

## Relationship Between Coronary Flow Reserve and Glycated Hemoglobin in Patients With Diabetes Mellitus Using Radionuclide Myocardial Perfusion Imaging

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### ABSTRACT

**Objective:** To evaluate the relationship between coronary flow reserve (CFR) and glycosylated hemoglobin (HbA1c) in patients with type 2 diabetes mellitus using radionuclide myocardial perfusion imaging (MPI).

**Study Design:** Analytical Cross-Sectional Study.

**Place and Duration of Study:** Armed Forces Institute of Cardiology (AFIC), Rawalpindi, Pakistan, from Jun to Dec 2025.

**Methodology:** Ninety-eight adults (18–70 years), irrespective of gender, with type 2 diabetes mellitus referred for myocardial perfusion imaging were screened. Consecutive sampling was used to enroll all eligible patients who met the inclusion criteria during the study period. Patients with obstructive substantial valvular disease, left ventricular ejection fraction less than 50%, and coronary artery disease, arrhythmias, or advanced renal impairment were excluded. All participants underwent standardized SPECT myocardial perfusion imaging with pharmacological stress were indicated to all patients. Coronary flow reserve was calculated from stress-to-rest myocardial tracer uptake. Glycemic control was assessed by HbA1c using a Roche analyzer.

**Results:** There were ninety-eight patients; 45 (45.9%) had adequate glycemic control (HbA1c <7%), while 53 (54.1%) had poor control (HbA1c ≥7%). with comparable mean ages between groups (48.42±12.31 vs. 48.59±10.89 years). A statistically significant inverse relationship was witnessed between HbA1c levels and CFR. ( $r = -0.289$ ,  $p = 0.004$ ) Compared to patients with good glycemic control, those with poor glycemic control had noticeably lower CFR.

**Conclusion:** Coronary flow reserve using radionuclide myocardial perfusion imaging provides a valuable noninvasive tool for early detection of microvascular dysfunction. Clinically, this underscores the importance of strict glycemic control to preserve coronary microvascular integrity and potentially reduce long-term cardiovascular risk.

**Keywords:** Coronary Flow Reserve; Diabetes Mellitus; Glycated Hemoglobin; Myocardial Perfusion Imaging; Single Photon Emission Computed Tomography.

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### INTRODUCTION

Coronary flow reserve (CFR) is a functional parameter that helps us predict the capacity of coronary circulation beyond anatomical stenosis.<sup>1</sup> Impaired CFR is a sensitive marker of early coronary microvascular dysfunction, conferring a 3.4–3.8-fold higher risk of mortality and major adverse events, while ischemic heart disease causes over 20 million deaths annually world wide.<sup>2</sup> In Pakistan, a study reported that nearly 25% of adults aged ≥40 years have coronary artery disease, underscoring the clinical relevance of CFR assessment in this high-risk population.<sup>3</sup>

Diabetes mellitus affects 589 million adults worldwide, is projected to reach 853 million by 2050,

and causes about 3.4 million deaths annually, with over 80% of cases in low- and middle-income countries.<sup>4</sup> These processes promote coronary microvascular dysfunction even without angiographically significant coronary artery disease (CAD).<sup>5</sup> Glycated hemoglobin (HbA1c) is a laboratory value of long-term glucose control and has been consistently associated with both microvascular and macrovascular complications of diabetes.<sup>6</sup>

The burden of diabetes is particularly alarming in South Asia. According to the International Diabetes Federation, Pakistan ranks among the countries with the highest prevalence of diabetes worldwide.<sup>7</sup> National Diabetes Survey of Pakistan (NDSP 2016–2017) stated an overall prevalence of diabetes of approximately 26–28 % in adults, with a substantial proportion of undiagnosed cases.<sup>8</sup> This high prevalence, combined with the increased susceptibility

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of South Asians to endothelial dysfunction and microvascular disease at relatively lower body mass indices, places this population at heightened cardiovascular risk.

Given the paucity of local data, this study aims to assess the relationship between HbA1c levels and CFR in patients with type 2 DM undergoing radionuclide MPI at a tertiary cardiac center in Pakistan. Establishing this association may facilitate earlier identification of subclinical coronary microvascular dysfunction and support timely preventive strategies in this high-risk population.

**METHODOLOGY**

This analytical cross-sectional research was conducted at the Armed Forces Institute of Cardiology (AFIC), Rawalpindi, Pakistan, from Jun to Dec 2025. The research was accepted by the Institutional Ethical Review Board (IERB # 9/25 dated 24<sup>th</sup> July 2025), and every participant gave their informed consent at the outset. Consecutive sampling was used to enroll all eligible patients who met the inclusion criteria during the study period.

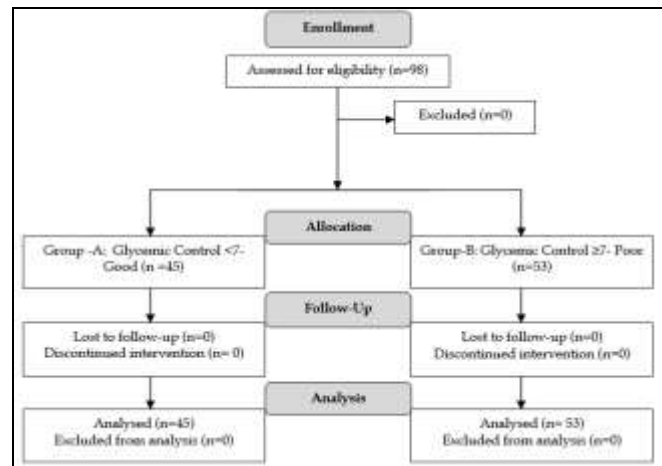
The sample size was calculated using the World Health Organization's sample size calculator, With reference to the reported mean Coronary Flow Reserve (CFR) value of 2.46±0.70 in patients with diabetes mellitus, a study power of 90%, confidence level of 95%, and margin of error of 5%, the calculated sample size was 98 patients, which was achieved throughout the study duration.<sup>10</sup>

**Inclusion Criteria:** Adult patients of both genders between the ages of 18 and 70 who have been diagnosed with type 2 diabetes of at least three years' duration, normal coronary arteries on invasive coronary angiography or computed tomography coronary angiography, and referral for clinically indicated myocardial perfusion imaging were included.

**Exclusion Criteria:** Individuals having a left ventricular ejection fraction of less than 50% and a history of ischemic heart disease, significant valvular heart disease, cardiac arrhythmias, or renal failure, as described having a glomerular filtration rate of less than 30 ml/min/1.73 m<sup>2</sup> were excluded.

Eligible participants were recruited consecutively from cardiology outpatient departments (OPD). Diagnosis of diabetes mellitus was confirmed according to the American Diabetes Association criteria. The clinical assessment, which noted the

person's age, sex, length of time with diabetes, and comorbidities, including high blood pressure and high cholesterol, as well as their medications, smoking, and exercise. Glycemic control was assessed either through the institution's laboratory analysis of hemoglobin A1c or obtained from hospital records within a month of the imaging. Patients were divided into good (HbA1c <7.0%) and poor (HbA1c ≥7.0%) control categories. (Fig-1). Baseline lab tests included fasting blood glucose, blood lipid levels, and tests for renal function for safety and eligibility regarding the pharmacological stress tests. Myocardial perfusion imaging was done using the radionuclide single-photon emission computed tomography. For patients who could not perform exercise stress testing, pharmacological stress was done using adenosine. In accordance with the stress and rest phase institutional protocol, a technetium-99m labeled radiotracer was given during stress and rest phases. Imaging data were acquired and reconstructed using institutionally validated parameters. Data interpretation was performed by experienced nuclear medicine specialists who were unaware of the patients' HbA1c levels.



**Figure: Patient Flow Diagram**

Coronary flow reserve was calculated as the ratio of myocardial tracer uptake during pharmacological stress to that at rest, with a value <2.0 indicating impaired coronary microvascular function.<sup>9</sup> Left ventricular ejection fraction and perfusion findings were recorded. Following completion of imaging, patients were monitored for adverse reactions related to pharmacological stress agents. All clinical, laboratory, and imaging data were entered into a structured database with anonymization to ensure confidentiality.

## Relationship Between Coronary Flow Reserve

The statistical analysis was carried out using version 23 of the Statistical Package for the Social Sciences. Descriptive statistics summarize baseline characteristics and outcomes in the form of frequencies/percentages (gender, hypertension, smoking) and Mean±SD (LVEF, CFR); not normally distributed variables (age, weight, height) are reported as median (IQR). Spearman's Correlation analysis was applied to find the relationship between HbA1c and CFR. Chi-square test applied to find the association of categorical variables (gender, smoking status, and hypertension) with HbA1c categories. Independent t-test applied to find the mean difference of (age, LVEF) across HbA1c categories, Mann-Whitney test applied to find median (IQR) of (weight, height, HDL and LDL), Binary logistic regression analysis was performed to identify clinical and biochemical factors independently associated with impaired coronary flow reserve in patients with diabetes mellitus, *p*-value ≤0.05 considered statistically significant.

### RESULTS

The study involved 98 patients in total, of whom 45(45.9%) had good glycemic control (HbA1c <7%), and 53(54.1%) had poor glycemic control (HbA1c ≥7%). The median age was similar between the groups, being 48.0(38.0-58.0) years in the good control group and 50.0(38.0-55.0) years in the poor control group. In terms of gender, among patients with good glycemic control, 15(33.3%) were female, and 30(66.7%) were male, whereas in the poor control group, 14(26.4%) were female, and 39 (73.6%) were male (*p*=0.455). Physical activity, hypertension, and family details of CAD did not significantly change between the groups, significant lower Coronary Flow Reserve (CFR) (1.91±0.53 vs. 2.47±0.71, *p*<0.001). Other variables, including mean (LVEF and CFR), Median (weight, total cholesterol, LDL, HDL, serum creatinine, and duration of T2DM), did not differ significantly. Table-I.

Table-II presents the clinical and biochemical factors associated with Coronary Flow Reserve (CFR) in patients with Type 2 Diabetes Mellitus (n=98). On univariate logistic regression analysis, high HbA1c (>7%) showed a statistically significant association with impaired CFR (OR 3.587, 95% CI: 1.525-8.437, *p*=0.003), while HDL, total triglycerides, total cholesterol, and hypertension demonstrated *p*-values ≤0.25 and were therefore entered into the multivariate model. In multivariate analysis, only high HbA1c remained independently associated with impaired CFR (*p*=0.002), whereas age, weight, duration of

diabetes, LDL, serum creatinine, LVEF, dyslipidemia, and family history of CAD did not show significant associations (*p*>0.05). These findings indicate that poor glycemic control is the most important determinant of coronary microvascular dysfunction in this cohort.

**Table-I: Clinical Characteristics of the Study Population in Different Groups (n=98)**

Variables	Categories	Glycemic Control <7-Good (n =45)	Glycemic Control ≥7- Poor (n=53)	<i>p</i> -value
		Frequency (%)		
Gender	Female	15(33.3%)	14(26.4%)	0.45
	Male	30(66.7%)	39(73.6%)	
Smoking Status	Current	6(13.3%)	11(20.8%)	0.58
	Former	7(15.6%)	9(17.0%)	
	Never	32(71.1%)	33(62.3%)	
Physical Activity	Active	3(6.7%)	12(22.6%)	0.09
	Moderate	17(37.8%)	16(30.2%)	
	Sedentary	25(55.6%)	25(47.2%)	
Hypertension	No	28(62.2%)	28(52.8%)	0.34
	Yes	17(37.8%)	25(47.2%)	
Dyslipidemia	No	23(51.5%)	40(75.5%)	0.01
	Yes	22(48.9%)	13(24.5%)	
Family History CAD	No	33(73.3%)	32(60.4%)	0.17
	Yes	12(26.7%)	21(39.6%)	
		Mean ± SD		
LVEF (%)		60.93±3.88	60.83±4.69	0.90
CFR		2.47±0.71	1.91±0.53	<0.001
<b>Median (IQR)</b>				
Age (years)		48.0(38.0-58.0)	50.0(38.0-55.0)	0.88
Duration of T2DM (years)		12.0(7.0-16.0)	12.0(8.0-17.0)	0.80
Weight (kg)		70.0 (65.0-74.0)	69.0 (63.0-76.0)	0.73
Height (cm)		168.6 (160.6-174.0)	164.4 (157.9-171.1)	0.02
Total Cholesterol (mg/dL)		187.0 (170.0-195.0)	185.0 (155.0-204.0)	0.51
LDL (mg/dL)		98.0 (81.0-121.0)	108.0 (93.0-130.0)	0.23
HDL (mg/dL)		44.0 (38.0-49.0)	45.0 (39.0-51.0)	0.50
Serum Creatinine (mg/dL)		0.99 (0.93-1.08)	0.99 (0.88-1.11)	0.86

*\*CAD = Coronary Artery Disease, T2DM = Type 2 Diabetes Mellitus, LVEF = Left Ventricular Ejection Fraction, CFR = Coronary Flow Reserve, LDL = Low-Density Lipoprotein, HDL = High-Density Lipoprotein*

A significant negative weak correlation between CFR and HbA1c levels was found. The scatter plot indicates that as HbA1c increases—reflecting poorer glycemic control—CFR tends to decline, suggesting

impaired coronary microvascular function. The correlation coefficient ( $r = -0.289, p=0.004$ ) confirms an inverse statistically significant correlation, which indicates that increased levels of HbA1c could be linked with a decrease in coronary flow reserve, as demonstrated in Figure-2.

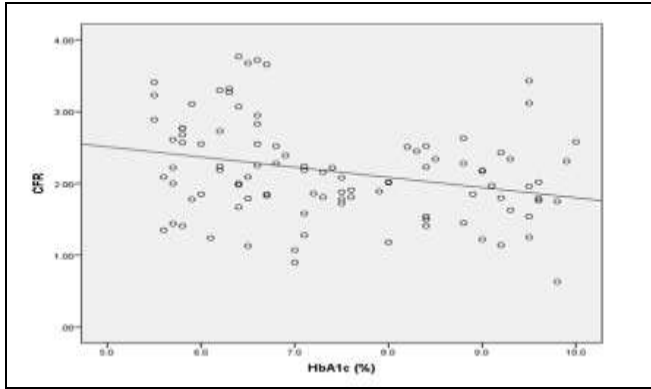


Figure-2: Correlation Between Coronary Flow Reserve and HbA1c Levels

dysfunction (CMD). This suggests that chronic hyperglycemia impairs coronary microvascular function irrespective of angiographic CAD, as Murthy *et al.*, showed that reduced CFR was associated with a nearly twofold higher risk of cardiac mortality, with diabetic patients without obstructive CAD exhibiting outcomes comparable to non-diabetics with CAD.<sup>11</sup>

Our results are consistent with contemporary literature. Chen *et al.*, (2023) reported that intensified glycemic control (target HbA1c=6.5–7.0%) was associated with a significant reduction in major adverse cardiovascular events by approximately 10–15% and a lower risk of microvascular complications in patients with coronary heart disease and T2DM, underscoring the pathophysiological relevance of sustained hyperglycemia in vascular dysfunction.<sup>12</sup> Similarly, Zhang *et al.*, (2022) showed that coronary microvascular dysfunction assessed by angiography-derived index of microcirculatory resistance (IMR) independently predicted adverse outcomes in diabetic

Table-II: Clinical and Biochemical Factors Related to Coronary Flow Reserve in Patients with Diabetes Mellitus (n = 98)

Variables	Study Parameter		Univariate logistic regression		Multivariate logistic regression	
	Median (IQR)	p-value	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age	51.0(43.0-54.0)	0.323	1.017 (0.981-1.053)	0.357	-	-
Weight (kg)	70.0 (64.0-74.0)	0.869	1.002 (0.954-1.053)	0.926	-	-
Duration of T2DM (yrs)	13.0(7.0-17.0)	0.543	1.021 (0.943-1.105)	0.611	-	-
LDL (mg/dL)	109.0 (92.0-128.0)	0.23	0.430 (0.992-1.020)	0.430	-	-
HDL (mg/dL)	42.0 (38.0-49.0)	0.50	0.981 (0.950-1.016)	0.207*	0.971(0.927-1.018)	0.226
Total Triglycerides (mg/dL)	160.0(133.0-188.0)	0.176	1.007 (0.996-1.018)	0.234*	1.006(0.994-1.018)	0.356
Serum Creatinine (mg/dL)	0.98(0.88-1.10)	0.771	0.685 (0.046-1.127)	0.784	-	-
Total Cholesterol (mg/dL)	191.5 (164.0-209.0)	0.132	1.007 (0.995-1.020)	0.253*	1.009(0.995-1.023)	0.194
LVEF (%)	60.7 ± 4.1	0.618	0.989 (0.901-1.086)	0.817	-	-
	Frequency (%)					
High HbA1c (>7)	30.0(30.6%)	0.003*	3.587 (1.525 - 8.437)	0.003*	0.248(0.101-0.611)	0.002*
Hypertension	Yes	21.0 (21.4%)	0.600 (0.267-1.351)	0.217*	0.681(0.284-1.635)	0.390
	No	21.0 (21.4%)				
Dyslipidemia	Yes	14 (14.3%)	0.833(0.360-1.929)	0.670	-	-
	No	28.0 (28.6%)				
Family History of CAD	Yes	13 (13.3%)	1.239(0.528-2.907)	0.622	-	-
	No	29 (29.6%)				

\*T2DM = Type 2 Diabetes Mellitus; CAD = Coronary Artery Disease, HbA1c = Glycated Hemoglobin A1c, LDL = Low-Density Lipoprotein, LVEF= Left Ventricular Ejection Fraction, HDL = High-Density Lipoprotein.

DISCUSSION

The present study demonstrates a strong association between glycemic control and coronary microvascular function in patients with type 2 diabetes mellitus (T2DM), highlighting HbA1c as an independent determinant of coronary flow reserve (CFR). In our study of 98 patients, those with poor glycemic control (HbA1c ≥ 7%) had significantly lower CFR compared with patients with good glycemic control (1.91±0.53 vs. 2.47±0.71,  $p<0.001$ ), despite no significant differences in age, duration of diabetes, left ventricular ejection fraction, or lipid profile. These findings emphasize that chronic hyperglycemia itself plays a pivotal role in coronary microvascular

patients with chronic coronary syndrome, with elevated IMR associated with approximately a two-fold higher risk of major adverse cardiovascular events (adjusted HR,  $p<0.05$ ), even in the absence of obstructive CAD.<sup>13</sup> A systematic review and meta-analysis by Jensen *et al.*, further confirmed the prognostic value of reduced CFR in patients with non-obstructive CAD, with notable consistency across imaging modalities and patient subgroups.<sup>14</sup>

Experimental and imaging-based evidence also supports early microvascular involvement in diabetes. Patients with higher HbA1c (>7%) were more likely to exhibit perfusion defects, with reported odds ratios ranging from 2.5 to 3.6 (95% CI 1.5–8.4,  $p<0.01$ ),

highlighting HbA1c as an independent predictor of subclinical ischemia. These findings support the notion of the study by Green *et al.*, that chronic hyperglycemia contributes to microvascular dysfunction beyond traditional cardiovascular risk factors, aligning with our results where high HbA1c emerged as the sole independent predictor of impaired coronary flow reserve (CFR).<sup>15</sup> Advanced functional imaging studies have reinforced the importance of myocardial blood flow and flow reserve in risk stratification beyond angiographic findings. Mechanistically, chronic hyperglycemia promotes endothelial dysfunction, oxidative stress, and microvascular remodeling, which collectively impair coronary vasodilatory capacity.<sup>17,18</sup> Notably, multivariate analysis identified elevated HbA1c as the only independent predictor of impaired CFR (adjusted OR 0.248(0.101-0.611),  $p=0.002$ ),<sup>19,20</sup> consistent with previous studies suggesting that metabolic factors may have a greater impact than traditional risk markers in coronary microvascular dysfunction.<sup>21,22</sup>

The study confirmed that the observed inverse correlation between HbA1c and CFR ( $r=-0.289$ ,  $p=0.004$ ) further supports a dose-response relationship between chronic hyperglycemia and coronary microvascular impairment.

### LIMITATIONS OF STUDY

The aforementioned limitations include the study's cross-sectional design, sample size, and single-center data collection, which may limit generalizability. Additionally, CFR was evaluated using SPECT instead of PET, and there was no complete control of the study's dietary and medication time factors.

### CONCLUSION

The findings indicate that assessment of CFR using radionuclide myocardial perfusion imaging provides early detection of microvascular dysfunction. Clinically, this underscores the importance of strict glycemic control to preserve coronary microvascular integrity and potentially reduce long-term cardiovascular risk. Incorporating CFR evaluation into routine risk stratification strategies may facilitate timely therapeutic interventions and improve cardiovascular outcomes in diabetic populations, particularly in regions with a high prevalence of diabetes, such as Pakistan.

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### Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MF & SS: Data acquisition, data analysis, critical review, approval of the final version to be published.

MNK & KN: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

ARK & SM: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## Relationship Between Coronary Flow Reserve

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