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Original Research Article

Association between Glycated Hemoglobin Levels and Cardiovascular Risk Markers in Patients with Type 2 Diabetes Mellitus: A Prospective Observational Study

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a globally prevalent metabolic disorder with well-established links to cardiovascular morbidity and mortality. Glycated hemoglobin (HbA1c) serves as the gold-standard indicator of long-term glycemic control; however, the precise quantitative relationship between HbA1c levels and a composite panel of cardiovascular risk markers including inflammatory, lipidemic, and hemodynamic indices remains incompletely characterized in South Asian populations.

Methods: In this prospective observational study conducted between March 2024 and February 2025 across two tertiary care hospital attached with medical college in Gujarat, India, we enrolled 350 adults aged 30–70 years with confirmed T2DM of at least two years duration. Participants were stratified by HbA1c: Group A (<7.0%), Group B (7.0–8.9%), and Group C (≥9.0%). Primary cardiovascular risk markers measured included high-sensitivity C-reactive protein (hsCRP), low-density lipoprotein cholesterol (LDL-C), triglycerides, high-density lipoprotein cholesterol (HDL-C), systolic and diastolic blood pressure, and estimated glomerular filtration rate (eGFR). Pearson correlation and multivariate linear regression analyses were employed.

Results: HbA1c correlated significantly with hsCRP ($r = 0.61$, $p < 0.001$), LDL-C ($r = 0.54$, $p < 0.001$), systolic blood pressure ($r = 0.47$, $p < 0.001$), and triglycerides ($r = 0.43$, $p < 0.001$), while showing an inverse association with HDL-C ($r = -0.39$, $p < 0.001$) and eGFR ($r = -0.33$, $p < 0.001$). On multivariate regression, poor glycemic control (HbA1c ≥9%) was independently associated with elevated hsCRP ($\beta = 0.48$, 95% CI: 0.39–0.57) and LDL-C ($\beta = 0.38$, 95% CI: 0.29–0.47) after adjustment for age, sex, BMI, diabetes duration, and pharmacotherapy.

Conclusions: Suboptimal glycemic control is independently and dose-dependently associated with an adverse cardiovascular risk profile in patients with T2DM. These findings underscore the critical importance of achieving and maintaining individualized HbA1c targets to attenuate multifactorial cardiovascular risk.

Keywords: Type 2 diabetes mellitus; glycated hemoglobin; cardiovascular risk; high-sensitivity C-reactive protein; dyslipidemia; metabolic syndrome; HbA1c.

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Introduction

Type 2 diabetes mellitus (T2DM) represents one of the foremost non-communicable disease burdens of the 21st century. According to the International Diabetes Federation (IDF) Diabetes Atlas 10th Edition, approximately 537 million adults (20–79 years) were living with diabetes globally in 2021, a figure projected to rise to 783 million by 2045. India alone harbors over 74 million individuals with T2DM, rendering it the nation with the second-largest diabetic population worldwide [1]. Beyond hyperglycemia, T2DM engenders a systemic metabolic dysregulation that profoundly elevates the risk of macrovascular complications principally coronary artery disease, cerebrovascular accidents, and peripheral arterial disease as well as microvascular sequelae such as nephropathy, retinopathy, and neuropathy [2]. Glycated hemoglobin (HbA1c) is the established clinical benchmark for gauging long-term glycemic control, reflecting mean plasma glucose concentrations over the preceding two to three months [3]. The landmark United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that each 1% reduction in HbA1c was associated with a 37%

decrease in the risk of microvascular complications and a 14% reduction in myocardial infarction events [4]. Despite this evidence, the mechanistic interplay between sustained hyperglycemia and the spectrum of cardiovascular risk markers encompassing systemic inflammation, atherogenic dyslipidemia, endothelial dysfunction, and hypertension have not been comprehensively delineated in contemporary South Asian cohorts, where a unique cardiometabolic risk phenotype, including higher visceral adiposity and earlier onset of insulin resistance, is well recognized [5]. High-sensitivity C-reactive protein (hsCRP), a sensitive biomarker of systemic low-grade inflammation, has emerged as an independent predictor of major adverse cardiovascular events (MACE) in both diabetic and non-diabetic populations [6].

Materials and Methods

This prospective observational cohort study was conducted at the outpatient endocrinology and general medicine clinics of two tertiary care hospital attached with medical college, Gujarat, India between March 2024 and February 2025. All participants provided written informed consent in accordance with the Declaration of Helsinki. Eligible participants were adults aged 30–70 years with a confirmed diagnosis of T2DM according to the World Health Organization (WHO) 2019 diagnostic criteria for at least two years prior to enrollment. T2DM diagnosis was established based on a fasting plasma glucose ≥126 mg/dL, a 2-hour plasma glucose ≥200 mg/dL during a 75-g oral glucose tolerance test, an HbA1c ≥6.5%, or a random plasma glucose ≥200 mg/dL with classic hyperglycemic symptoms. Exclusion criteria included: (i) Type 1 diabetes or other specific types of diabetes; (ii) established cardiovascular disease (prior myocardial infarction, coronary revascularization, stroke, or heart failure); (iii) advanced chronic kidney disease (eGFR <30 mL/min/1.73m²); (iv) active malignancy, autoimmune disease, or systemic inflammatory conditions; (v) pregnancy or lactation; (vi) hemoglobinopathies that may confound HbA1c interpretation; and (vii) initiation or dose modification of lipid-lowering or antihypertensive therapy within three months preceding enrollment.

Trained research nurses performed all measurements following standardized protocols. Height and weight were measured with participants in light clothing and without shoes; body mass index (BMI) was calculated as weight (kg) divided by height squared (m²). Waist circumference was measured at the midpoint between the last rib and the iliac crest. Blood pressure was recorded in the right arm after five minutes of seated rest, using a validated digital sphygmomanometer. the mean of two readings separated by five minutes was used for analysis. All blood samples were drawn after an overnight fast of at least 10 hours. Venous blood (12 mL) was collected in appropriate vacutainer tubes and processed within two hours of collection. HbA1c was measured by high-performance liquid chromatography (HPLC) using the Tosoh G8 analyzer which meets National Glycohemoglobin Standardization Program (NGSP) certification standards. Fasting plasma glucose (FPG) was assayed by the glucose oxidase–peroxidase method. A full lipid profile including total cholesterol, LDL-C, HDL-C, and triglycerides was obtained. High-sensitivity CRP was quantified by particle-enhanced immunoturbidimetry with an analytical sensitivity of 0.1 mg/L. Serum creatinine was measured enzymatically, and eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Spot urine albumin-to-creatinine ratio (ACR) was performed; microalbuminuria was defined as ACR 30–300 mg. Participants were classified into three mutually exclusive glycemic strata based on their HbA1c at enrollment: Group A (well-controlled, HbA1c <7.0%), Group B (moderately controlled, HbA1c 7.0–8.9%), and Group C (poorly controlled, HbA1c ≥9.0%). These thresholds were selected in accordance with the American Diabetes Association (ADA) Standards of Medical Care in Diabetes and the International Diabetes Federation guidelines for individualized glycemic targets.

Statistical analyses were performed using SPSS version 26.0. Continuous variables are expressed as mean ± standard deviation (SD) or median (interquartile range, IQR) based on normality assessment by the Shapiro-Wilk test. Categorical variables are expressed as number and percentage. Between-group comparisons for continuous variables were performed by one-way analysis of variance (ANOVA) with Tukey's post-hoc test for normally distributed data, and by the Kruskal-Wallis test with Dunn's post-hoc correction for non-normally distributed data. Chi-squared tests were used for categorical comparisons. Pearson correlation coefficients were computed to examine bivariate associations between HbA1c and cardiovascular risk markers. Multivariate linear regression was conducted to assess independent associations after adjustment for age, sex, BMI, diabetes duration, statin use, antihypertensive use, and metformin dose. A two-tailed p-value of <0.05 was considered statistically significant. Statistical power was calculated a priori; a sample size of 350 provided 85% power to detect correlation coefficients of $r \geq 0.18$ at an alpha of 0.05.

Results

A total of 412 potentially eligible individuals were screened; 62 were excluded in which 22 had established cardiovascular disease, 18 had eGFR <30 mL/min/1.73m², 14 met other exclusion criteria, and 8 declined participation. The final

analysis included 350 participants: 112 in Group A (HbA1c <7.0%), 143 in Group B (HbA1c 7.0–8.9%), and 95 in Group C (HbA1c ≥9.0%). Baseline characteristics are summarized in Table 1. The three groups were well-matched for age and sex distribution. Diabetes duration was significantly longer in Group C (10.2 ± 5.1 years) compared to Groups A and B ($p < 0.05$). BMI was highest in Group C (29.8 ± 4.8 kg/m²).

All three groups had similar proportions on metformin and statin therapy. hsCRP levels demonstrated a progressive and statistically significant rise across glycemic strata: 2.14 ± 0.87 mg/L in Group A, 3.52 ± 1.23 mg/L in Group B, and 5.18 ± 1.76 mg/L in Group C ($p < 0.001$ for trend). Pearson correlation revealed a strong positive association between HbA1c and hsCRP ($r = 0.61$, 95% CI: 0.53–0.68, $p < 0.001$). On multivariate linear regression adjusting for potential confounders, the association remained robust ($\beta = 0.48$, 95% CI: 0.39–0.57, $p < 0.001$), indicating that HbA1c independently explained approximately 29% of the variance in hsCRP levels. LDL-C was significantly higher in Group C (128.9 ± 28.2 mg/dL) compared with Group A (98.4 ± 22.1 mg/dL; $p < 0.001$). Similarly, triglycerides were highest in Group C (198.7 ± 52.6 mg/dL). Conversely, HDL-C followed an inverse trend, being lowest in Group C (40.1 ± 7.9 mg/dL) compared to Group A (48.7 ± 9.3 mg/dL; $p < 0.001$). Bivariate correlations with HbA1c were moderate-to-strong for LDL-C ($r = 0.54$, $p < 0.001$), triglycerides ($r = 0.43$, $p < 0.001$), and HDL-C ($r = −0.39$, $p < 0.001$). Systolic blood pressure was significantly elevated in Group C (141.2 ± 15.6 mmHg) versus Group A (128.4 ± 12.1 mmHg; $p < 0.001$) and correlated moderately with HbA1c ($r = 0.47$, $p < 0.001$).

eGFR demonstrated a significant inverse correlation with HbA1c ($r = −0.33$, $p < 0.001$). The prevalence of microalbuminuria rose steeply with worsening glycemic control: 7.1% in Group A, 19.6% in Group B, and 43.2% in Group C ($\chi^2 = 47.3$, $p < 0.001$). Table 2 presents adjusted regression coefficients for the association between HbA1c and each cardiovascular risk marker after controlling for age, sex, BMI, diabetes duration, statin use, and antihypertensive therapy. HbA1c remained an independent predictor of all cardiovascular risk markers examined, with the strongest associations observed for hsCRP ($\beta = 0.48$) and LDL-C ($\beta = 0.38$).

Table 1: Baseline Clinical and Biochemical Characteristics by HbA1c Stratum.

Characteristic	Group A: HbA1c. <7% (n=112)	Group B: HbA1c. 7 -9 % (n=143)	Group C: HbA1c. >9% (n=95)
Age (years), mean ± SD	54.2 ± 8.6	56.7 ± 9.1	55.4 ± 8.9
Male sex, n (%)	58 (51.8)	76 (53.1)	49 (51.6)
Duration of diabetes (years)	6.3 ± 3.9	8.7 ± 4.5	10.2 ± 5.1
BMI (kg/m²)	26.4 ± 3.7	28.1 ± 4.2	29.8 ± 4.8
Systolic BP (mmHg)	128.4 ± 12.1	135.7 ± 14.3	141.2 ± 15.6
Diastolic BP (mmHg)	79.2 ± 8.4	82.6 ± 9.1	85.3 ± 9.7
FBG (mg/dL)	112.3 ± 18.6	154.7 ± 24.1	198.5 ± 31.4
Total cholesterol (mg/dL)	178.2 ± 29.4	192.6 ± 31.7	207.3 ± 34.8
LDL-C (mg/dL)	98.4 ± 22.1	114.7 ± 25.8	128.9 ± 28.2
HDL-C (mg/dL)	48.7 ± 9.3	44.2 ± 8.7	40.1 ± 7.9
Triglycerides (mg/dL)	142.6 ± 38.4	168.3 ± 45.2	198.7 ± 52.6
hsCRP (mg/L)	2.14 ± 0.87	3.52 ± 1.23	5.18 ± 1.76
eGFR (mL/min/1.73m²)	84.3 ± 18.7	78.6 ± 21.2	71.4 ± 23.8
Microalbuminuria, n (%)	8 (7.1)	28 (19.6)	41 (43.2)
On metformin, n (%)	109 (97.3)	138 (96.5)	90 (94.7)
On statin therapy, n (%)	72 (64.3)	89 (62.2)	58 (61.1)

Table 2: Bivariate Correlations and Multivariate Regression Coefficients for HbA1c vs. Cardiovascular Risk Markers

Variable	r	95% CI	p-value	β (Adjusted)
hsCRP (mg/L)	0.61	0.53–0.68	<0.001	0.48
LDL-C (mg/dL)	0.54	0.46–0.62	<0.001	0.38
Systolic BP (mmHg)	0.47	0.38–0.55	<0.001	0.31
Triglycerides (mg/dL)	0.43	0.34–0.52	<0.001	0.28
HDL-C (mg/dL)	−0.39	−0.48–−0.30	<0.001	−0.25
eGFR (mL/min/1.73m²)	−0.33	−0.42–−0.24	<0.001	−0.21

Discussion

The principal finding of this prospective study is that increasing HbA1c levels are independently and dose-dependently associated with an adverse cardiovascular risk profile encompassing systemic inflammation (hsCRP), atherogenic dyslipidemia (elevated LDL-C and triglycerides, depressed HDL-C), elevated blood pressure, and impaired renal function in patients with T2DM. These associations persisted after rigorous adjustment for demographic, anthropometric, pharmacological, and clinical confounders, reinforcing the independent role of chronic hyperglycemia in promoting multifactorial cardiovascular risk. The strong positive correlation between HbA1c and hsCRP ($r = 0.61$) observed in our cohort is consistent with prior evidence. A meta-analysis of 18 prospective studies by Pradhan et al. demonstrated that elevated hsCRP was associated with a 26% increased risk of developing T2DM, and longitudinal data from the Women's Health Initiative corroborated the bidirectional inflammatory relationship in established T2DM [7]. The mechanistic basis likely involves advanced glycation end-product-mediated activation of the receptor for AGEs (RAGE) signaling cascade, NF-κB-dependent upregulation of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), and subsequent hepatic induction of CRP synthesis [8]. Our findings extend these observations by demonstrating that even the transition from Group A (HbA1c <7%) to Group B (HbA1c 7–8.9%) is associated with a clinically meaningful 64% relative increment in mean hsCRP, suggesting that inflammation amplification occurs early in the trajectory of glycemic decompensation.

The atherogenic dyslipidemia observed in our Group C participants aligns with the established pathophysiology of diabetic dyslipidemia. Hyperglycemia impairs lipoprotein lipase (LPL) activity and promotes hepatic very-low-density lipoprotein (VLDL) overproduction, resulting in hypertriglyceridemia and reduced HDL-C secondary to accelerated HDL catabolism [9]. The association between HbA1c and LDL-C, while partially mediated by concomitant insulin resistance and hepatic LDL receptor downregulation, is noteworthy given that elevated small dense LDL particles — the atherogenically predominant LDL subfraction in T2DM — are not fully captured by conventional LDL-C measurements [10]. Future studies employing nuclear magnetic resonance (NMR) lipoprotein profiling would enable more precise characterization of this relationship.

The independent association of HbA1c with systolic blood pressure merits clinical attention. Hyperglycemia-induced endothelial dysfunction — characterized by reduced nitric oxide (NO) bioavailability, increased endothelin-1 expression, and activation of the renin-angiotensin-aldosterone system (RAAS) — may contribute to arterial stiffness and blood pressure elevation independent of traditional cardiovascular risk factors [11]. The UKPDS 35 landmark data demonstrated that each 1% increment in HbA1c was associated with a 1.6 mmHg rise in systolic blood pressure, a finding broadly corroborated by our regression coefficient ($\beta = 0.31$) [4]. Our observation of a markedly higher prevalence of microalbuminuria in Group C (43.2%) compared to Group A (7.1%) highlights the concurrent nephrotoxic burden of sustained hyperglycemia. Early diabetic nephropathy, manifesting as microalbuminuria, is itself a potent cardiovascular risk factor, independently predicting coronary artery disease and heart failure [12]. These data collectively support the concept of cardiorenal risk clustering in poorly controlled T2DM, with implications for the preferential use of renoprotective and cardioprotective agents such as SGLT2 inhibitors and GLP-1 receptor agonists as second-line pharmacotherapy [13].

The dose-dependent and independent nature of the HbA1c–cardiovascular risk marker associations demonstrated herein has direct clinical relevance. First, these data provide further empirical justification for aggressive pursuit of individualized glycemic targets, particularly for younger patients with long life expectancy and limited comorbidities in whom the absolute risk reduction from improved glycemic control may be substantial [9]. Second, the strong association between HbA1c and hsCRP suggests that anti-inflammatory strategies — including structured physical activity, dietary modification, and pharmacological agents with pleiotropic anti-inflammatory properties — may complement glycemic control in attenuating cardiovascular risk. Third, the concurrent dyslipidemia and blood pressure elevation in poorly controlled patients underscore the necessity of multifactorial risk factor management rather than glycemia-centric treatment paradigms.

Strengths of this study include its prospective design, standardized measurement protocols, comprehensive cardiovascular risk marker assessment, multivariable adjustment for key confounders, and adequate sample size with a priori power calculation. The two-center design enhances generalizability within the South Asian population context.

Several limitations warrant acknowledgment. The observational design precludes causal inferences; residual confounding by unmeasured variables including dietary intake, physical activity level, medication adherence, and psychological stress cannot be excluded. The single time-point HbA1c measurement does not capture glycemic variability, which may independently contribute to cardiovascular risk. The study population derived

from tertiary care centers may not be fully representative of community-dwelling individuals with T2DM. Additionally, advanced cardiovascular risk markers such as carotid intima-media thickness (CIMT), flow-mediated dilation (FMD), and coronary artery calcium (CAC) scoring were not assessed. Future longitudinal studies should examine incident cardiovascular events as the primary endpoint.

Conclusion

This prospective observational study provides robust evidence that suboptimal glycemic control, as indexed by HbA1c, is independently associated with a composite of adverse cardiovascular risk markers in patients with T2DM.

The associations are graded, clinically meaningful, and persist after adjustment for key confounders. hsCRP and atherogenic dyslipidemia represent the most strongly associated risk factors, with implications for targeted anti-inflammatory and lipid-modifying strategies. These findings reinforce the imperative for individualized, evidence-based glycemic control as a cornerstone of comprehensive cardiovascular risk reduction in T2DM and highlight the urgent need for integrated, multidisciplinary management models particularly in South Asian populations bearing a disproportionate diabetes burden.

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