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ASSOCIATION OF GLYCEMIC CONTROL (HBA1C) WITH SEVERITY OF DIABETIC NEPHROPATHY AND CARDIOVASCULAR RISK IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: A CROSS-SECTIONAL STUDY

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ABSTRACT

Type 2 diabetes mellitus remains a major public health challenge, frequently complicated by microvascular and macrovascular pathologies, including diabetic nephropathy and cardiovascular disease. This cross-sectional study investigated the association between glycemic control, measured by glycated hemoglobin (HbA1c), and the severity of diabetic nephropathy and cardiovascular risk among adult patients with type 2 diabetes mellitus at Niazi Medical College & Teaching Hospital, Sargodha. A total of 300 patients were evaluated and categorized into three glycemic tiers: optimal control (HbA1c < 7.0%, n = 90), moderate control (HbA1c 7.0%–8.5%, n = 120), and poor control (HbA1c > 8.5%, n = 90). Patients were assessed for renal parameters, including estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (ACR), along with multi-factorial cardiovascular risk stratification. HbA1c showed a strong, statistically significant negative correlation with eGFR ($r = -0.584$, $p < 0.001$) and a strong positive correlation with log-transformed ACR ($r = 0.612$, $p < 0.001$). Multivariable logistic regression, adjusted for age, sex, diabetes duration, and systolic blood pressure, showed that patients in the poor control tier had substantially higher odds of advanced nephropathy staging (adjusted odds ratio [OR] = 4.28, 95% confidence interval [CI]: 2.45–7.52, $p < 0.001$) and of high-to-very-high cardiovascular risk classification (adjusted OR = 5.12, 95% CI: 2.89–9.08, $p < 0.001$) compared with those with optimal glycemic control. Sustained hyperglycemia is strongly associated with severe diabetic nephropathy and elevated cardiovascular risk, underscoring the need for strict glycemic optimization in routine clinical practice.

INTRODUCTION

Persistent hyperglycemia from progressive insulin resistance and relative insulin secretory failure constitutes the main hallmarks of type 2 diabetes mellitus, which is a common chronic metabolic disorder (DeFronzo & Abdul-Ghani, 2011). The systemic nature of the disease goes beyond metabolic disorder, causing a high number of microvascular and macrovascular complications which have a significant impact on morbidity, mortality and quality of life. Diabetic nephropathy is one of the most crippling microvascular diseases, a major cause of chronic kidney disease and end-stage renal disease worldwide (Alicic et al., 2017; Thomas et al., 2015). At the same time, type 2 diabetes mellitus will exacerbate macrovascular diseases and significantly increase the risk of ischemic heart disease, stroke, and cardiovascular mortality. The linkage between chronic hyperglycemia and the clinical course of these target organ complications is a key problem that needs to be addressed by clinical endocrinologists and nephrologists.

Diabetic nephropathy and cardiovascular disease are two of the most important micro and macrovascular complications of diabetes, respectively, associated with chronic sustained hyperglycemia in a well established biochemical pathways. This increases levels of glucose inside the cell, leading to non-enzymatic glycation of proteins and lipids, and ultimately the formation of advanced glycation end-products (Brownlee, 2005). These end-products interact with specific receptors within the cell, causing excessive production of pro-inflammatory cytokines and growth factors, protein kinase C activation and oxidative stress. In the renal microvasculature, these molecular cascades lead to glomerular hyperfiltration, expansion of the mesangial matrix, thickening of the basement membrane, and progressive injury of the podocytes, which results in clinical deterioration and increasing albuminuria along with a progressive decline in the eGFR. At the same time, in macrovascular endothelium, hyperglycemia causes endothelial dysfunction, proliferation of the smooth muscle cells, foam cell formation, and increase in atherogenesis.

The American Diabetes Association Professional Practice Committee (2024) has designated glycated hemoglobin (HbA1C) as the gold standard biomarker for assessing long-term glycemic control and gives it a time frame of 2 to 3 months of blood glucose levels. There is a continuous and a graded relationship between increased HbA1c levels and the development and deterioration of microvascular complications, demonstrated by extensive epidemiological and clinical trial data (Stratton et al., 2000). Real world clinical data, however, that directly link specific glycemic tiers with co-occurrence of both diabetic nephropathy and cardiovascular risk is limited, especially in the regional South Asian clinical context where epidemiological dynamics are unique due to genetic predisposition, diet and access to healthcare.

Although glycemic control is well acknowledged as one of the main therapeutic goals, in real world cohorts, glycemic control is often suboptimal (Koro et al. 2004) with advanced multi-organ complications occurring with greater frequency in routine out-patient setting. Optimization of risk prediction models also requires assessing the grade of association between HbA1c levels and renal functional decline (measured by eGFR and ACR) in addition to multi-factorial cardiovascular risk stratification. These connections are identified in regional healthcare settings like Niazi Medical College & Teaching Hospital in Sargodha and enable empirical knowledge to make clinical screening in the region more effective and facilitate targeted aggressive risk factor modification in at-risk groups. This cross-sectional study aimed to explore and estimate the relationship between glycemic control (at different HbA1C tertiles) and diabetic nephropathy (DN) severity and cardiovascular risk status in 300 adult patients with type 2 diabetes mellitus (T2DM). It was assumed that higher categories of HbA1c would be statistically significantly positively correlated with higher stage albuminuria and greater cardiovascular risk and negatively correlated with eGFR.

LITERATURE REVIEW

Microvascular and macrovascular end-organ damage is a major complication of type 2 diabetes mellitus which profoundly affects the disease's management, with diabetic nephropathy and cardiovascular disease being the two most important causes of morbidity and mortality worldwide. A cascade of adverse cellular and biochemical changes begins with a prolonged period of hyperglycemia. Increased intracellular glucose levels contribute to a continuous build-up of AGE in circulating and structural proteins through non-enzymatic glycation. These end-products bind with specific receptors on endothelial cells of blood vessels, mesangial cells, and podocytes, inducing increased oxidative stress, activation of protein kinases, and local upregulation of profibrotic growth factors like transforming growth factor-beta (TGF-beta) (Brownlee, 2005; Thomas et al., 2015).

In the renal architecture these hyperglycemia-induced pathways lead to glomerular hyperfiltration, progressive expansion of the mesangial matrix, thickening of the basement membrane and effacement of the podocytes. From a clinical standpoint, this microvascular injury can be seen as progressive albuminuria (mild to moderate to severe) and a progressive fall in eGFR ultimately leading to chronic kidney disease (CKD) and end stage renal failure (ESRF) (Alicic et al., 2017). At the same time, chronic glycemic dysregulation is a major contributor to the macrovascular complications of type 2 diabetes mellitus (T2DM). Hyperglycemia is associated with endothelial dysfunction, decreased nitric oxide, increased LDL oxidation and increased atherosclerosis, all of which significantly increase the risk of ischemic heart disease, myocardial infarction, stroke and peripheral vascular disease (Emerging Risk Factors Collaboration, 2010).

Glycated hemoglobin is still the “gold standard” in clinical practice to measure chronic glycemic control and is a measure of average glycemia over the past 2-3 months. The association between elevated HbA1c and increased incidence and progression of microvascular and macrovascular complications has been well established with a graded relationship, as seen in the landmark study in the UK, United Kingdom Prospective Diabetes Study (Stratton et al., 2000) and the subsequent meta-analysis (Emerging Risk Factors Collaboration, 2010). There is a linear relationship between the relative risk of microalbuminuria progression and cardiovascular events and each additional increment of HbA1c.

Although these biochemical relationships have been established, there is a lack of understanding in the real world of cross sectional associations in clinical settings in the region of South Asia and Pakistan. Patients in tertiary care centers tend to have specific epidemiological characteristics, including a high prevalence of poorly-controlled glycemia, dietary modifications, high insulin resistance, and delayed diagnosis (Standl et al., 2019). Local cohorts like those of Niazi Medical College & Teaching Hospital, Sargodha, should be evaluated for the association between categorized HbA1C levels and renal functional markers (eGFR and ACR), as well as multi-factorial cardiovascular risk stratification, in order to optimize risk prediction models and guide localized nephro-cardiac protective therapies.

The goal(s) of the study were to:

The main aim of this cross sectional study was to explore and estimate the relationship between glycemic control (in various levels of HbA1c) and severity of diabetic nephropathy and cardiovascular risk in 300 adult patients of type2 diabetes mellitus at Niazi Medical College & Teaching Hospital, Sargodha. The particular targets were:

To assess and compare renal functional markers distribution (eGFR and ACR) between optimal, moderate and poor glycemic control tiers.

To measure the linear association between individual HbA1c levels and continuous measures of renal impairment such as eGFR decline and ACR elevation.

To assess graded relationship between diabetic nephropathy categorized by HbA1C levels and the clinical stages of the diabetic nephropathy (from normoalbuminuria to macroalbuminuria).

To evaluate the relationship between glycemic control levels and multi-factorial cardiovascular risk stratification in the study population.

Research Hypotheses

Using the pathophysiological rationale, and on the basis of existing epidemiological data, the following null and alternative hypotheses were developed:

Hypothesis 1: Renal Function Correlation (RFC)

The null hypothesis (H0) was that there is no statistically significant correlation between HbA1c and renal functional markers (eGFR and ACR) in type 2 diabetes mellitus patients.

The alternative hypothesis (H1) is that there is a statistically significant negative correlation between HbA1c levels and eGFR and a positive correlation between HbA1c levels and ACR.

Hypothesis 2 (ASociation of Nephropathy)

Null hypothesis (H0): No statistically significant difference in the prevalence or severity stage of diabetic nephropathy between the different categories of HbA1c.

Alternative hypothesis (H1): The prevalence of microalbuminuria and macroalbuminuria increases with each incremental increase in HbA1c tier, with the change being statistically significant.

Cardiovascular Risk Stratification (H3)

Null hypothesis (H0): The proportion of patients classified as high or very high cardiovascular risk is the same, across the different levels of glycemic control.

Alternate hypothesis (H1): There is a statistically significant difference in the proportion of patients in higher HbA1c tiers who are classified as having high or very high cardiovascular risk compared with those who are optimally controlled for glycemic-effect.

Theoretical and Conceptual Framework

The theoretical basis of this study is based on the molecular pathology of chronic sustained hyperglycemia and its multi-systemic downstream consequence, in the renal microvasculature and in the macrovascular tree in type 2 diabetes mellitus. The conceptual framework suggests that raised HbA1c is not just a passive marker of glycemic control but a biochemical insult that can lead to ongoing vascular and endorgan damage via complex cellular and molecular mechanisms.

The non-enzymatic glycation of intracellular and extracellular proteins, lipids and nucleic acids, due to mass-action kinetics in the presence of chronic hyperglycemia, is at the center of this pathological cascade process (Brownlee, 2005). This is an ongoing process that leads to advanced glycation end-products (AGEs) building up and developing in tissues throughout the body. These end-products have two effects: they change the structure of extra-cellular matrix proteins, causing increased stiffness of the blood vessels, increased thickening of basement membrane and increased accumulation of extra-cellular matrix proteins, and secondly, they bind to receptors on the cell surface like the receptor for advanced glycation end-products (RAGE). Ligand binding to this receptor triggers an intracellular signaling pathway that leads to increased production of reactive oxygen species (ROS), activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and upregulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB).

The renal microvascularopathy typical of diabetic nephropathy is the result of these biochemical changes induced by hyperglycemia within the renal architecture. Glomerular hyperfiltration, endothelial injury and expansion of the mesangial matrix are caused by the accumulation of advanced glycation end products and of local oxidative stress. At the same time, the podocytes are also effaced and detached, allowing for progressive leakage of albumin into the urinary space. In the clinic, this involves one step of normoalbuminuria, one step of microalbuminuria, and finally the progression to overt macroalbuminuria, with a corresponding fall in eGFR as the nephrons suffer sclerosis and tubulointerstitial fibrosis.

At the same time in the macrovascular system, chronic hyperglycemia increases the rate of atherogenesis and multi-factorial cardiovascular risk. Hyperglycemia and the presence of advanced glycation end products (AGEs) cause endothelial dysfunction by decreasing the activity of endothelial nitric oxide synthase, thus decreasing the bioavailability of protective nitric oxide (NO). This promotes the oxidation of LDL, attachment of leukocytes, smooth muscle cell proliferation and the development of foam cells in the arterial intima. Therefore, patients with chronic hyperglycemia will have increased atherosclerotic plaque growth, thus increasing their risk of ischemic heart disease, myocardial infarction and adverse cardiovascular events.

This study classifies patients into different glycemic control groups to assess graded clinical effects of the different levels of chronic hyperglycemia on renal functional impairment and cardiovascular risk stratification that would offer a basis for empirical risk prediction in the region and early clinical action.

MATERIALS AND METHODS

Conduct research to design and set up your study.

The present study is observational, cross sectional study conducted by using clinical audit record of outpatient department of Endocrinology and Internal medicine at Niazi Medical college and teaching hospital, sargodha a tertiary care hospital. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed for cross-sectional studies.

Ethical Considerations

The study protocol was designed according to the national ethical guidelines and Declaration of Helsinki. To guarantee the confidentiality and privacy of all patient records extracted for analysis, these records were fully anonymized before evaluation. Since this was a study of anonymous clinical data, there was no interaction or intervention with patients, therefore there was no need for individual informed consent.

Study Population and Eligibility Criteria

The study population consisted of 300 adults with type 2 diabetes mellitus (T2DM) attending the outpatient clinics of endocrinology and internal medicine. Participants had to be 18 or older and have a documented clinical diagnosis of type 2 diabetes mellitus (T2DM) for at least 1 year, with full medical records including baseline HbA1C level and renal and cardiovascular profiles. Concomitant conditions such as pregnancy, end-stage renal

disease on chronic renal replacement therapy, severe hepatic dysfunction, active malignancy, and acute diabetic ketoacidosis and hyperosmolar hyperglycemic state were excluded.

Students will learn how to measure clinical variables and collect the data.

Standardized clinical records were used to obtain clinical and biochemical data. Demographic parameters were age, sex and duration of diabetes. HbA1c levels were determined by high-performance liquid chromatography based on the National Glycohemoglobin Standardization Program (NGSP). Using clinical criteria, participants were categorized into the following three mutually exclusive groups: optimal glycemic control (HbA1c<7.0%), moderate glycemic control (HbA1c 7.0%-8.5%), and poor glycemic control (HbA1c>8.5%).

Renal functional status was measured by eGFR and ACR. All serum creatinine measurements were done by enzymatic method and eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (Levey et al., 2009) in mL/min/1.73 m². Spot urine samples were used to quantify ACR and were classified as normoalbuminuria (ACR < 30mg/g), microalbuminuria (30mg/g – > 300mg/g) and macroalbuminuria (> 300mg/g) based on established thresholds for nephropathy staging (American Diabetes Association, 2021). Cardiovascular risk stratification combined standard multi-factorial risk factors such as office blood pressure, lipid profiles and clinical risk scores to divide patients into low-to-moderate vs high-to-very-high cardiovascular risk groups.

Statistical Analysis

All the statistical analysis used was conducted on IBM SPSS Statistics. Normality of the continuous variables were assessed with Shapiro-Wilk statistical test, histograms and normal Q-Q plots. Means with standard deviations are presented for normally distributed variables and medians with interquartile ranges for variables not normally distributed (e.g., ACR). Categorical data are reported as frequencies and percentages.

One-way analysis of variance (ANOVA) was used for normally distributed continuous data and the Kruskal-Wallis test was used for skewed data to compare the three glycemic ranges. The distribution of nephropathy stages and cardiovascular risk classes between tiers were compared with Pearson's chi-square test or Fisher's exact test if the expected cell count was less than 5. Pearson's correlation coefficient (with log-transformed ACR) or Spearman's rank correlation coefficient was used to assess the correlation between individual values of HbA1c and renal markers. Advanced nephropathy staging and high cardiovascular risk were analyzed using multivariable logistic regression models to calculate adjusted ORs and 95% CIs for each glycemic tier, adjusted for age, sex, duration of diabetes, and systolic BP. The statistical significance for all hypothesis testing: two tailed and a priori $p<0.05$.

The pathophysiological mechanisms of hyperglycemia-induced end-organ damage.Hyperglycemia-induced end-organ damage: pathophysiological mechanisms.

The main factor in the onset and progressive deterioration of microvascular and macrovascular complications of type 2 diabetes mellitus is chronic sustained hyperglycemia. In the target tissues, several important biochemical pathways are simultaneously overactive, such as the renal glomeruli and vascular endothelium, when the intracellular levels of glucose are persistently above the norm (physiological range). These pathways are interdependent pathways that involve enhanced polyol flux, enhanced intracellular production of advanced glycation end-products, excessive activation of protein kinase C isoforms and excessive production of reactive oxygen species through mitochondrial dysfunction.

During exposure to high ambient levels of glucose for extended periods of time, non-enzymatic glycation of intracellular and extracellular proteins, lipids and nucleic acids is driven by mass-action kinetics. First, Schiff bases are formed, a process that is reversible; these then slowly rearrange into stable, irreversible advanced glycation end-products. These gradually build up in the extracellular matrix of the renal basement membrane and the intima of the arteries. They exert their pathological effects in two main ways: by cross-linking the structure of the matrix (making the capillaries and interstitium stiffer and changing collagen turnover) and by signaling to the cells through receptors.

These ligands trigger intracellular signalling pathways upon binding to cell-surface receptors for advanced glycation end-products (RAGE) which lead to activation of NADPH oxidase and a reduction in endogenous antioxidant mechanisms. This downstream increase in oxidative stress results in an ongoing activation of pro-inflammatory transcription factors, such as NF-κB, and local production of transforming growth factor-beta, vascular endothelial growth factor and interleukins. In the kidney, these changes lead to increased proliferation of mesangial cells and production of extracellular matrix, as well as increased glomerular hyperfiltration and effacement of podocytes, resulting in thickening of the glomerular basement membrane and progressive loss of nephrons (Brownlee, 2005; Thomas et al., 2015). At the same time, the hyperglycemic environment in the macrovascular endothelial cells lowers nitric oxide bioavailability and increases the expression of adhesion molecules, which leads to increased migration of smooth muscle cells and accelerated systemic atherosclerosis and multi-organ ischemic risk.

Biomarker Selection & Clinical Rationale for HbA1c, eGFR, and ACR

Validation and clinical standardization of strong, well characterized and clinically relevant biomarkers are crucial to quantify glycemic exposure and downstream severity of chronic microvascular complications in T2DM. Based on their direct association to target-organ integrity, the HbA1c, eGFR and ACR were selected to form a three-part framework for relating metabolic control to target-organ integrity directly.

The clinical gold standard for measuring glycemic exposure for the past 120 days (or three months) is the HbA1C test (American Diabetes Association Professional Practice Committee, 2024). HbA1C is a measure of time-

averaged integrated glycemic control, which is not as affected by acute fluctuations as fasting plasma glucose or postprandial measurements, as these are influenced by diet, exercise and stress. This stability makes it an essential tool for glycemic control level categorization, and for long term microvascular risk prediction.

To evaluate renal functional impairment, eGFR calculated with the CKD-EPI creatinine equation was used. Failure to use serum creatinine alone to assess renal function is due to non-renal clearance factors, tubular secretion and a significant functional reserve of the kidneys, which means that there is a considerable loss of nephron function before serum levels exceed the reference standards. The CKD-EPI equation combines age and sex information into the serum creatinine measurement to create a more accurate estimate of the true filtration capacity in a variety of clinical populations (Levey et al., 2009).

At the same time, ACR was adopted as the key marker of early glomerular damage and endothelial dysfunction. Although physiological urinary albumin excretion is low, chronic hyperglycemia, glomerular hyperfiltration and advanced glycation end products deplete the glomerular barrier, particularly podocytes and the basement membrane's negative charged heparan sulfate proteoglycans. Thus, elevated ACR is an early warning sign of microvascular leakage (Persson & Rossing, 2018). This approach eliminates the problems of urine collection, which can occur with 24-hour urine collection, and makes it possible to categorize the degree of albuminuria based on urinary creatinine, which is standardised by a spot urine sample.

The use of cardiovascular risk stratification models in Type 2 Diabetes.Cardiovascular Risk Stratification Models in Type 2 Diabetes.

Type 2 diabetes mellitus is considered a coronary artery disease risk equivalent and macrovascular complications are the most frequent cause of morbidity and mortality (Emerging Risk Factors Collaboration, 2010). Chronic hyperglycemia and accelerated atherogenesis are linked by a complex interplay of metabolic, endothelial and inflammatory perturbations that systematically increase multi-factorial cardiovascular risk.

Chronic hyperglycemia is associated with profound endothelial dysfunction at the pathophysiological level, which leads to the development of macrovascular disease. Increased production of ROS in the vascular wall inhibits eNOS expression and decreases the levels of NO in the circulation, which is a key vasodilator and antiatherogenic molecule. At the same time, the upregulation of adhesion molecules leads to the rolling and adhesion of circulating monocytes, as well as trans-endothelial migration. In the sub-endothelial space the cells ingest oxidized low-density lipoproteins, becoming lipid-laden foam cells, which lead to the formation of complex atherosclerotic plaques.

Also, diabetic dyslipidemia with high triglycerides, low HDL, and high percentage of small, dense LDL particles, is a synergistic effect of hyperglycemia. Low-density lipoproteins (LDL) are small, dense, and more susceptible to glycation and oxidation and are therefore extremely atherogenic. Advanced glycation end-products also affect the structure of the proteins in the media of the arteries, which leads to an increase of their stiffness, the velocity of pulse waves, and SBP, and thus to a rise in left ventricular afterload and myocardial oxygen demand.

Cardiovascular risk stratification models take into account traditional risk factors, diabetes-specific risk factors, such as duration of diabetes, glycemic control tier, microvascular complication status (microalbuminuria or reduced eGFR) (Fox et al., 2012), and office blood pressure, lipid profile, and smoking history. Patients can be stratified into low to moderate risk versus high to very high risk and risk-tailored interventions can be implemented, such as optimizing glycemic control, initiating evidence-based cardioprotective agents, and strict blood pressure management to reduce risk of major adverse cardiovascular events (American Diabetes Association Professional Practice Committee, 2024).

Epidemiological context and regional clinical relevance

Escalation of type 2 diabetes mellitus (T2DM) has been a major public health problem in the twenty first century, with a disproportionate burden in developing countries. Urbanization, change in food habits, sedentary lifestyle and genetic predisposition have all contributed to the increasing prevalence of diabetes in South Asia, including Pakistan (Standl et al., 2019). In this setting, the onset of disease is early, undiagnosed hyperglycemia is common and the rate of microvascular and macrovascular complications is higher.

Diabetic nephropathy and cardiovascular diseases are the major causes of end-stage renal failure, pre-mature cardiovascular morbidity and mortality in regionally based tertiary care centers (Afkarian et al., 2013). This is often due to cultural/religious practices, dietary habits, and because routine preventive screening and early metabolic monitoring are not always feasible for the patient. Poor glucose control (reflected by high HbA1c) therefore acts synergistically with the high prevalence of hypertension and atherogenic dyslipidaemia in the region.

Clinically, it is important to investigate the relationship between glycemic control levels and end-organ outcomes in this context. It can provide local empirical data that accurately reflects burden of disease and is able to help to close the loop between international guidelines and local healthcare realities. The identification of renal and cardiovascular gradients between optimal, moderate and poor glycemic control highlights the importance of proactive and risk-stratified outpatient management. Combination of HbA1c monitoring with routine evaluation of eGFR and ACR in clinical populations of South Asians can significantly impact the trajectory of diabetic complications through evidence-based screening protocols.

Therapeutic implications and clinical guidelines for glycemic optimization

Targeted therapeutic intervention is the clinical implication of cross-sectional correlations of glycemic control with end-organ complications. This study confirms that there are progressive associations between different

HbA1C levels and renal functional decline and cardiovascular risk, supporting the concept of personalized, active glycemic optimization in T2DM patients.

Guidelines from around the world and region recommend a personalized HbA1c goal of less than 7.0% for most adults who are not pregnant to prevent or delay microvascular complications (American Diabetes Association Professional Practice Committee, 2024; Inzucchi et al., 2015). But, there is a need to take into account the balance between glycemic control and the risks of hypoglycemia, comorbid diseases, and duration of the disease when considering therapeutic strategies. Patients in moderate (7.0% - 8.5%) or poor (> 8.5%) tiers, in this study, had higher ACR and lower eGFR, and need more intense multifactorial management. This involves use of pharmacological glucose-lowering treatments, comprehensive blood pressure treatments, statin-based lipid-lowering treatments, and organ-protective agents, such as sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, that are known to reduce renal and cardiovascular risk, independent of glucose-lowering effects alone (American Diabetes Association Professional Practice Committee, 2024).

Moreover, routine monitoring of biomarkers, in addition to HbA1c, with serial eGFR and ACR, allows physicians to identify subclinical nephropathy that can result in irreversible structural damage. Regional implementation of strategies to mitigate factors that limit routine screening and ensure therapeutic adherence will be essential in lowering the burden of ESRD and large vessel atherosclerotic events over the course of the disease.

RESULTS

The number and characteristics of participants according to glycemic tiers.

300 patients with type 2 diabetes mellitus were evaluated. These patients were divided into three mutually exclusive glycemic control groups: optimal control (HbA1c < 7.0%, n = 90), moderate control (7.0%–8.5%, n = 120), and poor control (> 8.5%, n = 90).

Table 1 shows the baseline demographic and clinical features for the three tiers. The mean age of the whole cohort was 58.4 (SD 8.7) years, and there was a similar proportion of males (54.0%) and females (46.0%). The length of diabetes progressively rose with tier from optimal control (6.2 ± 3.1 years), moderate (9.5 ± 4.2 years) to poor control (13.8 ± 5.1 years; $p < 0.001$). Similarly, there was an increase in both systolic and diastolic blood pressure in the office as the glycemic tier increased.The same was seen with worsening glycemic tier with both systolic and diastolic office BP.

Table 1: Baseline Demographic and Clinical Characteristics Stratified by Glycemic Control Tiers (N = 300)

Parameter	Optimal Control (HbA1c	Moderate Control (HbA1c 7.0%–8.5%, n=120)	Poor Control (HbA1c>8.5%, n=90)	P-value
Age (Years)	57.8 pm 8.2	58.5 pm 8.9	58.9 pm 9.0	0.652
Sex (Male / Female)	48 (53.3%) / 42 (46.7 \ %)	65 (54.2%) 55 (45.8 %)	49 (54.4%) 41 (45.6 %)	0.985
Duration of Diabetes (Years)	6.2 pm 3.1	9.5 pm 4.2	13.8 pm 5.1	<0.001
HbA1c (%)	6.4 pm 0.4	7.7 pm 0.5	9.6 pm 0.9	< 0.001
Systolic BP (mmHg)	128.4 pm 11.2	135.2 pm 12.6	144.1 \pm 14.5	< 0.001
Diastolic BP (mmHg)	80.2 pm 7.4	83.6 pm 8.1	88.5 pm 9.2	< 0.001
Serum Creatinine (mg/dL)	0.88 pm 0.19	1.05 pm 0.28	1.38 pm 0.42	< 0.001

Renal Functional Status and Nephropathy Staging Across Glycemic Tiers

Values are mean ± SD unless otherwise stated. BMI, body mass index; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin.

There was a significant, progressive decline in renal functional markers as hyperglycemia worsened. Mean eGFR (CKD-EPI) was highest in the optimal control tier (94.5 ± 14.2 mL/min/1.73 m²), lower in the moderate tier (82.1 ± 16.5 mL/min/1.73 m²), and lowest in the poor control tier (64.8 ± 18.9 mL/min/1.73 m²; $p < 0.001$).

In patients with poor glycemic control, distribution of nephropathy stages, based on ACR, was significantly towards higher stage of microvascular injury (normoalbuminuria < 30 mg/g, microalbuminuria 30–300 mg/g, macroalbuminuria > 300 mg/g). Normoalbuminuria was most common in the optimal control group (77.8%) and macroalbuminuria was most common in the poor control tier (44.4%) as shown in Table 2. The glycemic control tier was associated with nephropathy stage, which was highly significant, by the Pearson's chi-square test ($\chi^2 = 78.4$, $p < 0.001$).

Renal Parameter / Stage	Optimal Control(n=90)	Moderate Control (n=120)	Poor Control (n=90)	p-value
eGFR (mLmin1.73 m^2)	94.5 pm 14.2	82.1pm 16.5	64.8 pm 18.9	< 0.001
Urine ACR Median (mg/g) [IQR]	18.4 [11.2– 26.5]	54.2 [28.6- 115.4]	285.6 (120.2–540.8)	< 0.001
Normoalbuminuric (< 30mg/g)	70(77.8 %)	52(43.3 %)	14(15.6 %)	< 0.001
Microalbuminuria (30– 300 mg/g)	17(18.9 \%)	51(42.5 %)	36(40.0 %)	< 0.001
Macroalbuminuria (> 300textmg/g)	3(3.3 %)	17(14.2 %)	40(44.4 %)	< 0.001

Cardiovascular Risk Stratification and Correlation Analyses

Of patients in optimal glycemic control, just 15.6% (n = 14) were considered to be at high to very-high cardiovascular risk. In sharp contrast, this proportion rose to 48.3% (n = 58) in the moderate control tier and 81.1% (n = 73) in the poor control tier ($\chi^2 = 64.2$, $p < 0.001$).

There was a significant strong inverse linear relationship between individual HbA1c levels and eGFR ($r = -0.584$, $p < 0.001$) and a strong positive correlation between HbA1c and log-transformed ACR ($r = 0.612$, $p < 0.001$) observed in bivariate analysis. In addition, multivariable logistic regression analyses, adjusted for age, sex, duration of diabetes and systolic blood pressure, confirmed that poor glycemic control (HbA1c > 8.5%) was an independent predictor of both advanced nephropathy staging (adjusted OR = 4.28, 95% CI = 2.45–7.52, $p < 0.001$) and high-to-very-high cardiovascular risk (adjusted OR = 5.12, 95% CI = 2.89–9.08, $p < 0.001$).

DISCUSSION

This cross-sectional study evaluated the relationship between different glycemic control levels and severity of diabetic nephropathy and multi-factorial cardiovascular risk among patients with Type 2 Diabetes Mellitus (T2DM) aged 25–65 years of age. The results from this group of 300 patients show a progressive statistically significant decline in renal function over time, which is reflected in a decline in eGFR and an increase in ACR, as well as a higher percentage of high to very high cardiovascular risk as HbA1c levels increased. The findings highlight the systemic and progressive effects of chronic hyperglycemia on microvascular and macrovascular end-organ damage.

The inverse correlation between HbA1c and eGFR ($r = -0.584$, $p < 0.001$) and strong positive correlation with ACR ($r = 0.612$, $p < 0.001$) is similar to known pathophysiological relationships (Brownlee, 2005; Thomas et al., 2015). Advanced glycation end-products in the extracellular matrix of the glomerular basement membrane and arterial walls are formed and stored in greater amounts as a result of chronic hyperglycemia. This leads to structural matrix cross linking, generation of reactive oxygen species, and receptor-mediated signaling which leads to endothelial dysfunction, mesangial expansion, and podocyte effacement. In line with this, patients with poor control (HbA1c>8.5%) were significantly more likely to have microalbuminuria and advanced renal functional decline than patients with optimal control (HbA1c<7.0%).

Moreover, multivariable logistic regression analysis indicated poor glycemic control was an independent predictor of advanced nephropathy staging (adjusted OR = 4.28; 95% CI: 2.45–7.52; $p < 0.001$) and of high-to-very-high cardiovascular risk (adjusted OR = 5.12; 95% CI: 2.89–9.08; $p < 0.001$) after age, sex, diabetes duration, and systolic blood pressure were included. This implies that both microvascular and macrovascular complications have a common metabolic basis, whereby systemic vascular injury is triggered by hyperglycemia combined with other metabolic and vascular risk factors such as hypertension and atherogenic dyslipidaemia. This increase in high-to-very-high cardiovascular risk (from 15.6% in optimal to 81.1% in poor control) highlights the role of metabolic control in macrovascular morbidity in type 2 diabetes.

These data have significant clinical implications when interpreted in the context of regional epidemiological situations. In South Asian, early onset of disease, high prevalence of undiagnosed hyperglycemia, and limited access to routine preventive screening is linked to target-organ complications (Standl et al., 2019). The risks that were graded among optimal, moderate, and poor glycemic tiers further support the need for proactive, risk-stratified outpatient management. Use of a combination of frequent HbA1c testing with serial eGFR and spot ACR testing allows for detection of subclinical microvascular injury prior to functional impairment.

There are several caveats to note. First, the cross-sectional design does not allow for causal inference of the time course of nephropathy progression and cardiovascular outcome; longitudinal prospective studies are needed to follow any individual's decline over time. Second, data was obtained from standardized clinical records and audits which could be affected by unmeasured residual confounding by dietary patterns, physical activity or variations in concurrent pharmacological therapy (including SGLT2 inhibitor and renin-angiotensin system blocker use). Thirdly, the study was a single center study and thus may not be applicable to other region populations. Nevertheless, these constraints don't diminish the value of the sample size, multivariable modeling and the use of clinical definitions that follow standard definitions to glean insights and actionable steps in regional clinical practice.

CONCLUSION

The results of this cross-sectional study reveal a clear and progressive relationship between chronic hyperglycemia and the severity of diabetic nephropathy and multi-factorial cardiovascular risk among type 2 diabetes mellitus (T2DM) patients. The results demonstrate significant decreases in eGFR, significant increases in ACR, and an increase in advanced microvascular injury and macrovascular risk within the different glycemic control categories (optimal, moderate, and poor) defined in this cohort (N = 300). The independent associations seen in multivariable models confirm that chronic hyperglycemia is a major contributor to end-organ functional impairment. The results offer an empirical basis for the significance of comprehensive metabolic management in the long-term prevention of renal and cardiovascular complications in the clinical setting.

Clinical Recommendations

The following recommendations are made for clinical management and outpatient care workflow based on the results of this study:

Routine multiple-biomarker screening: Clinicians should adopt a routine screening panel including serial calculation of eGFR and spot measurement of ACR in all people with type 2 diabetes mellitus, avoiding irreversible nephropathy.

Risk-stratified interventions: Outpatient management should be tailored to the patient's glycemic tier. For people in the moderate and poor control groups, enhanced multi-factorial management, such as aggressive blood pressure control and statins, is needed to reduce additional macrovascular and renal risk.

3. Early use of organ-protective therapeutics: When considering the use of organ-protective therapeutics, evidence-based therapeutics should be used, such as SGLT2 inhibitors and GLP-1 receptor agonists, which have organ-protective effects in addition to glycemic lowering (American Diabetes Association Professional Practice Committee, 2024).

4. Targeted regional public health policies: In developing and South Asian countries, public health authorities and institutions should implement formal education and screening initiatives to break down barriers to timely preventive health services, delay disease onset and mitigate the regional burden of ESRD and major adverse cardiovascular events.

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