



High HbA1C and Glycemic Control as Diabetic Nephropathy Etiology

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Abstract

Background: Type 2 Diabetes Mellitus (T2DM) is a metabolic disorder characterized by insulin resistance, leading to microangiopathic complications such as diabetic nephropathy (DN). DN involves changes in the kidney's glomeruli, leading to albuminuria and potentially progressing to end-stage renal disease (ESRD). Hyperglycemia, a hallmark of diabetes, contributes to long-term organ damage, making DM a significant global health concern. **Methods:** This study included 48 participants aged 30 to 65 years, divided into diabetic patients and controls. Blood samples were collected for analysis of urea, creatinine, and HbA1c levels. **Results:** The HbA1c levels in the patient group (8.57 ± 1.75) exhibited a statistically significant increase ($P \leq 0.05$) compared to the control group (5.28 ± 0.78). However, there was no significant difference in urea levels between patients (45.88 ± 37.91) and controls (33.02 ± 18.87) ($P \leq 0.05$). Similarly, there was no significant variance in creatinine levels between patients (1.37 ± 1.78) and controls (1.06 ± 1.55) ($P \leq 0.05$). Elevated HbA1c levels might be a cause of disease severity and complexity in diabetes, emphasizing the need for comprehensive glycemic

control. **Conclusion:** Regular monitoring of HbA1c levels is crucial for early detection and management of DN in diabetic patients. Increased microalbuminuria correlates with elevated HbA1c levels, highlighting the importance of glycemic control in preventing kidney function impairment. This study demonstrated the significance of comprehensive glycemic management strategies in mitigating DN progression and reducing morbidity in diabetic populations.

Keywords: Type 2 Diabetes Mellitus (T2DM), Diabetic Nephropathy (DN), HbA1c Levels, Glycemic Control, Microalbuminuria

Introduction

Type 2 Diabetes Mellitus (T2DM) is a metabolic disorder characterized by hyperglycemia resulting from insulin resistance (Goyal et al., 2021). Insulin resistance leads to microangiopathic complications, such as diabetic nephropathy, where changes in the glomerulus cause an increase in albumin excretion in urine (Hyvönen et al., 2015). Over time, diabetic nephropathy can progress to end-stage renal disease (Hyvönen et al., 2015). Hyperglycemia, or elevated blood sugar, is a hallmark indicator of diabetes mellitus, a group of metabolic disorders arising from abnormalities in insulin synthesis, action, or both (Baynes, 2015; Ubeid, 2020). Chronic hyperglycemia associated with diabetes is implicated in long-term damage and dysfunction of various organs, including the heart, blood vessels, kidneys, eyes, and nerves (AL-Fatlawi & Jwad, 2022).

Significance | High HbA1c levels correlate with diabetic nephropathy severity, urging comprehensive glycemic control for mitigating complications and improving diabetic outcomes.

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Editor Md Shamsuddin Sultan Khan And accepted by the Editorial Board Mar 11, 2024 (received for review Jan 4, 2024)

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Please cite this article.

Iman Kamel Aati, Hawrra Jabbar Mohammed, Muhanad Mahdi Mohammed et al. (2024). High HbA1C and Glycemic Control as Diabetic Nephropathy Etiology, Journal of Angiotherapy, 8(3), 1-6, 9547

The prevalence of Diabetes Mellitus (DM) has increased significantly in recent decades, with projections indicating a global occurrence of 592 million cases by 2035 (Quinn et al., 2019). Insulin, a crucial polypeptide hormone, is released by the islets of Langerhans in the pancreas. Insulin facilitates the entry of blood glucose into body cells, where it can be metabolized to produce energy (Ahmad, 2014). However, individuals with diabetes are unable to properly utilize glucose, leading to abnormally high blood glucose levels, a condition known as hyperglycemia (Beale, 2013).

The escalating incidence of diabetes has become a significant public health concern worldwide. The disease arises from a combination of risk factors, including genetics, environmental factors, impaired insulin release, sedentary lifestyles, physical inactivity, smoking, alcohol consumption, dyslipidemia, hyperinsulinemia, reduced β -cell sensitivity, and elevated glucagon activity (Alam et al., 2021).

All types of diabetes share similar symptoms, although their severity may vary. Type 1 diabetes symptoms typically develop more rapidly compared to type 2 diabetes, initially presenting gradually and progressing over time to the point where complications arise, often leading to diagnosis (American Diabetes Association, 2016).

Long-term complications of diabetes encompass various health issues, including retinal disease leading to vision loss, nephropathy resulting in renal failure, peripheral neuropathy causing nerve damage and increasing the risk of foot ulcers, amputations, and Charcot joints, as well as autonomic neuropathy leading to symptoms affecting the gastrointestinal, genitourinary, cardiovascular, and sexual systems (Balaji et al., 2019; Punthakee et al., 2018).

Diabetic nephropathy (DN) stands as one of the most prevalent and perilous complications of diabetes mellitus, significantly increasing rates of morbidity and mortality among individuals with diabetes (Samsu, 2021). Over years of uncontrolled diabetes, the delicate filtration mechanism of the kidneys begins to deteriorate. Initially, larger blood proteins such as albumin leak from the kidneys, resulting in albuminuria, or the presence of albumin in urine (Yadav et al., 2020). As albumin levels rise, the kidneys' ability to filter urine normally declines, leading to the retention of various waste products in the body.

Diabetic nephropathy is closely associated with chronic kidney disease (CKD), nephrotic syndrome, and proteinuria (Sagoo et al., 2020). In the initial stages of diabetic nephropathy, the glomerular filtration rate (GFR) is typically higher than usual but deteriorates over time (Samsu et al., 2021). The presence of urinary proteinuria can be identified through the urine dipstick test, known as overt nephropathy (Samsu et al., 2021). Diabetic nephropathy is recognized as one of the leading causes of chronic renal failure, particularly prevalent in individuals with insulin-dependent diabetes mellitus (IDDM), where it manifests in approximately 40% of cases (Selby et al., 2020; Pelle et al., 2020).

In 2017, diabetes affected 8.8% of the global population, totaling 424.9 million individuals (Lovic et al., 2020). Projections indicate that by 2045, this number will soar to 693 million (Atlas et al., 2021). Pakistan ranked third globally in diabetes cases in 2022, with 7.5 million reported cases (Adnan et al., 2020). In 2020, Pakistan recorded 33 million diabetes cases (Basit et al., 2020). Additionally, approximately 32.3% of patients in Pakistan are afflicted with diabetic nephropathy (Sawaf et al., 2022).

Serum creatinine is a metabolic byproduct of the muscle protein creatine, with typical blood levels ranging between 0.8 and 1.4 mg/dL, higher in men due to greater muscle mass (Bhatia et al., 2019). Urea, a metabolic product of protein metabolism, normally ranges from 7 to 20 mg/dL in blood (Pathan et al., 2020). These measures are crucial in evaluating renal function.

Poor glycemic control, characterized by chronic hyperglycemia, is indicated by an elevation in HbA1c levels (Shahbazian et al., 2013). Hyperglycemia serves as a risk factor for diabetic nephropathy, which involves a series of glomerular alterations including lumen widening, tubular epithelium flattening, sclerosis, basal membrane thickening, and mesangial matrix expansion (WHO, 2019). Kidney damage is evidenced by markers such as serum creatinine, with elevated levels reflecting decreased renal clearance (Zhao et al., 2018). Glycemic control plays a crucial role in the development of diabetes-related complications (Khaw et al., 2004).

Hyperglycemia is a significant contributing factor to the onset of diabetes mellitus. Diabetic nephropathy (DN) results in morphological and structural damage to the kidneys' glomeruli, tubules, and arteries, impairing their vital functions. Diabetes-related metabolic issues lead to proximal tubular basement membrane thickening, which is associated with glomerular changes, including thickening of the glomerular basement membrane (Saxena et al., 2019).

Therefore, understanding the relationship between glycemic control, renal function markers, and DN progression is crucial for guiding clinical management and implementing preventive measures. By elucidating these associations, this study determined the development of targeted interventions aimed at mitigating the burden of DN in diabetic populations.

Materials and methods

Sample

The study was conducted following the issuance of Ethical clearance by the Health Research Ethics Committee of the Faculty of Al-Sader Teaching Hospital and medical laboratories from August 2023 to September 2023. The investigation included 48 participants within the age range of 30 to 65 years. Participants were divided into two groups: 24 diabetic patients and 24 individuals in the control group. The study's ethics approval was obtained from medical laboratories and participants (the diabetic patients and control healthy group)

prior to enrollment, all participants provided written informed consent.

Blood Collection and Laboratory Analysis Procedure

Seven milliliters of whole blood were collected from each participant, including both patients and controls, using a medical syringe. Four milliliters of the collected blood were placed in a gel tube and allowed to clot at room temperature for twenty minutes. Subsequently, the blood samples were centrifuged at 3000 rpm for ten minutes to perform the urea and creatinine tests, which were measured using a spectrophotometer. Additionally, three milliliters of blood were collected in an EDTA tube for the purpose of the HbA1c test, which was measured using I-Chroma.

For the urea test, the spectrophotometer measured the colored complex produced by urea in the sample. Reagents and materials were brought to room temperature before the procedure. The contents of canister A2 were mixed with the contents of canister A, incubated at 37°C for five minutes, and then mixed well until ready to use. The absorbance (A) of the sample, standard, and blank were measured at 600 nm wavelength, and the absorbance at 500 nm wavelength was measured for A2 in comparison to the reagent blank. The urea content in the sample was determined using the formula: $\text{Result} = A_{\text{Sample}} / A_{\text{Standard}} \times \text{Standard Concentration}$ (mg/dL).

For the HbA1c test, 100 μL of hemolysis buffer was added to the detection buffer tube, and 5 μL of blood from the EDTA tube was added to the mixture. After thorough mixing, the sample combination was extracted and placed into the test cartridge's sample well. The cartridge was then inserted into the I-Chamber slot at 30°C, and the test result was displayed on the device's screen.

Statistical analysis

Statistical analysis was performed using MedCalc version 19.1 (free trial version) and Microsoft Excel 2010. Student's t-tests were used for comparisons, with a p-value of less than 0.05 considered statistically significant and a p-value of less than 0.001 considered statistically highly significant for all analyses. Regression correlation analysis was conducted to assess the correlation between different parameters.

Results

Our study findings underscore a notable increase in HbA1c levels among individuals with diabetes mellitus compared to the control group. However, no significant differences were observed in serum creatinine and blood urea levels between the two groups. These findings enhance our comprehension of the complex interplay between glycemic control and renal function in individuals with diabetes mellitus, underscoring the importance of comprehensive monitoring and management strategies for this population. Prospective longitudinal studies are imperative to elucidate the

long-term implications of glycemic control on renal function and disease progression in individuals with diabetes mellitus.

HbA1c Levels

The study revealed a mean HbA1c level of 8.57 ± 1.75 in patients with diabetes mellitus, significantly higher ($p \leq 0.05$) than the mean HbA1c level of 5.28 ± 0.78 in the control group (Table 1). This disparity highlights the challenge of achieving optimal glycemic control among individuals with diabetes mellitus, with elevated HbA1c levels indicating suboptimal management of blood glucose levels. Additionally, it suggests a greater risk of diabetic complications, such as nephropathy, associated with poor glycemic control in diabetic individuals compared to the control group.

Serum Creatinine Levels

Contrary to the notable difference in HbA1c levels, our analysis found no statistically significant differences in serum creatinine levels between individuals with diabetes mellitus and the control group (Table 1). The mean serum creatinine level was 1.37 ± 1.78 in patients with diabetes mellitus, compared to 1.06 ± 1.55 in the control group, with no significant difference observed ($p > 0.05$). This suggests that renal function, as assessed by serum creatinine levels, may not be significantly impaired in individuals with diabetes mellitus compared to healthy controls.

Blood Urea Levels

Similarly, no statistically significant differences were found in blood urea levels between individuals with diabetes mellitus and controls (Table 1). The mean blood urea level was 45.88 ± 37.91 in patients with diabetes mellitus, compared to 33.02 ± 18.87 in the control group, with no significant difference observed ($p > 0.05$). This indicates that renal function, as assessed by blood urea levels, may also remain relatively unaffected in individuals with diabetes mellitus compared to healthy controls.

Microalbumin Levels

However, the study did find a significantly higher ($p \leq 0.05$) mean microalbumin level in patients with diabetes mellitus compared to the control group (Table 3). Specifically, the microalbumin levels were 102.72 ± 81.90 in the study group and 16.27 ± 12.10 in the control group. Elevated microalbumin levels are indicative of early kidney damage and are commonly used as a marker for diabetic nephropathy. Therefore, the increased microalbumin levels observed in the study group further support the notion of renal dysfunction in individuals with diabetes mellitus.

Discussion

Our study demonstrated the importance of comprehensive monitoring and management of glycemic control in individuals with diabetes mellitus to mitigate the risk of renal complications. Increased HbA1c levels served as a significant predictor of disease severity and complexity, necessitating regular follow-up and intervention in diabetes management. However, the lack of

Table 1. HbA1c, Urea and Creatinine Concentrations in control and diabetic patients. n=24 patient and control in each group.

Diabetic patients (N=24)	Control (N=24)	Parameters
8.57 a± 1.75	5.28 b±0.78	HbA1c
45.88 a± 37.91	33.02a ± 18.87	Urea
1.37a±1.78	1.06a±1.55	Creatinine

Value is shown as mean± standard deviation.

Different letter denotes a significant difference between values ($p < 0.05$).

The comparable letters indicate a difference in values that is not statistically significant ($p > 0.05$).

noticeable differences in urea and creatinine levels between diabetic patients and controls might be an effective management strategy in maintaining renal function in this population. The present study evaluated the levels of HbA1c, microalbumin, urine, and serum creatinine in both diabetes patients and healthy individuals. Additionally, it aimed to investigate the association of glycosylated Hb with UACR and serum creatinine levels in type 2 diabetes mellitus patients. The study revealed that mean levels of HbA1c, microalbumin, and serum creatinine were significantly elevated in the study groups compared to the control group. Furthermore, mean levels of urinary ACR were notably higher in diabetic patients compared to the control group. A significant positive correlation was observed between UACR and HbA1c in diabetic patients ($r = 0.44$).

Haque et al. (2009) also reported significant positive correlations of HbA1c with serum creatinine and urinary ACR in type 2 diabetic patients (with p values of 0.008 and <0.001 , respectively) (Haque et al., 2011). Previous studies by Sheik et al. (2009) found significant positive correlations of HbA1c with microalbuminuria ($p < 0.05$) and serum creatinine ($p < 0.001$) in type 2 diabetes mellitus patients. Several other studies related to diabetes were noted. Raja et al. (2019) reported interesting findings in diabetes studies. Khanna et al. (2019) conducted a study on serum uric acid levels in acute stroke. Sanyukta et al. (2020) explored the association of Spot Urinary Albumin Creatinine Ratio (UACR) with Coronary Artery Disease. Ambad et al. (2020) investigated the relationship between uric acid and creatinine in pre-diabetic and diabetic patients.

Additional studies included Walinjkar et al. (2019) examining platelet indices as predictors of microvascular complications in type 2 diabetes, Warjekar et al. (2020) studying microalbuminuria and uric acid in type 2 diabetes mellitus, and Bhinder et al. (2018) conducting a study on Carotid Intima-Media Thickness in prediabetes and its correlation with cardiovascular risk factors.

In comparison to non-diabetic controls, our study revealed that the diabetic population exhibited moderate renal impairment based on the parameters examined. As outlined by Nathan et al. (2007), the HbA1c test displays the average plasma glucose over an eight to twelve-week period preceding the test. Unlike fasting plasma glucose tests or oral glucose tolerance tests (OGTT), HbA1c testing does not require prior preparation and can be performed at any time, making it the preferred method for assessing glycemic control in diabetes. Recently, there has been increasing interest in using HbA1c for diagnosing diabetes and screening individuals at high risk of developing the disease (Committee, 2009).

The search for a glucose substitute for diagnosing diabetes has persisted due to challenges associated with testing fasting plasma glucose levels and conducting OGTTs, as well as the daily fluctuations in glucose levels. Both the American Diabetes Association (ADA) and an international committee have officially

recommended the use of HbA1c for diagnosing diabetes (Committee, 2009).

Our research suggests that elevated HbA1c levels serve as a significant predictor of the complexity and severity of diabetes and should be considered in the ongoing management of diabetes patients. Consistent with the findings of Biri et al.'s study in 2021, which also reported higher HbA1c values in diabetes patients, our results indicated that the HbA1c values of diabetic patients were higher than those of the control group.

The investigation results revealed no significant difference in urea and creatinine levels between the patient and control groups. Several factors could contribute to this observation, including the patients' balanced diet, which may help maintain kidney function despite elevated blood glucose levels. Additionally, the commitment of diabetic patients to regular treatments and efforts to maintain normal blood sugar levels, along with lifestyle choices such as abstaining from smoking, avoiding weight gain, and lacking a family history of renal failure or heart disease, may play a role. These factors, considered additional risk factors, could potentially impact blood sugar levels.

Various researchers, such as Shrestha et al. (2008), have also found a non-significant relationship between creatinine levels in diabetic patients. Proper and timely management of blood glucose levels can prevent the progression of diabetes to renal damage. Management strategies may include dietary adjustments, regular exercise, maintaining a healthy weight, monitoring lipid profiles, and appropriate medication use.

Dietary modifications, such as consuming complex carbohydrates, fiber, protein, and low-glycemic foods, can help regulate blood sugar levels effectively. Moderate exercise, which aids in reducing obesity and promotes insulin-independent glucose transfer into muscles, can also contribute to managing blood glucose levels (Alam et al., 2021).

Anyway, blood urea and serum creatinine levels serve as straightforward diagnostic indicators for evaluating kidney function and damage in individuals with uncontrolled diabetes.

However, this study has limitations, including a small sample size and unobserved parameters related to serum creatinine and HbA1c levels. Variables such as anemia, history of blood transfusions, frequency of anti-diabetic medication use, nutritional intake, physical activity levels, muscle mass, high-protein diets, and other medications affecting serum creatinine levels and HbA1c at the time of data collection could influence the results.

Conclusion

Early detection of diabetic nephropathy through monitoring HbA1c levels is crucial for reducing morbidity. Our study indicates that HbA1c levels can predict decreased renal function before serum creatinine changes occur. Regular HbA1c monitoring and

tailored treatment plans can delay diabetic nephropathy onset. Additionally, we found a significant positive correlation between urinary microalbumin, serum creatinine, UACR, and HbA1c levels. This suggests increased urine microalbumin excretion as glycosylated hemoglobin rises, possibly due to hyperglycemia-induced protein glycation and oxidative stress. These findings emphasize the importance of glycemic control in preventing early kidney function impairment in diabetic patients.

Author contribution

I.K.A., H.J.M. performed analysis, analyzed data, M.M.M., R.N.R.A. reviewed, edited, and prepared the manuscript. All authors approved the manuscript for publication.

Acknowledgment

The authors were thankful to Al-Sadr Teaching Hospital and the medical laboratories

Competing financial interests

The authors have no conflict of interest.

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