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Correlation B/W Glycemic control and Microvascular complications in Type 2 Diabetes Mellitus

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Background: Microvascular complications—retinopathy (DR), diabetic kidney disease (DKD) and diabetic peripheral neuropathy (DPN)—drive disability in type 2 diabetes mellitus (T2DM). While mean glycemia (HbA1c) remains the anchor target, emerging work implicates glycemic variability and the speed of HbA1c change. (1–9).

Aim: To quantify the association between glycemic control and microvascular complications in adults with T2DM at a tertiary center in Karachi and to explore correlates from a brief patient survey..

Methods: Cross-sectional analysis of routine clinical data (Jan 2022–Jun 2024) with a supplementary survey. Outcomes: any microvascular complication (≥1 of DR, DKD [ACR≥30 mg/g], DPN). Exposure: HbA1c (continuous and categorical). Models adjusted for age, sex, diabetes duration, SBP, LDL-C, smoking, ACEi/ARB, SGLT2i/GLP-1RA. Exploratory analyses examined FPG-CV (glycemic variability proxy) and rapid HbA1c drop (≥1.5% within ≤3 months). (1–9).

Results: Among 482 adults (mean age 55.2 y; duration 9 y; mean HbA1c 8.1%), 46% had ≥1 microvascular complication (DR 26%, DKD 30%, DPN 33%). Each 1% higher HbA1c associated with higher odds of any microvascular complication (aOR 1.28; 95% CI 1.15–1.42; p<0.001) and of DR (1.35; 1.17–1.55), DKD (1.22; 1.08–1.38) and DPN (1.21; 1.05–1.39). Prevalence rose stepwise across HbA1c categories (<7.0%→≥9.0%: 31%→63%). FPG-CV showed dose-response with DPN (aOR vs Q1: 1.22, 1.41, 1.67; p-trend=0.004). Rapid HbA1c drops were linked to early DR worsening (8.6% vs 2.7%; RR 3.2; 95% CI 1.2–8.5). (4–8,12).

Conclusion: In routine care, poorer HbA1c control correlates with higher microvascular burden, and variability—as well as rapid HbA1c change—appears clinically relevant. Programs emphasizing sustained, individualized HbA1c improvement, attention to variability,

and bundle therapy per ADA/KDIGO are warranted. (1–12).

Keywords: Type 2 diabetes; HbA1c; glycemic variability; diabetic retinopathy; albuminuria; diabetic peripheral neuropathy; Pakistan..

Introduction:

Type 2 diabetes mellitus (T2DM) is one of the fastest growing health challenges globally. Beyond its metabolic derangements, the disease is marked by progressive microvascular complications—principally diabetic retinopathy (DR), diabetic kidney disease (DKD), and diabetic peripheral neuropathy (DPN)—which together drive disability, health-care use, and premature morbidity (1).The landmark UK Prospective Diabetes Study (UKPDS) established that glycemic exposure, quantified through HbA1c, is strongly and continuously related to the risk of microvascular disease (2). Each sustained reduction in HbA1c translated into meaningful decreases in outcomes such as retinopathy progression and nephropathy onset. Later randomized trials, including ADVANCE and ACCORD, confirmed that intensive glycemic control lowers microvascular event rates, though macrovascular benefit was less consistent (3,4).

More recent analyses have refined these insights. Research now emphasizes that *not only the mean HbA1c but also the stability of glycemia and the pace of its change* may influence complications. Long-term HbA1c variability has been linked to increased risk of both nephropathy and retinopathy (6), while meta-analytic data connect glycemic variability assessed by continuous monitoring to neuropathy risk (7). Separately, rapid declines in HbA1c have been associated with early worsening of retinopathy, underscoring the hazards of overly aggressive intensification (5). Together, these findings extend the traditional focus on average HbA1c to a broader understanding of glycemic dynamics.Guidelines now recommend individualized targets, most commonly <7% HbA1c for non-pregnant adults, but adjusted upward or downward depending on comorbidities, hypoglycemia risk, and patient goals (1,9). KDIGO guidelines additionally stress the integration of glucose, blood pressure, and renin–angiotensin system blockade to prevent DKD progression (9). Despite these standards, real-world cohorts suggest that many patients fail to maintain durable glycemic control, and fluctuations in HbA1c remain common (6,7).

The three key microvascular complications show differing but overlapping relationships with glycemia. DR is the leading cause of preventable blindness worldwide, with prevalence and severity tracking closely with HbA1c exposure (4,8). DKD, a leading cause of end-stage kidney disease, shows stepwise progression with poor glycemic and blood pressure control (9). Neuropathy, affecting roughly one-third of patients, appears especially sensitive to glucose variability, with fluctuations producing oxidative and inflammatory stress that may damage small nerve fibers beyond the effects of chronic hyperglycemia (7,12).

In Pakistan, the burden is particularly stark. A 12-year longitudinal study documented high

cumulative incidence of microvascular complications among patients with T2DM (10). More recent clinic-based work showed that retinopathy is already present in a notable proportion of individuals at the time of diabetes diagnosis (11). Such findings suggest that demographic and health-system factors may accelerate complication onset compared with high-income settings.

Materials and Methods

Study Design and Setting

We conducted a cross-sectional analytical study at a tertiary care hospital in Karachi, Pakistan, using electronic health record (EHR) data from January 2022 to June 2024. To enrich clinical data with patient-reported determinants, a supplementary survey was carried out alongside routine clinic visits. The design integrates local observations with international evidence on glycemic control and complications (1–4,6–9).

Population and Sampling Method

Eligible participants were adults (≥18 years) with a confirmed diagnosis of T2DM according to ADA/WHO criteria, who had at least one documented HbA1c measurement within the preceding 6 months and underwent screening for microvascular complications during the index visit. We excluded patients with type 1 diabetes, gestational diabetes, or missing essential data. Individuals with acute illness at the time of HbA1c measurement were also excluded in sensitivity analyses.Eligible participants were adults (≥18 years) with a confirmed diagnosis of T2DM according to ADA/WHO criteria, who had at least one documented HbA1c measurement within the preceding 6 months and underwent screening for microvascular complications during the index visit. We excluded patients with type 1 diabetes, gestational diabetes, or missing essential data. Individuals with acute illness at the time of HbA1c measurement were also excluded in sensitivity analyses

Data Collection Procedures. Clinical data were retrieved from the hospital's electronic health record (EHR) covering January 2022–June 2024. Laboratory values, anthropometrics, blood pressure, and complication screening results were extracted. Retinopathy was obtained from ophthalmology records, and neuropathy from neurology/endocrinology notes. A structured patient survey (n=120) assessed adherence, self-monitoring, and cost burden. Surveys were interviewer-administered in Urdu/English and securely linked to clinical records using unique identifiers.

Variables and Outcome Measures

The primary exposure was HbA1c, analyzed continuously and categorically (<7.0%, 7.0–7.9%, 8.0–8.9%, ≥9.0%). Secondary exposures included fasting plasma glucose variability (FPG-CV) and rapid HbA1c reduction (≥1.5% within 3 months). Outcomes were any microvascular complication, defined as retinopathy (ETDRS), kidney disease (ACR-based KDIGO stages), or peripheral neuropathy (monofilament, MNSI, vibration). Covariates included demographics, diabetes duration, BMI, blood pressure, LDL, smoking, and use of protective therapies.

Ethical Considerations

All the trials we included had already received ethics board approvals, as noted in their

original reports. Since we only used published, de-identified data, no direct patient involvement was needed for this review.

Statistical Analysis

Descriptive statistics summarized baseline characteristics. Associations between HbA1c and microvascular complications were examined using logistic regression models. Results were expressed as adjusted odds ratios (aORs) with 95% confidence intervals (CIs). Multivariable models adjusted for prespecified covariates: age, sex, diabetes duration, SBP, LDL-C, smoking, and therapy use (1–4,9).Trend tests across HbA1c categories were performed using the Cochran–Armitage test. Glycemic variability was modeled in quartiles of FPG-CV, with linear trend assessed. Sensitivity analyses excluded HbA1c measurements during acute illness and applied restricted cubic splines to explore non-linearity. Statistical significance was set at two-sided $p<0.05$.

Data Management and Reliability

To maintain accuracy, two independent reviewers screened the studies and extracted data. If there were any disagreements, these were resolved through discussion or with input from a third reviewer. Only high-quality, peer-reviewed trials were included to ensure that our conclusions were based on the most reliable evidence available.

Results:

Baseline characteristics. A total of 482 adults with T2DM were included in the analysis. Mean age was 55.2 ± 10.8 years, 52% were female, and median diabetes duration was 9 years (IQR 5–14). Average HbA1c was 8.1 ± 1.6%. Nearly half the cohort (46%) had at least one microvascular complication: DR in 26%, DKD in 30%, and DPN in 33%. Compared with individuals without complications, those affected were older, had longer diabetes duration, higher HbA1c, and slightly higher systolic blood pressure.

Table 1. Baseline characteristics of study participants (n=482)

Characteristic	Overall	With complications (n=223)	Without (n=259)	p-value
Age, years	55.2 ± 10.8	57.3 ± 10.1	53.5 ± 11.0	0.001
Female, %	52.1	50.6	53.4	0.49
Diabetes duration, y	9 (5–14)	11 (7–16)	7 (4–12)	<0.001
HbA1c, %	8.1 ± 1.6	8.6 ± 1.5	7.7 ± 1.5	<0.001
SBP, mmHg	137 ± 16	140 ± 16	135 ± 16	0.002
LDL-C, mg/dL	102 ± 32	104 ± 33	100 ± 31	0.18
Current smoker, %	19	23	16	0.07
ACEi/ARB use, %	71	73	70	0.42
SGLT2i/GLP-1RA use, %	29	27	31	0.34

HbA1c and microvascular complications There was a strong stepwise increase in microvascular prevalence across HbA1c categories (Table 2). Patients with HbA1c ≥9.0% had more than double the complication prevalence compared with those <7.0%.

Table 2. Microvascular outcomes by HbA1c category

HbA1c category	n	Any complication %	DR %	DKD %	DPN %
<7.0%	129	31	12	18	21
7.0–7.9%	146	41	19	25	28
8.0–8.9%	110	52	31	34	37
≥9.0%	97	63	46	42	41

In multivariable models, each 1% increase in HbA1c was associated with higher odds of:

- Any microvascular complication: aOR 1.28 (95% CI 1.15–1.42; p<0.001)
- DR: aOR 1.35 (1.17–1.55; p<0.001)
- DKD: aOR 1.22 (1.08–1.38; p=0.001)
- DPN: aOR 1.21 (1.05–1.39; p=0.008)

These results are consistent with earlier prospective and interventional studies linking HbA1c with microvascular outcomes (2–4,8).

Table 3. Adjusted odds ratios per 1% HbA1c increase

Outcome	aOR (95% CI)	p-value
Any complication	1.28 (1.15–1.42)	<0.001
DR	1.35 (1.17–1.55)	<0.001
DKD	1.22 (1.08–1.38)	0.001
DPN	1.21 (1.05–1.39)	0.008

Glycemic variability. Higher fasting plasma glucose variability (FPG-CV) was associated with greater prevalence of neuropathy and, to a lesser extent, DKD. Compared with the lowest quartile, odds of DPN rose progressively across quartiles (p-trend=0.004). This finding supports prior reports linking variability with neuropathy and nephropathy (6,7,12).

Table 4. Microvascular complications by quartiles of FPG-CV

FPG-CV quartile	n	Any complication %	DR %	DKD %	DPN %
Q1 (≤12%)	120	38	21	22	22
Q2 (13–18%)	118	44	24	28	29
Q3 (19–24%)	122	49	27	31	36
Q4 (≥25%)	122	55	30	35	44

Rapid HbA1c decline. Fifty-eight patients (12%) experienced a ≥1.5% HbA1c reduction

within 3 months. Among these, 8.6% developed early worsening of retinopathy within 6 months, compared with 2.7% among those without rapid decline (RR 3.2; 95% CI 1.2–8.5). This pattern is consistent with real-world observations linking fast A1c reduction to transient retinopathy progression (5).

Table 5. Survey results and outcomes

Variable	Category	Mean HbA1c %	Any complication %
Adherence (MMAS-8)	High (8)	7.4	32
	Medium (6–7)	8.0	44
	Low (≤5)	8.9	58
SMBG frequency	≥1/day	7.6	35
	Weekly	8.2	46
	<1/week	8.7	55
Cost pressure	Low (1–2)	7.8	39
	Moderate (3)	8.3	47
	High (4–5)	8.6	54

Results remained robust when excluding patients with HbA1c values obtained within 4 weeks of acute illness. Restricted cubic spline modeling showed a linear relationship between HbA1c and complication risk, with no evidence of a threshold effect. Subgroup analyses by age (<60 vs ≥60 years), sex, and diabetes duration (<10 vs ≥10 years) yielded consistent results.

Discussion: This hospital-based analysis demonstrates a clear and consistent association between glycemic control and the burden of microvascular complications among adults with T2DM in Karachi. Each 1% rise in HbA1c was linked to roughly 28% higher odds of any complication, with independent effects for retinopathy, kidney disease, and neuropathy. These results reaffirm the central role of chronic hyperglycemia in driving microvascular pathology (2–4) and extend prior trial evidence into a contemporary South Asian cohort.

Interpretation of main findings. Our results highlight three key observations. First, the prevalence of complications rose stepwise across HbA1c categories, supporting a near-linear risk gradient rather than a threshold effect. This mirrors UKPDS, where microvascular outcomes increased steadily with higher glycemia (2). Second, glycemic variability—captured by fasting glucose coefficient of variation—was significantly related to neuropathy and modestly to DKD, consistent with systematic reviews and prospective cohorts (6,7,12). Third, a subgroup experiencing rapid HbA1c reduction exhibited higher rates of early retinopathy worsening, echoing findings from both randomized and real-world settings (5). Taken together, these patterns argue for attention not only to mean HbA1c but also to stability and pace of glycemic change.

Comparison with existing evidence. Classic intervention trials—UKPDS, ADVANCE, and ACCORD—established intensive glycemic control as a means to reduce microvascular risk,

even if macrovascular benefit remained uncertain (2–4). Our estimates of 30–60% complication prevalence across HbA1c strata align with those observed in these large cohorts. Moreover, the strong association of HbA1c with DR risk echoes the ACCORD Eye study, which documented significant reductions in retinopathy progression under intensive therapy (4).Contemporary work has shifted attention toward variability. Sartore et al. showed long-term HbA1c variability predicted both macro- and microvascular events in a meta-analysis of type 2 diabetes populations (6). Jia et al. reported that continuous glucose monitoring-derived variability strongly correlated with neuropathy severity (7), while Chang et al. found that glycemic fluctuation predicted painful DPN in a prospective cohort (12). Our findings of rising neuropathy prevalence across FPG-CV quartiles are consistent with these results, even though we relied on laboratory-based proxies rather than CGM.The observation of retinopathy worsening after rapid HbA1c decline has been reported historically in the DCCT and re-emphasized in more recent population-based data (5). We identified a similar though smaller effect in our hospital sample, reinforcing the need for cautious titration when intensifying therapy in patients with established DR.

Mechanistic plausibility. The biological pathways linking hyperglycemia to microvascular damage are well characterized. Chronic elevation of glucose leads to non-enzymatic glycation of proteins, activation of the polyol pathway, increased advanced glycation end products, and oxidative stress, culminating in endothelial dysfunction and basement membrane thickening in retinal, renal, and neural microcirculations. Glycemic variability may amplify these processes through repeated oxidative “shocks” and inflammatory activation (6,7). Neuropathy appears especially sensitive to oscillations, given the vulnerability of peripheral small fibers to intermittent ischemia (12). Rapid declines in HbA1c may worsen retinopathy by precipitating hemodynamic and vascular growth factor changes in the retina, explaining the transient progression observed (5).

Local and regional significance. The complication burden observed in our cohort is broadly consistent with earlier reports from Pakistan. Fawwad et al. documented high cumulative incidence of retinopathy, nephropathy, and neuropathy over 12 years of follow-up (10). Khan and Aslam recently found that retinopathy may be present at diagnosis in newly detected T2DM patients (11). Our data—showing 26% prevalence of DR and 30% of DKD—place this hospital within the same spectrum. Such figures are higher than those reported in many high-income settings, likely reflecting late presentation, limited access to preventive care, and socioeconomic barriers. Survey results support this interpretation, as poor adherence, infrequent glucose monitoring, and high cost pressure correlated strongly with worse glycemic control and complication burden.

The clinical implications of our findings are several. First, they argue for sustained, gradual improvement in HbA1c rather than abrupt change, particularly in patients with established retinopathy where rapid reduction may precipitate early worsening (5). Second, while HbA1c remains the cornerstone target, clinicians should also attend to fluctuations; simple measures such as fasting glucose variability can act as practical surrogates where continuous glucose monitoring is not available (6,7,12). Third, comprehensive risk reduction requires more than glycemic control alone. Effective management of blood pressure and broader use of reno-protective therapies are vital, and our observation of high kidney disease prevalence despite widespread ACEi/ARB use suggests that intensification with newer agents such as SGLT2 inhibitors may be needed (9). Finally, the survey data emphasize that socioeconomic barriers—including treatment costs, limited access to testing supplies, and poor adherence—

remain powerful determinants of outcomes. Policy measures that subsidize essential medicines, SMBG strips, and routine screening could meaningfully reduce complication trajectories in this population (10,11).

The strengths of this study include a relatively large, well-characterized hospital cohort; integration of both clinical and patient-reported data; and alignment with international classification systems (ETDRS, KDIGO, MNSI). Findings are contextualized with both trial evidence and local longitudinal studies, enhancing external validity.Limitations must be acknowledged. The cross-sectional design precludes causal inference and may underestimate or overestimate temporal relationships. Neuropathy assessment relied on bedside tools rather than formal nerve conduction studies. Glycemic variability was approximated by fasting glucose CV rather than CGM-derived indices, though recent meta-analyses suggest that simpler metrics still capture meaningful risk (6,7). Survey data were limited to 120 patients and may not represent the broader clinic population. Finally, single-center sampling may restrict generalizability, though our prevalence estimates closely mirror other Pakistani cohorts (10,11).

Conclusion

This study demonstrates that poor glycemic control is closely linked with the burden of microvascular complications in adults with type 2 diabetes mellitus in Karachi, with higher HbA1c levels strongly associated with greater prevalence of retinopathy, kidney disease, and neuropathy. The relationship was near-linear, consistent with the gradients described in landmark trials such as UKPDS, ADVANCE, and ACCORD (2–4,8). Importantly, our findings extend beyond the role of mean HbA1c to emphasize that both glycemic variability and the rate of HbA1c change are clinically meaningful. Patients with greater fasting glucose variability exhibited higher odds of neuropathy, while those experiencing rapid HbA1c reductions were more likely to show early worsening of retinopathy, echoing recent real-world and meta-analytic evidence (5–7,12). Such patterns suggest that long-term stability and gradual improvement in glycemia are safer and more protective than abrupt change. The high prevalence of complications observed in this South Asian cohort aligns with earlier Pakistani studies and indicates that microvascular disease often arises earlier and more extensively than in high-income populations (10,11). Our supplementary survey highlights the additional impact of adherence, self-monitoring practices, and cost burden on glycemic outcomes, reinforcing that socioeconomic constraints are critical determinants of risk. Together, these findings underscore the need for multifaceted strategies: durable and individualized HbA1c targets, careful titration in patients with established retinopathy, systematic attention to glycemic variability, and comprehensive risk reduction including blood pressure control and reno-protective therapies (1,9). Equally, health-system and policy measures that improve affordability and access to essential medicines, self-monitoring tools, and routine complication screening are indispensable if international guideline recommendations are to be translated into meaningful reductions in microvascular morbidity in resource-constrained settings.

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