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Relation of HbA1c with Severity of CAD (SYNTAX score)

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Abstract
Introduction: Coronary artery disease (CAD) continues to be the primary cause of death globally. Glycated hemoglobin (HbA1c), a recognized indicator of prolonged glycemic regulation, has been associated with both microvascular and macrovascular consequences. Nonetheless, scant evidence correlate HbA1c with the angiographic severity of coronary artery disease as assessed by the SYNTAX score in diabetic individuals.
Aim: The present study was done with an aim to evaluate the relationship between HbA1c level and severity of coronary artery disease in diabetic patients using SYNTAX score in a cohort of proven Coronary Artery Disease (CAD) on angiography.
Material and methods: A cross-sectional study was performed at a tertiary care hospital over six months, enrolling 170 diabetic patients with angiographically verified coronary artery disease (CAD). Patients were categorized into four HbA1c quartiles: <6.7%, 6.7-7.1%, 7.1-7.6%, and >7.6%. The complexity of coronary lesions was evaluated using the SYNTAX score, and vascular involvement was recorded. The statistical analysis encompassed ANOVA, chi-square tests, Pearson's correlation, and multivariate logistic regression.
Results: The average age of the group was 58.4 ± 9.2 years, comprising 68.2% men. Common comorbidities included hypertension (62.9%), dyslipidemia (48.8%), and a history of smoking (39.4%). The average HbA1c was 7.24 ± 0.68%. SYNTAX scores shown a progressive increase across quartiles (14.2 ± 4.8, 18.5 ± 5.1, 21.7 ± 6.2, and 26.3 ± 7.1; $p < 0.001$). The prevalence of multivessel disease increased from 22.5% in the lowest HbA1c group to 70.4% in the highest ($p < 0.001$). HbA1c had a substantial correlation with the SYNTAX score ($r = 0.62$, $p < 0.001$) and served as an independent predictor of severe coronary artery disease (OR 1.45; 95% CI: 1.18-1.78; $p < 0.001$).
Conclusion: In diabetic patients, elevated HbA1c levels are highly correlated with higher SYNTAX scores and a greater prevalence of multivessel coronary artery disease (CAD). HbA1c functions as an independent indicator of CAD severity, highlighting the significance of effective glycemic management in reducing coronary atherosclerotic load.

Keywords: Cardiovascular risk, Glycated Haemoglobin, Syntax Score, Type 2 Diabetes

Introduction

Coronary Artery Disease (CAD) is the leading cause of death worldwide. Major efforts have been made to find novel useful non-invasive biomarkers for CAD. The biomarkers may be involved in the pathogenesis of CAD or the formation of risk factors, such as DNA methylation signatures affecting HLA-G gene were correlated with plaque load changes, which was predictive for disease severity [1].

Glycated hemoglobin (HbA1c) is a product of the binding of hemoglobin and blood sugar in red blood cells in human blood. It is a recognised indicator of long-term glycaemic regulation in individuals with Diabetes Mellitus (DM), and heightened HbA1c levels correlate with an augmented risk of subsequent microvascular and macrovascular complications [2]. Research has repeatedly demonstrated that excellent glycaemic management, defined as HbA1c $\leq$ 7%, leads to a reduced occurrence of microvascular problems in both type 1 and type 2 diabetes mellitus [3]. A recent investigation indicated that elevated HbA1c levels are predictive of cardiovascular disease and mortality in individuals without diabetes mellitus [4].

Limited studies have demonstrated that HbA1c is predictive of coronary artery disease, and only a handful have connected HbA1c with angiographically confirmed CAD using the SYNTAX score. An assessment of the burden of coronary artery disease can be derived by evaluating each lesion using the syntactic score acquired from angiography. The SYNTAX Score (SS) was established during the SYNTAX study to define and objectively measure the severity and extent of coronary artery disease. This scoring method was employed in this investigation to evaluate the severity of coronary artery disease [5, 6].

The present study was done with an aim to evaluate the relationship between HbA1c level and severity of coronary artery disease in diabetic patients using SYNTAX score in a cohort of proven Coronary Artery Disease (CAD) on angiography.

Material and Methods

The present cross-sectional study was conducted at Department of cardiology, Topiwala National Medical College & BYL Nair Ch. Hospital for a period of 6 months. Ethical clearance for conducting the research was taken from institutional ethics committee of college and hospital before commencement of study. Written informed was taken from patients after explaining them about the study.

Through consecutive sampling a total of 170 patients were included in the study after applying the inclusion and exclusion criteria.

Inclusion Criteria

1. All diabetic patients (prior history of diabetes and HbA1c level more than 6.5%)
2. Patients with confirmed Coronary Artery Disease (CAD) (50% reduction in luminal width by visual examination of epicardial coronary arteries (≥50% blockage in ≥1 coronary artery).

Exclusion Criteria

1. Patients exhibiting a reduction of less than 50% in the luminal diameter of epicardial coronary arteries on angiography were excluded from the study.
2. Patients with a history of past revascularization via PCI or CABG, as well as those with known hemoglobinopathies, anemia, or a recent history of blood transfusion, were excluded from the trial.

The pertinent patient information, including name, age, gender, history of diabetes, smoking, dyslipidemia, hypertension, and other comorbidities, was recorded.

Patients were classified as hypertensive based on JNC 8 (The Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) criteria, diabetic according to ADA (American Diabetes Association) criteria, and dyslipidemic per NCEP (National Cholesterol Education Program) criteria. Furthermore, the utilization of antihypertensive, antidiabetic, or lipid-lowering drugs served as criteria for hypertension, diabetes, and dyslipidemia, respectively was also noted A history of tobacco smoking, whether present or former, for a duration of 6 months was classified as smoking positive. The angiography details were acquired and assessed utilizing the Syntax score. The Syntax scores were computed using a professional online tool. The serum concentration of Hemoglobin A1c (HbA1c) was assessed using the immunoturbidimetric technique. Patients were categorized into four groups (interquartiles) based on HbA1c levels: less than 6.7%, 6.7% to 7.1%, 7.1% to 7.6%, and greater than 7.6%. The severity of coronary artery disease was evaluated using the SYNTAX score and the quantity of affected coronary arteries. We analyzed various quartiles of HbA1c in relation to the SYNTAX score and the quantity of affected vessels. The severity of coronary artery disease was evaluated using the SYNTAX score and the quantity of affected coronary arteries. Diabetic individuals were categorized into four quartiles based on HbA1c levels. Data are presented as frequencies and percentages for categorical variables and as mean±standard deviation (SD) for continuous variables, unless stated otherwise. Group differences were evaluated utilizing chi-square and ANOVA methodologies. The correlation between continuous variables was assessed using Pearson correlation coefficients. Regression analysis was used to demonstrate the association between the severity of coronary artery disease (CAD) and HbA1C levels. Multivariate logistic regression was employed to demonstrate that HbA1c levels serve as an independent predictor of the severity of coronary artery disease (CAD). A P-value of less than 0.05 was deemed statistically significant. The analysis was conducted with SPSS Version 25.0.

Results

The mean age of participants was 58.4 ± 9.2 years (range: 38-78 years). The male-to-female ratio was almost 2.1:1, with 116 males (68.2%) and 54 females (31.8%). Mean duration of diabetes was 9.6 ± 4.3 years. 107 patients (62.9 %) patients had diabetes. 83 patients (48.8 %) had dislipidemia and 67 patients (39.4%) had history of smoking as shown in table 1.

Table 1: Baseline characteristics of patients

Variable	Total
Age (years), mean ± SD	58.4 ± 9.2
Male sex	116 (68.2%)
Female sex	54 (31.8%)
Hypertension	107 (62.9%)
Dyslipidemia	83 (48.8%)
Smoking history	67 (39.4%)
Family history of CAD	41 (24.1%)
Duration of diabetes (years), mean ± SD	9.6 ± 4.3

Mean HbA1c level in the patients was 7.24 ± 0.68%. 40 (23.5%) belonged to the lowest HbA1c quartile (<6.7%), 42 (24.7%) to the second quartile (6.7-7.1%), 44 (25.9%) to the third quartile (7.1-7.6%), and 44 (25.9%) to the highest quartile (>7.6%) as shown in figure 1.

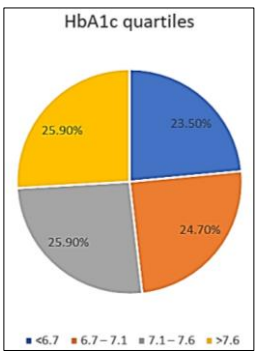

Fig 1: Distribution of patients according to HbA1c Quartiles

Patients with HbA1c values below 6.7% exhibited a mean SYNTAX score of 14.2 ± 4.8, whereas those in the highest quartile beyond 7.6% demonstrated a significantly elevated mean score of 26.3 ± 7.1. The intermediate quartiles (6.7-7.1% and 7.1-7.6%) exhibited incremental increases with mean SYNTAX scores of 18.5 ± 5.1 and 21.7 ± 6.2, respectively. The ascending trend among quartiles was statistically significant ($p < 0.001$) as shown in table 2.

Table 2: Mean SYNTAX Score Across HbA1c Quartiles

HbA1c Quartile	Mean SYNTAX Score ± SD	p-value
<6.7%	14.2 ± 4.8	<0.001
6.7-7.1%	18.5 ± 5.1	
7.1-7.6%	21.7 ± 6.2	
>7.6%	26.3 ± 7.1	

In the lowest HbA1c group (<6.7%), the predominant proportion of patients (77.5%) exhibited single-vessel disease, whereas merely 7.5% presented with triple-vessel disease. As HbA1c levels escalated, the prevalence of individuals with multivessel disease significantly increased. In the upper HbA1c quartile (>7.6%), 40.9% of patients exhibited triple-vessel disease, whereas merely 29.6% retained single-vessel involvement. This relationship was statistically significant ($p < 0.001$), highlighting that inadequate glycemic control is associated with more severe coronary artery disease as shown in table 3.

Table 3: Coronary Vessel Involvement Across HbA1c Quartiles

HbA1c Quartile	Single Vessel Disease (%)	Double Vessel Disease (%)	Triple Vessel Disease (%)	p-value
<6.7%	77.5	15.0	7.5	<0.001
6.7-7.1%	61.9	21.4	16.7	
7.1-7.6%	47.7	25.0	27.3	
>7.6%	29.6	29.5	40.9	

A robust positive connection was identified ($r = 0.62$, $p < 0.001$), signifying that elevated HbA1c levels were consistently linked to increased SYNTAX scores as shown in table 4.

Table 4: Correlation Between HbA1c and SYNTAX Score

Variable Pair	R-value	p-value
HbA1c vs SYNTAX score	0.62	<0.001

Upon controlling for traditional cardiovascular risk variables including age, sex, hypertension, dyslipidemia, and smoking, HbA1c was identified as the sole independent and statistically significant predictor of severe coronary artery disease (OR: 1.45, 95% CI: 1.18-1.78, $p < 0.001$). Other risk factors exhibited trends but did not attain statistical significance as shown in table 5.

Table 5: Multivariate Logistic Regression for Predictors of Severe CAD (SYNTAX >22)

Variable	Odds Ratio (OR)	95% CI	p-value
Age	1.08	0.94-1.23	0.21
Male sex	1.12	0.82-1.46	0.34
Hypertension	1.25	0.91-1.72	0.11
Dyslipidemia	1.18	0.87-1.54	0.17
Smoking	1.31	0.97-1.74	0.08
HbA1c	1.45	1.18-1.78	<0.001

Discussion

This cross-sectional study of 170 diabetic patients with angiographically confirmed coronary artery disease (CAD) revealed a significant, stepwise correlation between HbA1c levels and the severity of angiographic disease: higher HbA1c quartiles were associated with progressively elevated mean SYNTAX scores and an increased prevalence of multivessel disease. HbA1c continued to serve as an independent predictor of severe coronary artery disease (SYNTAX >22) following adjustment for traditional cardiovascular risk variables.

These findings align with other previous studies that associate chronic hyperglycemia (indicated by HbA1c) with more extensive and intricate coronary atherosclerosis. Yan *et al* conducted a cross-sectional analysis that similarly revealed a favorable association between HbA1c and SYNTAX score, indicating that HbA1c may represent the complexity of coronary lesions observed in angiography.[1] Recent cohort analyses and cross-sectional studies indicate that elevated HbA1c levels correlate with increased stenotic burden, higher SYNTAX scores, and greater prevalence of multivessel disease in both diabetic and non-diabetic populations, thereby reinforcing the generalizability of our findings [7, 8].

Numerous studies have demonstrated a link between HbA1c levels and the severity of coronary artery disease (CAD). Nevertheless, only a few research have employed the SYNTAX score to demonstrate the correlation between elevated HbA1c levels and the severity of coronary artery disease (CAD). In a study conducted by Ayhan *et al* in 2012, only HbA1c was identified as an independent risk factor for the existence of severe coronary artery disease, as assessed by the Gensini score [9]. Mi Shu-Hua *et al* have also identified HbA1c as an independent determinant of coronary artery disease, as indicated by the Gensini score [10]. Ghaffari *et al* employed multivariate logistic regression analysis to demonstrate that HbA1c levels exceeding 5.8% serve as an independent predictor of Califf scores more than 6 (OR = 3.17, 95% CI 1.79-5.69; p = 0.001) [11]. Ikeda *et al* demonstrated that HbA1c is substantially correlated with the complexity of coronary lesions [12]. Ravipati *et al* in 2006 demonstrated a correlation between escalating mean HbA1c levels and the severity of coronary artery disease in diabetic patients [13]. Kaya *et al* identified a cutoff value of 6.0% for HbA1c that predicted severe atherosclerosis, with a sensitivity of 54% and a specificity of 74% [14]. In accordance with our findings, Karakoyun S *et al* employed the SYNTAX score to demonstrate the correlation between elevated HbA1c levels and the severity of CAD [15].

From a clinical perspective, our findings substantiate the significance of glycemic control in cardiovascular risk management. Randomized trials (e.g., ACCORD/ADVANCE/VADT) have produced intricate and occasionally contradictory evidence regarding intensive glycemic reduction and macrovascular outcomes; however, current guidelines persist in advocating for personalized HbA1c targets and thorough risk-factor management, especially in patients with pre-existing cardiovascular disease. Our finding that HbA1c independently forecasts angiographic severity indicates that HbA1c offers additional, clinically significant insights into coronary atherosclerotic burden, which may aid in risk assessment and therapeutic planning for diabetic CAD patients [16,17].

Our study has several limitations, including a single-center design that may restrict external validity, the lack of

longitudinal follow-up for major adverse cardiovascular events (MACE) to correlate angiographic complexity with clinical outcomes in our cohort, and the absence of comprehensive plaque characterization (e.g., via intravascular imaging or CT angiography). Subsequent investigations should assess whether therapies that enhance HbA1c and/or diminish glycemic variability result in decreased complexity of coronary artery disease (CAD) and whether HbA1c-directed techniques optimize procedural planning (percutaneous coronary intervention vs coronary artery bypass grafting) or clinical outcomes. Recent interest in derived metrics, such as the stress-hyperglycemia ratio and time-in-range, may enhance the predictive capacity of HbA1c regarding CAD complexity and outcomes, warranting prospective investigation.

Conclusion

A notable positive correlation exists between HbA1c levels and the severity of coronary artery disease as evaluated by the SYNTAX score. Patients in elevated HbA1c quartiles demonstrated increasingly higher SYNTAX scores and a greater incidence of multivessel disease. HbA1c was identified as an independent predictor of severe coronary artery disease, even when controlling for traditional cardiovascular risk variables including age, hypertension, dyslipidemia, and smoking.

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