considering the Youden index and associated criterion (Figure 1), HbA1c >5.55 had 88% sensitivity and 54% specificity (ROC area under curve: 0.68, 95% CI: 0.569-0.791, p=0.002) for determining the coronary stenosis severity.

The history of medicines use before the FFR procedure was similar in both groups.

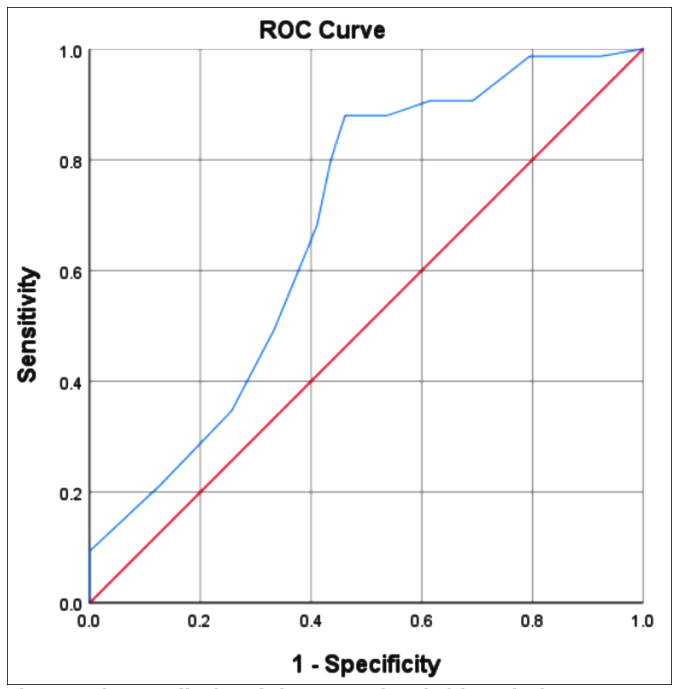

Figure 1: The cut-off value of HbA1c associated with FFR in the ROC curve.

DISCUSSION

To the best of authors' knowledge, this is the first study in the literature to evaluate the correlation between coronary artery lesion severity determined by FFR and HbA1C value in non-diabetic patients. In this study, the mean HbA1c levels were significantly higher in the patient group with low FFR compared to the group with high FFR (p <0.001) and there was a strong correlation.

In this study, the authors thought to use FFR findings instead of CAG findings in order to provide more meaningful findings.[11] HbA1c is one of the endogenous AGEs and is a parameter that indicates the long-term mean glycemic index. In a study evaluating the relationship between HbA1c and blood glucose levels in 131 cases, it was stated that there was a correlation between the mean blood glucose value and HbA1c values, and this correlation was extremely important in terms of CV mortality and morbidity, as well as in the follow-up of DM.[12]

Table I: Baseline characteristics and comorbidities of the study population, according to FFR lesion severity.

	FFR<0.8 (n=75)	FFR>0.8 (n=39)	Total (n=114)	p-value
Age (years)	58 (51-66)	57 (49-65)	58 (51-66)	0.794
Male gender, n (%)	48 (64)	29 (74.4)	77 (67.5)	0.262
SBP, mmHg	127 (116-135)	130 (110-140)	128 (112-140)	0.824
DBP, mmHg	70 (60-80)	70 (60-80)	70 (60-80)	0.836
Heart rate, min	70 (62-78)	77 (65-85)	72 (63-82)	0.169
NYHA Class I, n (%)	71 (94.7)	38 (97.4)	109 (95.6)	0.493
Chest pain, n (%)	69 (92)	35 (89.7)	104 (91.2)	0.686
Dyspnea, n (%)	15 (20)	10 (25.6)	25 (21.9)	0.490
Palpitation, n (%)	5 (6.7)	9 (23.1)	14 (12.3)	**0.011**
Fatigue, n (%)	6 (8)	7 (17.9)	13 (11.4)	0.113
Dizziness, n (%)	4 (5.3)	2 (5.1)	6 (5.3)	0.963
Syncope, n (%)	1 (1.3)	0 (0)	1 (0.9)	1.000
Smoking, n (%)	27 (36.0)	17 (43.6)	44 (38.6)	0.430
Alcohol use, n (%)	4 (5.3)	2 (5.1)	6 (5.3)	0.963
Hypertension, n (%)	32 (42.7)	19 (48.7)	51 (44.7)	0.538
CAD, n (%)	37 (49.3)	17 (43.6)	54 (47.4)	0.560
Hyperlipidemia, n (%)	41 (54.7)	23 (59.0)	64 (56.1)	0.660
COPD, n (%)	10 (13.3)	8 (20.5)	18 (15.8)	0.319
Thyroid disease, n (%)	6 (8.0)	4 (10.3)	10 (8.8)	0.686
Stroke/TIA	7 (9.3)	2 (5.1)	9 (7.9)	0.430
CKD, n (%)	3 (4.0)	2 (5.1)	5 (4.4)	0.780
Peripheral artery disease	4 (5.3)	1 (2.6)	5 (4.4)	0.493
Pacemaker / ICD / CRT	2 (2.7)	0 (0)	2 (1.8)	0.546
Anemia, n (%)	1 (1.3)	1 (2.6)	2 (1.8)	1.000

Data are given in number (percentile) or median [IQR]: (25th-75th percentile). DBP: Diastolic blood pressure; SBP: Systolic blood pressure; NYHA: New York Heart Association. CAD: Coronary artery disease; CKD: Chronic kidney disease; COPD: Chronic obstructive lung diseases; CRT: Cardiac resynchronization therapy; ICD: Implantable cardioverter defibrillator; TIA: Transient ischemic attack.

Table II: Biochemical and imaging findings of the patients.

Parameter mean (± standard deviation)	FFR<0.8 (n=75)	FFR>0.8 (n=39)	Total	p-value
Urea, mg/dL	32 (28-37)	31 (26-37)	32 (28-37)	0.514
Creatinine, mg/dL	0.88 (0.74-1.00)	0.90 (0.70-1.00)	0.88 (0.74-1.00)	0.998
Unic acid, mg/dl	5.3 (4.6-6)	5.6 (5-6.10)	5.4 (4.6-6)	0.101
Total cholesterol, mg/dL	189 (161-229)	181 (152-206)	186 (160-223)	0.190
Triglyceride, mg/dl	161 (111-216)	140 (103-185)	155 (107-201)	0.179
HDL, mg/dL	39 (31-48)	41 (35-51)	40 (33-50)	0.176
LDL, mg/dL	120 (96-149)	104 (85-134)	113 (91-143)	0.072
WBC, k/mm3	8.1 (7-8.9)	8.3 (7-10)	8.1 (7-9.1)	0.464
Hemoglobin, g/dL	13.9 (12.7-14.6)	13.5 (12.7-14.3)	13.8 (12.7-14.6)	0.573
Platelet	247 (223-279)	248 (217-285)	248 (222-281)	0.740
Fasting glucose, mg/dL	101 (93-106)	99 (89-107)	100 (92-107)	0.468
TSH, mU/L	1.74 (1.08-2.8)	1.96 (0.74-2.97)	1.88 (0.94-2.88)	0.935
T4	1.31 (1.13-1.68)	1.26 (1.15-1.60)	1.31 (1.13-1.67)	0.608
Ca, mg/dL	9.4 (9.1-9.8)	9.2 (8.9-9.6)	9.3 (8.9-9.7)	0.330
Sodium	140 (138-141)	140 (138-142)	140 (138-141)	0.348
Potasium	4.51 (4.26-4.73)	4.40 (4.20-4.73)	4.49 (4.24-4.73)	0.971
HbA1c	5.8 (5.7-6)	5.5 (5.2-6)	5.8 (5.5-6)	**0.002**
Sinus rhythm, n (%)	71 (94.7)	39 (100)	110 (96.5)	0.142
LVEF,%	60.00 (55-60)	60.00 (50-60)	60 (54-60)	0.165
LVEDD, cm	46.00 (44-51)	48.00 (44-52)	47 (44-51)	0.281
LVEDS, cm	29.00 (25-32)	30.00 (27-34)	29 (25-32)	0.144
LVDD, n (%)	51 (68)	22 (56.4)	73 (64.0)	0.221

Data are given in number (percentile) or median [IQR]: (25th-75th percentile). AS: Aortic stenosis; AR: Aortic regurgitation; Ca: Calcium; HbA1C: Hemoglobin A1c; HDL: High density lipoprotein; LDL: Low density lipoprotein; LVDD: Left ventricular diastolic dysfunction; LVEDD: Left ventricular end diastolic diameter; LVESD – left ventricular end systolic diameter; LVEF - left ventricular ejection fraction; Mg – magnesium; MR - mitral regurgitation; MS – mitral stenosis; P – phosphate; TSH - thyroid stimulating hormone; WBC - white blood cell.

In another study that included 346 patients to evaluate the relationship between HbA1c level and CAD severity in non-diabetic patients, it was found that as the HbA1c level increased, there was a significant increase in the mean number of diseased vessels ($p < 0.001$). In this study, a linear correlation was found between HbA1c level and CAD severity according to Syntax score ($p < 0.001$).[13] In addition, the mean age of the patients were 58.1 ± 10.4 years and 91.9% (318) were males. Although the mean age in this study was similar to the above-mentioned study, the percentage of male patients (67.5%) in this study was more balanced.

One of the confounding factors affecting HbA1c is the value of hemoglobin (Hb) as it changes HbA1c levels.[14] A low Hb value may lower the HbA1c level; this may show an association between CAD severity and lower HbA1c levels. In a study that included 119 acute coronary syndrome patients without diabetes, no significant difference was found for HbA1c values in multivariate logistic regression analysis in groups with Syntax score ≤22 and Syntax score >22. In conclusion, this study found that HbA1c value was not an independent predictor of CAD severity in nondiabetic adult patients.[10] However, in that study, the male gender ratio was very high and the mean hemoglobin value was low. This may have affected the study results. Another advantage of this study is that the mean hemoglobin values were within normal limits in both groups. In addition, no significant difference was found between the FFR groups in terms of Hb value in this study.

In a study including 299 people, who underwent CAG for suspected ischemia, there was a significant increase in the prevalence of CAD and the number of associated lesioned vessels with increasing HbA1c levels. The ideal cut-off value of HbA1c to predict the occurrence of CAD was found to be 5.6% (sensitivity: 60.5%, specificity: 52%).[15] Similarly, in the present study, the ideal cut-off value of HbA1c was determined as 5.55%. However, HbA1c cut-off value that we found for the relationship between FFR lesion severity and HbA1c differs from the study mentioned above, with sensitivity 88.0% and specificity 53.85%. FFR gives better information about lesion hemodynamics than CAG. This is one of the most important advantages of this study compared to other studies.

Despite the fact that there is the small number of patients included in the study, the statistical correlation between HbA1c levels and FFR severity supports that high HbA1c levels contribute to coronary lesion severity. Another limitation of the study was that the HbA1c value was based on a single measurement, so it may underestimate any relationship between HbA1c and FFR lesion severity.

CONCLUSION

HbA1c, which shows the long-term glycemic index, may be a predictor of CAD severity in non-diabetic patients, independent of traditional cardiovascular risk factors. HbA1c correlates with fractional flow reserve lesion severity in nondiabetic adult patients.

ETHICAL APPROVAL:
Ethics Committee approval for this study was received from the Bakircay University Medicine Faculty (Decision No. 263).

PATIENTS' CONSENT:
Written informed consents were obtained from all patients included in the study.

CONFLICT OF INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
MK: Conception and design of the study, analysis and drafting of manuscript.
TG: Acquisition and interpretation of data, and critical revision.

REFERENCES

1. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, *et al.* 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The task force for the diagnosis and management of chronic coronary syndromes of the european society of cardiology (ESC). *Eur Heart J* 2019; **41(3)**:407-7. doi.org/10.1093/eurheartj/ehz425.
2. Kawase Y, Matsuo H, Akasaka T. Clinical use of physiological lesion assessment using pressure guide wires: An expert consensus document of the Japanese association of cardiovascular intervention and therapeutics. *Cardiovasc Interv Ther* 2019; **34**:85-96. doi.org/10.1007/s12928-018-0559-0.
3. Yıldırır A. Practical tips for the measurement of fractional flow reserve (FFR). *Arch Turk Soc Cardiol* 2011; **39(5)**:433-5 doi: 10.5543/tkda.2011.01686.
4. Xaplanteris P, Fournier S, Pijls NHJ, Fearon WF, Barbato E, Tonino PAL, *et al*. Five-year outcomes with pci guided by fractional flow reserve. *N Engl J Med* 2018; **379(3)**:250-9. doi: 10.1056/NEJMoa1803538.
5. Scully TG, Toner L, Yeoh J, Farouque O, Yudi MB, Horrigan M, *et al.* Safety and long-term clinical outcomes of fractional flow reserve guided coronary revascularisation. *Heart Lung Circ* 2021; S1443-9506(21)00074-3. doi: 10.1016/j.hlc.2021.02.009.
6. Dar MI, Beig JR, Jan I, Shah TR, Ali M, Rather HA, *et al.* Prevalence of type 2 diabetes mellitus and association of HbA1c with severity of coronary artery disease in patients presenting as non-diabetic acute coronary syndrome. *Egypt Heart J* 2020; **72(1)**:66. doi: 10.1186/s43044-020-00101-0.
7. Timmer JR, Hoekstra M, Nijsten MW, van der Horst IC, Ottervanger JP, Slingerland RJ, *et al.* Prognostic value of admission glycosylated hemoglobin and glucose in nondiabetic patients with ST-segment elevation myocardial infarction treated with percutaneous coronary intervention/clinical perspective. *Circulation* 2011; **124**:704-11.
8. Hong LF, Li XL, Guo YL, Luo SH, Zhu CG, Qing P, *et al*. Glycosylated hemoglobin A1c as a marker predicting the severity

of coronary artery disease and early outcome in patients with stable angina. *Lipids Health Dis* 2014; **13**:89. doi: 10.1186/1476-511X-13-89.

9. Ikeda N, Iijima R, Hara H, Moroi M, Nakamura M, Sugi K. Glycated hemoglobin is associated with the complexity of coronary artery disease, even in non-diabetic adults. *J Atheroscler Thromb* 2012; **19(12)**:1066-72. doi: 10.5551/-jat.13722.
10. Habib S, Ullah SZ, Saghir T. The association between hemoglobin A1c and the severity of coronary artery disease in non-diabetic patients with acute coronary syndrome. *Cureus* 2020; **12(1)**:e6631. doi:10.7759/cureus.6631.
11. Jianjun Y, Xiaohua P, Xuemei T, Gang H, Hailong W. Comparison of outcomes between fractional-flow-reserveand angiography-directed intervention in non-st elevation acute coronary syndrome. *J Coll Physicians Surg Pak* 2019; **29(3)**: 268-73. doi: 10.29271/jcpsp.2019.03.268.
12. Motor S, Dokuyucu R, Sefil F, Rifaioğlu MM, Yengil E, Ulutaş KT, *et al.* Relationship between Hba1c and blood glucose level in hemodialysis patients with diabetes mellitus. *Dicle Med J* 2013; **40(4)**:616-20. doi: 10.5798/diclemed-j.0921.2013.04.0343.
13. Dutta B, Neginhal M, Iqbal F. Glycated hemoglobin (HbA1c) correlation with severity of coronary artery disease in non-diabetic patients - a hospital based study from North-Eastern India. *J Clin Diagn Res* 2016; **10(9)**:OC20-OC3. doi: 10.7860/JCDR/2016/22378.8525.
14. Adeoye S, Abraham S, Erlikh I, Sarfraz S, Borda T, Yeung L. Anemia and hemoglobin A1c level: Is there a case for redefining reference ranges and therapeutic goals? *Br J Med Pract* 2014; **7(1)**:a706.
15. Ashraf H, Boroumand MA, Amirzadegan A, Talesh SA, Davoodi G. Hemoglobin A1C in non-diabetic patients: An independent predictor of coronary artery disease and its severity. *Diabetes Res Clin Pract* 2013; **102(3)**:225-32. doi: 10.1016/j.diabres.2013.10.011.