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Role of Glycemic Control in Reducing Microvascular Complications in Type 2 Diabetes Mellitus

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Abstract

Background: Microvascular complications contribute significantly to morbidity in type 2 diabetes mellitus (T2DM). This study aimed to evaluate the relationship between glycemic control and the development and progression of microvascular complications in patients with T2DM.

Methods: A prospective, observational cohort study was conducted at a tertiary care center, enrolling 120 adults with T2DM stratified by baseline HbA1c (<7.0%, 7.0-8.5%, and >8.5%). Participants were followed for 3 years with regular assessments of nephropathy, retinopathy, and neuropathy. The primary outcome was a composite of incident or worsening microvascular complications.

Results: The primary composite outcome occurred in 37.5% of participants overall, with significant differences across glycemic control categories: 21.1% in the HbA1c <7.0% group, 35.0% in the HbA1c 7.0-8.5% group, and 58.8% in the HbA1c >8.5% group (p=0.004). After adjustment for confounders, the hazard ratios for the primary outcome were 1.76 (95% CI: 0.97-3.20, p=0.064) for the HbA1c 7.0-8.5% group and 3.12 (95% CI: 1.73-5.63, p<0.001) for the HbA1c >8.5% group, compared to the HbA1c <7.0% group. Each 1% increase in HbA1c was associated with a 42% increased risk of the composite outcome (adjusted HR: 1.42, 95% CI: 1.25-1.61, p<0.001). Other significant predictors included diabetes duration (adjusted HR per 5 years: 1.38, p<0.001), systolic blood pressure (adjusted HR per 10 mmHg: 1.25, p=0.001), and baseline microvascular status.

Conclusion: This study demonstrates a strong, graded association between glycemic control and microvascular complications in T2DM. Maintaining HbA1c below 7.0% was associated with significantly lower complication rates compared to higher levels. These findings support current guidelines recommending individualized glycemic targets, generally aiming for HbA1c <7.0% in most patients to reduce microvascular risk.

Keywords: Type 2 diabetes mellitus; Glycemic control; Microvascular complications; Diabetic nephropathy; Diabetic retinopathy; Diabetic neuropathy; HbA1c; Cohort study

INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents one of the most significant global health challenges of the 21st century, with the International Diabetes Federation estimating that approximately 537 million adults worldwide were living with diabetes in 2021, a number projected to rise to 783 million by 2045.(1) The increasing prevalence of T2DM poses substantial health and economic burdens, particularly due to its associated complications. Among these, microvascular complications—including diabetic nephropathy, retinopathy, and neuropathy—significantly contribute to morbidity, reduced quality of life, and premature mortality in patients with T2DM.(2)

Microvascular complications develop as a consequence of chronic hyperglycemia, which triggers a cascade of pathophysiological mechanisms that ultimately lead to small vessel damage throughout the body. The underlying pathogenesis involves several interconnected metabolic pathways, including increased polyol pathway flux, advanced glycation end-product formation, protein kinase C activation, and oxidative stress.(3) These mechanisms collectively contribute to vascular endothelial dysfunction, basement membrane thickening, and tissue hypoxia, which manifest as organ-specific complications.

Diabetic nephropathy affects approximately 20-40% of patients with T2DM and remains the leading cause of end-stage renal disease worldwide.(4) It typically progresses through stages of hyperfiltration, microalbuminuria, macroalbuminuria, and eventually, declining glomerular filtration rate leading to kidney failure. Diabetic retinopathy, affecting approximately one-third of patients with diabetes, is characterized by microvascular damage to the retina, potentially resulting in vision impairment and blindness if left untreated.(5) Diabetic neuropathy, the most common microvascular complication, affects up to 50% of patients with long-standing diabetes and encompasses a spectrum of clinical manifestations, from distal symmetric polyneuropathy to autonomic neuropathy affecting multiple organ systems.(2)

The relationship between hyperglycemia and microvascular complications has been firmly established through landmark studies. The UK Prospective Diabetes Study (UKPDS), one of the most influential clinical trials in diabetes research, demonstrated that intensive glycemic control significantly reduced the risk of microvascular complications in patients with newly diagnosed T2DM.(6) The study found a 25% reduction in microvascular endpoints with intensive therapy compared to conventional treatment. Furthermore, the UKPDS established that each 1% reduction in HbA1c was associated with a 37% decrease in the risk for microvascular complications, highlighting the importance of glycemic targets in diabetes management.

The concept of glycemic control encompasses not only the achievement of target glycated hemoglobin (HbA1c) levels but also the management of glycemic variability and the avoidance of hypoglycemia. HbA1c, which reflects average blood glucose levels over the preceding 2-3 months, has traditionally been the primary metric for assessing glycemic control. Current guidelines from major diabetes organizations recommend individualized HbA1c targets, generally aiming for <7.0% (53 mmol/mol) in most patients, with more stringent targets (e.g., <6.5% or 48 mmol/mol) for selected individuals with shorter disease duration, longer life expectancy, and no significant cardiovascular disease, provided these can be achieved without significant hypoglycemia.(7)

Beyond HbA1c, glycemic variability has emerged as an important consideration in diabetes management. Fluctuations in blood glucose levels, independent of average glycemia, may contribute to oxidative stress and vascular damage through acute glucose excursions. Continuous glucose monitoring (CGM) technologies have enabled more comprehensive assessment of glycemic patterns, including time in range (TIR), which represents the percentage of time spent within target glucose range (typically 70-180 mg/dL or 3.9-10.0 mmol/L). Emerging evidence suggests that TIR correlates with the risk of microvascular complications and may complement HbA1c as a glycemic target.(8)

The prevention and management of microvascular complications in T2DM require a multifaceted approach, with glycemic control as a cornerstone. The benefits of intensive glycemic control must be balanced against the risks, particularly hypoglycemia and weight gain. The timing of intervention is crucial, as the benefits of strict glycemic control are most pronounced early in the disease course, a concept known as "metabolic memory" or "legacy effect." The UKPDS follow-up demonstrated that early intensive glucose control continued to provide microvascular benefits for up to 10 years after the trial ended, despite the convergence of HbA1c levels between the original treatment groups.(9)

The approach to glycemic management has evolved significantly over recent decades, with an expanding armamentarium of pharmacological agents beyond traditional options such as metformin, sulfonylureas, and insulin. Newer classes of medications, including glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and dipeptidyl peptidase-4 (DPP-4) inhibitors, offer advantages in terms of efficacy, weight effects, and hypoglycemia risk. Some of these agents have demonstrated benefits beyond glycemic control, particularly SGLT2 inhibitors, which have shown renoprotective effects independent of their glucose-lowering properties.(10)

The management of hyperglycemia in T2DM requires an individualized approach that considers patient characteristics, comorbidities, and preferences. Factors such as age, disease duration, life expectancy, risk of hypoglycemia, comorbid conditions (particularly cardiovascular and renal disease), patient motivation, and healthcare resources all influence treatment strategies. Guidelines increasingly emphasize patient-centered care, shared decision-making, and consideration of the patient's social determinants of health in developing management plans.

Despite advances in pharmacotherapy, lifestyle modifications remain fundamental to diabetes management. Dietary interventions, physical activity, and weight management not only improve glycemic control but also address other risk factors for microvascular complications, such as hypertension and dyslipidemia. Structured education programs and diabetes self-management support are essential components of comprehensive care.

Early detection of microvascular complications through regular screening is crucial for timely intervention. Screening protocols typically include annual assessments for retinopathy (dilated eye examination), nephropathy (urine albumin-to-creatinine ratio and estimated glomerular filtration rate), and neuropathy (comprehensive foot examination including sensory testing). When complications are detected, intensified glycemic control, together with targeted interventions such as renin-angiotensin system inhibitors for nephropathy and laser photocoagulation for retinopathy, can slow progression and prevent adverse outcomes.

The management of microvascular complications in T2DM has benefited from technological advancements in both monitoring and treatment. CGM systems provide detailed information on glycemic patterns, facilitating more precise therapy adjustments. Closed-loop insulin delivery systems ("artificial pancreas") are showing promise in improving

glycemic control while reducing hypoglycemia risk. Telemedicine and digital health solutions are expanding access to specialist care and supporting patient self-management.

Research continues to explore novel therapeutic targets based on the pathophysiological mechanisms underlying microvascular complications. These include anti-inflammatory agents, antioxidants, inhibitors of advanced glycation end-products, and modulators of various metabolic pathways. Additionally, biomarkers that can predict individual susceptibility to complications or response to specific therapies are being investigated to enable more personalized approaches to prevention and treatment.

In conclusion, glycemic control remains a fundamental strategy for reducing the burden of microvascular complications in T2DM. The evidence supporting the relationship between hyperglycemia and small vessel disease is robust, and the benefits of achieving target glycemic levels, particularly early in the disease course, are well-established. Contemporary management approaches emphasize individualized glycemic targets, comprehensive risk factor control, regular screening for early detection of complications, and patient-centered care. As our understanding of the pathophysiology of microvascular complications deepens and therapeutic options expand, the outlook for patients with T2DM continues to improve, with the potential to significantly reduce the morbidity associated with these devastating complications.

AIMS AND OBJECTIVES

The primary aim of this study was to evaluate the impact of intensive glycemic control on the development and progression of microvascular complications in patients with type 2 diabetes mellitus (T2DM). Specifically, we sought to determine the relationship between different levels of glycemic control, as measured by HbA1c, and the incidence and severity of diabetic nephropathy, retinopathy, and neuropathy.

MATERIALS AND METHODS

Study Design and Setting

We conducted a prospective, observational cohort study between January 2019 and December 2023 at a tertiary care center specializing in diabetes management. The study protocol was approved by the institutional review board (approval number: DM-2018-437), and the research was performed in accordance with the Declaration of Helsinki. All participants provided written informed consent before enrollment.

Study Population

The study recruited 120 adult patients aged 30-75 years with a confirmed diagnosis of type 2 diabetes mellitus according to American Diabetes Association criteria. We used stratified sampling to ensure representation across different durations of diabetes (<5 years, 5-10 years, and >10 years) and baseline HbA1c categories (<7.0%, 7.0-8.5%, and >8.5%). Inclusion criteria comprised: diagnosis of T2DM for at least 6 months; ability to perform self-monitoring of blood glucose; absence of severe microvascular complications at baseline; and willingness to attend regular follow-up visits. Exclusion criteria encompassed: history of type 1 diabetes or secondary diabetes; estimated glomerular filtration rate <45 mL/min/1.73m²; history of cardiovascular events within the previous 6 months; pregnancy; life expectancy less than 3 years; participation in another clinical trial; and inability to comply with the study protocol. Of the 120 enrolled participants, 112 (93%) completed the minimum follow-up period of 3 years.

Baseline Assessment

All participants underwent comprehensive baseline assessment including medical history, physical examination, and laboratory evaluations. Demographic information and diabetes-related history were collected. Anthropometric measurements included height, weight, BMI, waist circumference, and blood pressure. Laboratory investigations comprised fasting and postprandial glucose, HbA1c, blood count, metabolic panel, lipid profile, and urine albumin-to-creatinine ratio. Microvascular assessment included dilated retinal examination, comprehensive foot examination with monofilament testing and vibration perception threshold, and cardiovascular autonomic function tests.

Follow-up and Monitoring

Participants were followed for a minimum of 3 years, with scheduled visits every 3 months for the first year and every 6 months thereafter. Follow-up assessments included vital signs, body weight, adverse events, HbA1c, fasting glucose, and safety parameters. Urine albumin-to-creatinine ratio was measured every 6 months, while comprehensive eye and neurological examinations were performed annually. Medication adjustments were made according to the treating physician's discretion, with all changes documented. Adherence to medications and lifestyle recommendations was assessed at each visit.

Outcome Measures

The primary outcome measure was a composite of incident or worsening microvascular complications, including: progression of diabetic retinopathy; development or progression of diabetic nephropathy; or development or worsening of diabetic peripheral neuropathy. Secondary outcomes included the individual components of the primary outcome analyzed separately, change in estimated glomerular filtration rate, incidence of severe hypoglycemia, all-cause hospitalization, health-related quality of life, and medication requirements. All microvascular assessments were performed by specialists blinded to the participants' glycemic status and other clinical parameters.

Statistical Analysis

Sample size calculation determined that 120 participants would provide 80% power to detect a 30% difference in the primary outcome between patients with good glycemic control (HbA1c <7.0%) and those with poor control (HbA1c >8.5%), assuming a two-sided alpha of 0.05 and allowing for 10% attrition. We performed all statistical analyses using SPSS version 28.0 (IBM Corp., Armonk, NY). Continuous variables were expressed as mean ± standard deviation or median with interquartile range depending on distribution normality assessed by the Shapiro-Wilk test. Categorical variables were presented as frequencies and percentages. Baseline characteristics were compared between glycemic control groups using one-way ANOVA or Kruskal-Wallis test for continuous variables and chi-square or Fisher's exact test for categorical variables.

We used Kaplan-Meier analysis to estimate the cumulative incidence of the primary composite outcome and its components, with differences between glycemic control groups assessed by the log-rank test. Cox proportional hazards regression models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) for the association between glycemic control and microvascular outcomes, adjusting for potential confounders including age, sex, diabetes duration, blood pressure, lipid levels, medication use, and baseline microvascular status. The proportional hazards assumption was verified using Schoenfeld residuals. We further examined the relationship between HbA1c as a continuous variable and microvascular outcomes using restricted cubic splines to account for potential non-linear associations.

Mixed-effects models were employed to analyze repeated measures data, including changes in HbA1c, renal function, and quality of life scores over time. To assess the potential influence of missing data, we performed sensitivity analyses using multiple imputation for participants lost to follow-up. We also conducted stratified analyses to evaluate whether the effect of glycemic control on microvascular outcomes varied by age, sex, diabetes duration, and presence of comorbidities. All statistical tests were two-sided, and p-values <0.05 were considered statistically significant. We applied Bonferroni correction for multiple comparisons when appropriate.

RESULTS

Baseline Characteristics of Study Participants

The study recruited 120 patients with type 2 diabetes mellitus who were followed for a minimum of 3 years. Table 1 presents the baseline demographic and clinical characteristics stratified by glycemic control categories. The mean age of participants was 58.3 ± 11.2 years, and 56.7% were male. The mean duration of diabetes was 7.8 ± 5.3 years, with significant differences observed across glycemic control groups (p=0.006). Participants with HbA1c >8.5% had a longer duration of diabetes (9.8 ± 6.0 years) compared to those with HbA1c <7.0% (6.2 ± 4.1 years). The mean HbA1c for the entire cohort was 7.8 ± 1.6%, with values of 6.2 ± 0.4%, 7.7 ± 0.5%, and 9.7 ± 1.1% for the <7.0%, 7.0-8.5%, and >8.5% groups, respectively (p<0.001).

Significant differences were observed in body mass index (p=0.041), HDL cholesterol (p=0.029), and triglyceride levels (p=0.011) across the glycemic control categories, with the poorest values noted in the HbA1c >8.5% group. Regarding medication use, significant differences were observed in the use of sulfonylureas (p=0.019) and insulin (p=0.026), with higher proportions in the HbA1c >8.5% group, likely reflecting the need for more intensive therapy in patients with poorer glycemic control. No significant differences were observed in the prevalence of hypertension or dyslipidemia across the groups.

Baseline Microvascular Status

Table 2 shows the baseline microvascular status of participants across glycemic control categories. Significant differences were observed in nephropathy status (p=0.042), with microalbuminuria present in 12.5%, 21.4%, and 34.2% of participants in the HbA1c <7.0%, 7.0-8.5%, and >8.5% groups, respectively. The median urine albumin-to-creatinine ratio (UACR) was significantly higher in the HbA1c >8.5% group (20.6 mg/g) compared to the HbA1c <7.0% group (10.2 mg/g) (p=0.009).

Similarly, significant differences were observed in retinopathy status across glycemic control categories (p=0.024). The prevalence of mild non-proliferative diabetic retinopathy (NPDR) was 10.0%, 14.3%, and 26.3% in the HbA1c <7.0%, 7.0-8.5%, and >8.5% groups, respectively. Moderate NPDR was present in 2.5%, 4.8%, and 7.9% of participants in the respective groups.

Regarding neuropathy parameters, the mean vibration perception threshold (VPT) was significantly higher in the HbA1c >8.5% group (14.8 ± 8.2 V) compared to the HbA1c <7.0% group (10.4 ± 5.9 V) (p=0.024). Although not statistically significant, abnormal monofilament test results (p=0.119) and neuropathy symptoms (p=0.147) were more prevalent in the HbA1c >8.5% group.

Incidence of Microvascular Complications

Of the 120 enrolled participants, 112 (93%) completed the minimum follow-up period of 3 years. Table 3 presents the incidence of primary composite outcome and individual microvascular complications by glycemic control category. The primary composite outcome occurred in 42 (37.5%) participants overall, with significant differences across glycemic

control categories: 21.1% in the HbA1c <7.0% group, 35.0% in the HbA1c 7.0-8.5% group, and 58.8% in the HbA1c >8.5% group (p=0.004).

Nephropathy progression was observed in 26 (23.2%) participants overall, with significant differences across glycemic control categories (10.5% vs. 20.0% vs. 41.2%, p=0.007). Similarly, retinopathy progression occurred in 23 (20.5%) participants, with a significant gradient across glycemic control categories (7.9% vs. 20.0% vs. 35.3%, p=0.013). Neuropathy progression was observed in 24 (21.4%) participants, with a non-significant trend across glycemic control categories (13.2% vs. 20.0% vs. 32.4%, p=0.127).

Regarding secondary outcomes, a decline in estimated glomerular filtration rate (eGFR) >30% occurred in 13 (11.6%) participants, with a non-significant trend across glycemic control categories (5.3% vs. 10.0% vs. 20.6%, p=0.114). Severe hypoglycemia, all-cause hospitalization, and initiation of insulin therapy were more frequent in the HbA1c >8.5% group, though the differences did not reach statistical significance.

Hazard Ratios for Microvascular Complications

Table 4 presents the hazard ratios for microvascular complications according to glycemic control status. In unadjusted analyses, compared to the HbA1c <7.0% group, the hazard ratios for the primary composite outcome were 1.89 (95% CI: 1.05-3.41, p=0.034) for the HbA1c 7.0-8.5% group and 3.47 (95% CI: 1.95-6.19, p<0.001) for the HbA1c >8.5% group. After adjustment for potential confounders, the hazard ratios were 1.76 (95% CI: 0.97-3.20, p=0.064) and 3.12 (95% CI: 1.73-5.63, p<0.001), respectively.

For nephropathy progression, the adjusted hazard ratios were 1.88 (95% CI: 0.91-3.89, p=0.089) for the HbA1c 7.0-8.5% group and 3.95 (95% CI: 1.99-7.82, p<0.001) for the HbA1c >8.5% group, compared to the HbA1c <7.0% group. For retinopathy progression, the adjusted hazard ratios were 2.54 (95% CI: 1.07-6.05, p=0.035) and 4.47 (95% CI: 1.93-10.35, p<0.001), respectively. For neuropathy progression, the adjusted hazard ratios were 1.51 (95% CI: 0.78-2.92, p=0.222) and 2.48 (95% CI: 1.32-4.66, p=0.005), respectively.

Changes in Metabolic Parameters During Follow-up

Table 5 shows the changes in HbA1c and other metabolic parameters during the follow-up period. The mean HbA1c decreased from baseline to 12 months in all groups, with the most pronounced reduction in the HbA1c >8.5% group (from 9.7 ± 1.1% to 8.4 ± 1.3%, p<0.001). However, a slight increase in HbA1c was observed from 12 to 36 months in all groups. The overall trend in HbA1c over the follow-up period was statistically significant (p=0.028).

The eGFR declined gradually over the follow-up period in all groups, with a significant overall trend (p=0.031). The decline was more pronounced in the HbA1c >8.5% group (from 79.1 ± 17.1 to 72.5 ± 19.3 mL/min/1.73m², p=0.027) compared to the HbA1c <7.0% group (from 83.9 ± 14.2 to 81.0 ± 16.1 mL/min/1.73m², p=0.278).

The median UACR increased over the follow-up period in all groups, with a significant overall trend (p=0.007). The increase was more pronounced in the HbA1c >8.5% group (from 20.6 to 31.4 mg/g, p=0.003) compared to the HbA1c <7.0% group (from 10.2 to 12.3 mg/g, p=0.385).

Risk Factors Associated with Microvascular Complications

Table 6 presents the risk factors associated with microvascular complications based on multivariable analysis. HbA1c was a significant predictor of the primary composite outcome (adjusted HR per 1% increase: 1.42, 95% CI: 1.25-1.61, p<0.001) and all individual microvascular complications. Other significant predictors of the primary composite outcome included diabetes duration (adjusted HR per 5 years: 1.38, 95% CI: 1.16-1.64, p<0.001), systolic blood pressure (adjusted HR per 10 mmHg: 1.25, 95% CI: 1.09-1.43, p=0.001), LDL cholesterol (adjusted HR per 10 mg/dL: 1.08, 95% CI: 1.01-1.15, p=0.027), current smoking (adjusted HR: 1.53, 95% CI: 1.02-2.30, p=0.040), baseline microalbuminuria (adjusted HR: 1.92, 95% CI: 1.35-2.73, p<0.001), baseline retinopathy (adjusted HR: 1.87, 95% CI: 1.29-2.72, p=0.001), and baseline abnormal VPT (adjusted HR: 1.68, 95% CI: 1.14-2.47, p=0.008).

Kaplan-Meier Analysis of Primary Composite Outcome

Table 7 and the corresponding Kaplan-Meier curve demonstrate the cumulative incidence of the primary composite microvascular outcome by glycemic control group. The 3-year cumulative incidence rates were 21.1% (95% CI: 13.5-31.7) in the HbA1c <7.0% group, 35.0% (95% CI: 25.2-47.0) in the HbA1c 7.0-8.5% group, and 58.8% (95% CI: 46.5-71.7) in the HbA1c >8.5% group (log-rank p<0.001). The median time to event was not reached in the HbA1c <7.0% and 7.0-8.5% groups, whereas it was 30.6 months (95% CI: 22.7-38.5) in the HbA1c >8.5% group.

The estimated 3-year event-free survival rates were 78.9% (95% CI: 68.3-86.5) in the HbA1c <7.0% group, 65.0% (95% CI: 53.0-74.8) in the HbA1c 7.0-8.5% group, and 41.2% (95% CI: 28.3-53.5) in the HbA1c >8.5% group. The log-rank test confirmed a statistically significant difference in the survival distributions across the three glycemic control groups (p<0.001).

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants

Characteristic	Overall (n=120)	HbA1c <7.0% (n=40)	HbA1c 7.0-8.5% (n=42)	HbA1c >8.5% (n=38)	p-value
Age (years)	58.3 ± 11.2	60.7 ± 10.5	57.9 ± 11.8	56.1 ± 11.0	0.137
Male sex, n (%)	68 (56.7)	22 (55.0)	25 (59.5)	21 (55.3)	0.894
Diabetes duration (years)	7.8 ± 5.3	6.2 ± 4.1	7.5 ± 5.2	9.8 ± 6.0	0.006
BMI (kg/m²)	29.4 ± 4.7	28.1 ± 4.2	29.6 ± 4.5	30.7 ± 5.1	0.041
Systolic BP (mmHg)	136.2 ± 16.8	132.4 ± 15.2	136.8 ± 16.5	139.7 ± 18.1	0.117
Diastolic BP (mmHg)	82.5 ± 9.3	80.1 ± 8.5	82.9 ± 9.2	84.6 ± 9.8	0.084
HbA1c (%)	7.8 ± 1.6	6.2 ± 0.4	7.7 ± 0.5	9.7 ± 1.1	<0.001
Fasting plasma glucose (mg/dL)	156.3 ± 48.7	123.4 ± 21.5	151.8 ± 32.6	195.3 ± 56.4	<0.001
Total cholesterol (mg/dL)	189.4 ± 42.3	178.2 ± 36.8	191.7 ± 42.5	198.9 ± 44.9	0.075
LDL cholesterol (mg/dL)	110.7 ± 34.5	102.3 ± 30.1	112.5 ± 33.8	117.8 ± 37.9	0.094
HDL cholesterol (mg/dL)	45.3 ± 11.2	48.6 ± 12.1	44.9 ± 10.8	42.1 ± 10.2	0.029
Triglycerides (mg/dL)	165.8 ± 78.4	137.2 ± 56.3	171.4 ± 81.2	189.7 ± 87.6	0.011
eGFR (mL/min/1.73m²)	81.5 ± 15.7	83.9 ± 14.2	81.3 ± 15.5	79.1 ± 17.1	0.357
Current smoker, n (%)	26 (21.7)	7 (17.5)	9 (21.4)	10 (26.3)	0.613
Hypertension, n (%)	74 (61.7)	22 (55.0)	26 (61.9)	26 (68.4)	0.437
Dyslipidemia, n (%)	82 (68.3)	24 (60.0)	29 (69.0)	29 (76.3)	0.274
Medications					
Metformin, n (%)	108 (90.0)	34 (85.0)	39 (92.9)	35 (92.1)	0.386
Sulfonylureas, n (%)	62 (51.7)	14 (35.0)	23 (54.8)	25 (65.8)	0.019
DPP-4 inhibitors, n (%)	42 (35.0)	17 (42.5)	15 (35.7)	10 (26.3)	0.288
SGLT-2 inhibitors, n (%)	28 (23.3)	12 (30.0)	10 (23.8)	6 (15.8)	0.311
GLP-1 receptor agonists, n (%)	16 (13.3)	7 (17.5)	6 (14.3)	3 (7.9)	0.425
Insulin, n (%)	34 (28.3)	6 (15.0)	12 (28.6)	16 (42.1)	0.026
ACE inhibitors/ARBs, n (%)	68 (56.7)	20 (50.0)	24 (57.1)	24 (63.2)	0.473
Statins, n (%)	76 (63.3)	23 (57.5)	27 (64.3)	26 (68.4)	0.574

Data are presented as mean ± standard deviation or number (percentage). p-values were calculated using one-way ANOVA for continuous variables and chi-square test for categorical variables. BMI = body mass index; BP = blood pressure; eGFR = estimated glomerular filtration rate; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

Table 2: Comparison of Baseline Microvascular Status Across Glycemic Control Categories

Microvascular Parameter	Overall (n=120)	HbA1c <7.0% (n=40)	HbA1c 7.0-8.5% (n=42)	HbA1c >8.5% (n=38)	p-value
Nephropathy status					0.042
Normoalbuminuria, n (%)	93 (77.5)	35 (87.5)	33 (78.6)	25 (65.8)	
Microalbuminuria, n (%)	27 (22.5)	5 (12.5)	9 (21.4)	13 (34.2)	
UACR (mg/g), median (IQR)	14.3 (8.1-32.6)	10.2 (6.8-21.7)	13.8 (7.9-31.4)	20.6 (9.7-54.2)	0.009
Retinopathy status					0.024
No retinopathy, n (%)	94 (78.3)	35 (87.5)	34 (81.0)	25 (65.8)	
Mild NPDR, n (%)	20 (16.7)	4 (10.0)	6 (14.3)	10 (26.3)	

Microvascular Parameter	Overall (n=120)	HbA1c <7.0% (n=40)	HbA1c 7.0-8.5% (n=42)	HbA1c >8.5% (n=38)	p-value
Moderate NPDR, n (%)	6 (5.0)	1 (2.5)	2 (4.8)	3 (7.9)	
Neuropathy parameters					
Abnormal monofilament test, n (%)	18 (15.0)	3 (7.5)	6 (14.3)	9 (23.7)	0.119
VPT (V), mean ± SD	12.6 ± 7.3	10.4 ± 5.9	12.7 ± 7.1	14.8 ± 8.2	0.024
Neuropathy symptoms, n (%)	32 (26.7)	7 (17.5)	11 (26.2)	14 (36.8)	0.147

Data are presented as mean ± standard deviation, median (interquartile range), or number (percentage). p-values were calculated using one-way ANOVA or Kruskal-Wallis test for continuous variables and chi-square test for categorical variables. UACR = urine albumin-to-creatinine ratio; NPDR = non-proliferative diabetic retinopathy; VPT = vibration perception threshold.

Table 3: Incidence of Primary Composite Outcome and Individual Microvascular Complications by Glycemic Control Category

Outcome	Overall (n=112)	HbA1c <7.0% (n=38)	HbA1c 7.0-8.5% (n=40)	HbA1c >8.5% (n=34)	p-value
Primary composite outcome	42 (37.5)	8 (21.1)	14 (35.0)	20 (58.8)	0.004
Nephropathy progression					
New-onset microalbuminuria, n (%)	18 (16.1)	3 (7.9)	6 (15.0)	9 (26.5)	0.079
Progression to macroalbuminuria, n (%)	8 (7.1)	1 (2.6)	2 (5.0)	5 (14.7)	0.097
Any nephropathy progression, n (%)	26 (23.2)	4 (10.5)	8 (20.0)	14 (41.2)	0.007
Retinopathy progression					
New-onset retinopathy, n (%)	14 (12.5)	2 (5.3)	5 (12.5)	7 (20.6)	0.130
Worsening of existing retinopathy, n (%)	9 (8.0)	1 (2.6)	3 (7.5)	5 (14.7)	0.145
Any retinopathy progression, n (%)	23 (20.5)	3 (7.9)	8 (20.0)	12 (35.3)	0.013
Neuropathy progression					
New abnormal monofilament test, n (%)	12 (10.7)	2 (5.3)	4 (10.0)	6 (17.6)	0.212
Significant decrease in VPT, n (%)	16 (14.3)	3 (7.9)	5 (12.5)	8 (23.5)	0.143
Any neuropathy progression, n (%)	24 (21.4)	5 (13.2)	8 (20.0)	11 (32.4)	0.127
Secondary outcomes					
Decline in eGFR >30%, n (%)	13 (11.6)	2 (5.3)	4 (10.0)	7 (20.6)	0.114
Severe hypoglycemia, n (%)	8 (7.1)	1 (2.6)	3 (7.5)	4 (11.8)	0.292
All-cause hospitalization, n (%)	22 (19.6)	5 (13.2)	7 (17.5)	10 (29.4)	0.188
Initiation of insulin therapy, n (%)	15 (13.4)	2 (5.3)	5 (12.5)	8 (23.5)	0.066

Data are presented as number (percentage). p-values were calculated using chi-square or Fisher's exact test. VPT = vibration perception threshold; eGFR = estimated glomerular filtration rate.

Table 4: Hazard Ratios for Microvascular Complications According to Glycemic Control Status

Outcome	HbA1c <7.0%	HbA1c 7.0-8.5%	HbA1c >8.5%
Primary composite outcome			
Unadjusted HR (95% CI)	1.00 (reference)	1.89 (1.05-3.41)	3.47 (1.95-6.19)

Outcome	HbA1c <7.0%	HbA1c 7.0-8.5%	HbA1c >8.5%
p-value	-	0.034	<0.001
Adjusted HR (95% CI)*	1.00 (reference)	1.76 (0.97-3.20)	3.12 (1.73-5.63)
p-value	-	0.064	<0.001
Nephropathy progression			
Unadjusted HR (95% CI)	1.00 (reference)	2.06 (1.01-4.21)	4.52 (2.32-8.80)
p-value	-	0.047	<0.001
Adjusted HR (95% CI)*	1.00 (reference)	1.88 (0.91-3.89)	3.95 (1.99-7.82)
p-value	-	0.089	<0.001
Retinopathy progression			
Unadjusted HR (95% CI)	1.00 (reference)	2.78 (1.18-6.57)	5.04 (2.21-11.49)
p-value	-	0.020	<0.001
Adjusted HR (95% CI)*	1.00 (reference)	2.54 (1.07-6.05)	4.47 (1.93-10.35)
p-value	-	0.035	<0.001
Neuropathy progression			
Unadjusted HR (95% CI)	1.00 (reference)	1.63 (0.85-3.13)	2.85 (1.54-5.27)
p-value	-	0.141	0.001
Adjusted HR (95% CI)*	1.00 (reference)	1.51 (0.78-2.92)	2.48 (1.32-4.66)
p-value	-	0.222	0.005

HR = hazard ratio; CI = confidence interval. *Adjusted for age, sex, diabetes duration, systolic blood pressure, LDL cholesterol, smoking status, and use of ACE inhibitors/ARBs.

Table 5: Changes in HbA1c and Other Metabolic Parameters During the Follow-up Period

Parameter	Baseline	12 months	24 months	36 months	p-value for trend
HbA1c (%)					
Overall	7.8 ± 1.6	7.3 ± 1.4	7.4 ± 1.5	7.5 ± 1.5	0.028
HbA1c <7.0% group	6.2 ± 0.4	6.4 ± 0.6	6.5 ± 0.8	6.7 ± 0.9	0.004
HbA1c 7.0-8.5% group	7.7 ± 0.5	7.2 ± 0.8	7.3 ± 1.0	7.4 ± 1.1	0.019
HbA1c >8.5% group	9.7 ± 1.1	8.4 ± 1.3	8.5 ± 1.4	8.6 ± 1.4	<0.001
Fasting plasma glucose (mg/dL)					
Overall	156.3 ± 48.7	145.2 ± 39.5	148.6 ± 41.2	150.3 ± 42.8	0.117
Systolic BP (mmHg)					
Overall	136.2 ± 16.8	132.7 ± 14.5	133.4 ± 15.1	134.2 ± 15.8	0.146
eGFR (mL/min/1.73m²)					
Overall	81.5 ± 15.7	80.2 ± 16.4	78.6 ± 17.2	77.1 ± 17.9	0.031
HbA1c <7.0% group	83.9 ± 14.2	83.1 ± 14.8	81.9 ± 15.5	81.0 ± 16.1	0.278
HbA1c 7.0-8.5% group	81.3 ± 15.5	80.1 ± 16.3	78.7 ± 16.9	77.3 ± 17.5	0.142
HbA1c >8.5% group	79.1 ± 17.1	77.1 ± 17.8	74.9 ± 18.6	72.5 ± 19.3	0.027
UACR (mg/g), median (IQR)					
Overall	14.3 (8.1-32.6)	15.8 (8.5-37.4)	17.6 (9.2-42.8)	19.3 (9.8-48.5)	0.007
HbA1c <7.0% group	10.2 (6.8-21.7)	10.9 (7.1-23.5)	11.5 (7.4-25.2)	12.3 (7.6-27.1)	0.385
HbA1c 7.0-8.5% group	13.8 (7.9-31.4)	15.2 (8.3-35.2)	16.9 (8.8-39.7)	18.3 (9.3-43.1)	0.168
HbA1c >8.5% group	20.6 (9.7-54.2)	23.8 (10.6-62.7)	27.5 (12.3-72.4)	31.4 (13.8-83.2)	0.003

Data are presented as mean ± standard deviation or median (interquartile range). p-values were calculated using repeated measures ANOVA or Friedman test. BP = blood pressure; eGFR = estimated glomerular filtration rate; UACR = urine albumin-to-creatinine ratio; IQR = interquartile range.

Table 6: Risk Factors Associated with Microvascular Complications (Multivariable Analysis)

Risk Factor	Primary Composite Outcome		Nephropathy Progression		Retinopathy Progression		Neuropathy Progression	
	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
HbA1c (per 1% increase)	1.42 (1.25-1.61)	<0.001	1.53 (1.32-1.77)	<0.001	1.48 (1.28-1.71)	<0.001	1.31 (1.14-1.51)	<0.001
Age (per 10 years)	1.24 (0.98-1.57)	0.076	1.18 (0.89-1.56)	0.243	1.35 (1.03-1.77)	0.032	1.29 (1.01-1.65)	0.043
Male sex	1.13 (0.76-1.68)	0.539	1.08 (0.67-1.73)	0.751	1.21 (0.78-1.89)	0.393	1.18 (0.77-1.80)	0.453
Diabetes duration (per 5 years)	1.38 (1.16-1.64)	<0.001	1.29 (1.06-1.57)	0.012	1.52 (1.25-1.85)	<0.001	1.36 (1.13-1.64)	0.001
Systolic BP (per 10 mmHg)	1.25 (1.09-1.43)	0.001	1.31 (1.13-1.53)	<0.001	1.22 (1.05-1.42)	0.009	1.18 (1.02-1.37)	0.029
BMI (per 5 kg/m²)	1.16 (0.94-1.42)	0.160	1.21 (0.96-1.52)	0.107	1.09 (0.87-1.37)	0.453	1.18 (0.95-1.47)	0.136
LDL cholesterol (per 10 mg/dL)	1.08 (1.01-1.15)	0.027	1.05 (0.97-1.13)	0.212	1.11 (1.03-1.19)	0.006	1.07 (0.99-1.15)	0.072
eGFR <60 mL/min/1.73m²	1.47 (0.93-2.33)	0.099	1.79 (1.08-2.97)	0.024	1.31 (0.79-2.18)	0.293	1.32 (0.81-2.15)	0.269
Current smoking	1.53 (1.02-2.30)	0.040	1.42 (0.89-2.27)	0.138	1.61 (1.04-2.50)	0.033	1.48 (0.96-2.29)	0.075
Use of ACE inhibitors/ARBs	0.76 (0.57-1.02)	0.068	0.68 (0.49-0.94)	0.020	0.82 (0.59-1.14)	0.236	0.84 (0.61-1.16)	0.291
Use of statins	0.81 (0.60-1.09)	0.162	0.86 (0.62-1.20)	0.379	0.74 (0.53-1.04)	0.085	0.87 (0.63-1.21)	0.413
Baseline microalbuminuria	1.92 (1.35-2.73)	<0.001	2.43 (1.67-3.53)	<0.001	1.45 (0.98-2.15)	0.063	1.36 (0.92-2.02)	0.125
Baseline retinopathy	1.87 (1.29-2.72)	0.001	1.41 (0.92-2.16)	0.112	2.76 (1.85-4.12)	<0.001	1.32 (0.87-2.00)	0.188
Baseline abnormal VPT	1.68 (1.14-2.47)	0.008	1.29 (0.83-2.01)	0.259	1.35 (0.88-2.07)	0.171	2.14 (1.42-3.22)	<0.001

HR = hazard ratio; CI = confidence interval; BP = blood pressure; BMI = body mass index; eGFR = estimated glomerular filtration rate; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; VPT = vibration perception threshold.

Table 7: Kaplan-Meier Cumulative Incidence of Primary Composite Microvascular Outcome by Glycemic Control Group

Time Point	HbA1c <7.0% (n=38)	HbA1c 7.0-8.5% (n=40)	HbA1c >8.5% (n=34)	Log-rank p-value
12 months	5.3% (2.0-13.4)	12.5% (6.5-23.3)	20.6% (12.2-33.5)	<0.001
24 months	13.2% (7.3-23.1)	22.5% (14.5-33.7)	41.2% (29.9-54.6)	<0.001
36 months	21.1% (13.5-31.7)	35.0% (25.2-47.0)	58.8% (46.5-71.7)	<0.001
Median time to event	Not reached	Not reached	30.6 (22.7-38.5)	<0.001

Time Point	HbA1c <7.0% (n=38)	HbA1c 7.0-8.5% (n=40)	HbA1c >8.5% (n=34)	Log-rank p-value
(months)				

Data are presented as cumulative incidence percentage (95% confidence interval). Median time to event is presented with 95% confidence interval in parentheses. The p-value is derived from log-rank test comparing the three glycemic control groups.

DISCUSSION

The present study demonstrates a strong association between glycemic control and the development and progression of microvascular complications in patients with type 2 diabetes mellitus. The findings indicate that the risk of microvascular complications increases progressively with worsening glycemic control, with patients maintaining HbA1c levels below 7.0% experiencing significantly fewer complications compared to those with higher levels. These results underscore the importance of achieving and maintaining optimal glycemic control in reducing the burden of microvascular disease in type 2 diabetes.

The relationship between hyperglycemia and microvascular complications observed in this study aligns with findings from landmark clinical trials. The UK Prospective Diabetes Study (UKPDS) demonstrated that intensive glycemic control (mean achieved HbA1c 7.0%) reduced the risk of microvascular complications by 25% compared to conventional treatment (mean achieved HbA1c 7.9%) in newly diagnosed patients with type 2 diabetes.(11) Similarly, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial showed that intensive glucose control (mean achieved HbA1c 6.5%) reduced the risk of microvascular events by 14% compared with standard control (mean achieved HbA1c 7.3%).(12) Our study extends these findings by demonstrating a dose-response relationship across a broader range of glycemic control categories, with adjusted hazard ratios for the primary composite outcome of 1.76 and 3.12 for the HbA1c 7.0-8.5% and >8.5% groups, respectively, compared to the <7.0% group.

Regarding specific microvascular complications, our study found that the association between glycemic control and complication risk was strongest for retinopathy, followed by nephropathy and neuropathy. This differential impact has been observed in previous studies. The Veterans Affairs Diabetes Trial (VADT) reported that intensive glycemic control significantly reduced the risk of progression of diabetic retinopathy (adjusted HR: 0.60, 95% CI: 0.42-0.87) but had no significant effect on nephropathy or neuropathy outcomes after 5.6 years of follow-up.(13) In contrast, the ADVANCE trial found a significant 21% reduction in nephropathy events (p=0.006) with intensive glycemic control but no significant effect on retinopathy.(12) These variations may reflect differences in study populations, definitions of outcomes, follow-up duration, and the relatively slow progression of some microvascular complications.

The cumulative incidence of the primary composite outcome in our study (37.5% over 3 years) was somewhat higher than reported in some previous cohorts. The Japan Diabetes Complications Study, which followed 1,294 patients with type 2 diabetes over 8 years, reported a cumulative incidence of 31.8% for the composite of retinopathy, nephropathy, and neuropathy.(14) This difference may be attributed to our inclusion of both incident and progressive microvascular complications in the primary outcome definition, as well as variations in baseline characteristics and diagnostic criteria.

Our finding that each 1% increase in HbA1c was associated with a 42% increased risk of the primary composite outcome (adjusted HR: 1.42, 95% CI: 1.25-1.61) is consistent with data from the UKPDS, which reported that each 1% reduction in HbA1c was associated with a 37% decrease in the risk for microvascular complications.(15) Similarly, a meta-analysis by Zhang et al. found that every 1% decrease in HbA1c was associated with a 13% reduction in the risk of diabetic retinopathy (RR: 0.87, 95% CI: 0.77-0.98), a 13% reduction in the risk of nephropathy (RR: 0.87, 95% CI: 0.78-0.96), and a 12% reduction in the risk of neuropathy (RR: 0.88, 95% CI: 0.78-0.98).(16)

Beyond glycemic control, our study identified several additional risk factors for microvascular complications, including diabetes duration, systolic blood pressure, LDL cholesterol, smoking status, and baseline microvascular status. These findings are consistent with the multifactorial etiology of diabetic complications and highlight the importance of comprehensive risk factor management. The Steno-2 study demonstrated that intensive multifactorial intervention targeting hyperglycemia, hypertension, dyslipidemia, and microalbuminuria reduced the risk of microvascular complications by approximately 50% compared with conventional treatment in patients with type 2 diabetes and microalbuminuria.(17) Similarly, the ADVANCE trial reported that the combination of intensive blood pressure and glycemic control resulted in a greater reduction in new or worsening nephropathy (33%, p=0.005) than either intervention alone.(18)

The observed changes in metabolic parameters during follow-up provide insights into the natural history of glycemic control and its relationship with microvascular outcomes. Despite initial improvements in HbA1c across all groups, a gradual increase was noted thereafter, reflecting the progressive nature of type 2 diabetes and the challenges of maintaining glycemic targets over time. This phenomenon, known as "glycemic drift," has been observed in numerous clinical trials, including the UKPDS, where HbA1c levels gradually increased over time in both intensive and

conventional treatment groups.(11) The more pronounced decline in renal function (eGFR) and increase in albuminuria (UACR) in the HbA1c >8.5% group underscore the detrimental effects of sustained hyperglycemia on kidney function.

The Kaplan-Meier analysis in our study revealed a clear separation of event curves according to glycemic control categories, with a 3-year event-free survival rate of 78.9% in the HbA1c <7.0% group compared to 41.2% in the HbA1c >8.5% group. This substantial difference highlights the cumulative burden of poor glycemic control over time. Interestingly, a follow-up of the UKPDS cohort demonstrated that the benefits of early intensive glycemic control persisted and even increased over time, despite the convergence of HbA1c levels between the original treatment groups - a phenomenon termed "metabolic memory" or "legacy effect."(19) After 10 years of post-trial follow-up, the intensive therapy group maintained a 24% risk reduction (p=0.001) for microvascular outcomes compared with the conventional therapy group, despite similar HbA1c levels during the follow-up period.

Recent studies have explored the concept of glycemic variability as an additional risk factor for microvascular complications, beyond mean glucose levels. The Diabetic Retinopathy Candesartan Trials (DIRECT) program found that HbA1c variability was independently associated with microvascular outcomes, with each 1% increase in HbA1c standard deviation associated with a 31% increased risk of retinopathy progression (HR: 1.31, 95% CI: 1.09-1.57).(20) Similarly, the Diabetes Control and Complications Trial (DCCT) reported that HbA1c variability contributed to the risk of retinopathy and nephropathy, independent of mean HbA1c levels.(21) Although our study did not specifically assess glycemic variability, this emerging concept warrants consideration in future research and clinical practice.

Several limitations of our study should be acknowledged. First, the observational design precludes definitive conclusions about causality, as the association between glycemic control and microvascular outcomes may be influenced by unmeasured confounders. Second, the relatively small sample size and moderate follow-up duration may have limited statistical power, particularly for less common outcomes and subgroup analyses. Third, as our study was conducted at a single tertiary care center, the findings may not be fully generalizable to all settings or populations. Finally, we did not assess the impact of specific glucose-lowering medications on microvascular outcomes, which may have independent effects beyond glycemic control.

Despite these limitations, the strengths of our study include the comprehensive assessment of all major microvascular complications, the stratified sampling approach to ensure representation across different glycemic control categories, the high retention rate (93%), and the adjustment for multiple potential confounders in the analysis.

CONCLUSION

In conclusion, this prospective cohort study demonstrates a strong, graded association between glycemic control and the risk of microvascular complications in patients with type 2 diabetes mellitus. Maintaining HbA1c levels below 7.0% was associated with significantly lower rates of nephropathy, retinopathy, and neuropathy compared to higher levels, particularly above 8.5%. Each 1% increase in HbA1c was associated with a 42% increased risk of the composite microvascular outcome, highlighting the importance of optimal glycemic control. Additionally, diabetes duration, blood pressure, lipid levels, smoking status, and baseline microvascular status were identified as significant predictors of complications, emphasizing the multifactorial nature of diabetic microvascular disease.

These findings reinforce current clinical practice guidelines recommending individualized glycemic targets, generally aiming for HbA1c levels below 7.0% in most patients with type 2 diabetes to reduce the risk of microvascular complications. However, the benefits of intensive glycemic control must be balanced against the potential risks, particularly hypoglycemia, and targets should be tailored based on individual factors such as age, diabetes duration, comorbidities, and patient preferences. Comprehensive management addressing multiple risk factors remains essential for preventing and delaying the progression of microvascular complications in type 2 diabetes mellitus.

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