International Journal of Research in Medical Sciences
Kumar V et al. Int J Res Med Sci. 2025 Jan;13(1):235-240
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20244121

Original Research Article

Correlation of serum homocysteine with HbA1c and kidney function in type 2 diabetic patients: insights from estimated glomerular filtration rate and renal impairment

Vineet Kumar[1]*, Yuvraj Gulati[2], Richa Giri[1], Verma Rajendra Kumar Babulal[1], Punit Varma[3], Chayanika Kala[4]

[1]Department of Medicine, GSVMMC, Kanpur, Uttar Pradesh, India
[2]Department of Nephrology, GSVMMC, Kanpur, Uttar Pradesh, India
[3]Department of Community Medicine, GSVMMC, Kanpur, Uttar Pradesh, India
[4]Department of Pathology, GSVMMC, Kanpur, Uttar Pradesh, India

Received: 10 November 2024
Revised: 12 December 2024
Accepted: 20 December 2024

***Correspondence:**
Dr. Vineet Kumar,
E-mail: v8090284201@gmail.com

ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a prevalent metabolic disorder associated with complications, particularly diabetic nephropathy (DN), a major cause of end-stage renal disease (ESRD). Early detection of DN is essential to prevent progression. Serum homocysteine (Hcy), a marker linked to oxidative stress and endothelial dysfunction, has shown potential in predicting vascular and renal complications. However, its relationship with glycemic control (HbA1c) and kidney function (eGFR) remains underexplored. This study examines these correlations in T2DM patients.
Methods: This cross-sectional study included 156 T2DM patients recruited from G.S.V.M. medical college, Kanpur (January 2023-April 2024). Serum Hcy, HbA1c, and eGFR were measured using standardized techniques. Pearson and Spearman correlations, along with multiple linear regression, were used to evaluate relationships while adjusting for confounders like age, diabetes duration, and lipid profile.
Results: Serum Hcy levels demonstrated a significant positive correlation with HbA1c ($r=0.47$, $p<0.01$), indicating an association with poorer glycemic control. Additionally, a negative correlation was observed between serum Hcy and eGFR ($r=-0.52$, $p<0.001$), suggesting that elevated homocysteine levels were associated with declining kidney function. These correlations remained significant after adjustments for confounders.
Conclusions: Elevated serum homocysteine is strongly associated with higher HbA1c and lower eGFR, suggesting its potential as a biomarker for glycemic control and renal impairment in T2DM. Routine homocysteine measurement could aid early DN detection and management. Further studies are needed to validate these findings.

Keywords: Serum homocysteine, HbA1c, eGFR, type 2 diabetes, Renal impairment, Biomarkers, DN

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a global health concern, characterized by chronic hyperglycemia due to insulin resistance and beta-cell dysfunction.[1] This condition is associated with severe long-term complications, particularly affecting the cardiovascular and renal systems, and often leading to DN and ESRD.[2] Among these complications, DN stands out as a prominent microvascular issue that significantly increases the risk of morbidity and mortality in diabetic patients, underscoring the need for effective management strategies.

In clinical practice, HbA1c serves as an established biomarker for assessing long-term glycemic control.

Elevated HbA1c levels have shown strong correlations with microvascular complications, including DN.[3] However, HbA1c alone may not provide a complete picture of renal dysfunction, particularly in the early stages of kidney impairment. To assess kidney function more directly, the eGFR is frequently used, as it provides an estimate based on serum creatinine levels.[4] Although eGFR is a critical measure, there remains an ongoing need for additional biomarkers that could offer earlier insights into kidney function decline in diabetic patients.

One potential candidate for this role is serum Hcy, a sulfur-containing amino acid involved in methionine metabolism.[5] Hcy has attracted attention as a biomarker with implications for both vascular and renal health. Elevated serum Hcy levels, a condition known as hyperHcymia, have been linked to endothelial dysfunction, oxidative stress, and inflammation, all of which contribute to the pathogenesis of diabetic complications, particularly nephropathy.[6] Mechanistically, high levels of Hcy can impair nitric oxide production, enhance oxidative stress, and activate inflammatory pathways, accelerating renal damage.[7]

Despite the observed connections between hyperhomocysteinemia, vascular dysfunction, and renal impairment, the specific relationship between serum Hcy, HbA1c, and eGFR in T2DM patients is still underexplored. This study seeks to investigate these relationships in order to evaluate the potential role of serum Hcy as a dual biomarker for both glycemic control and kidney function impairment in T2DM. By examining the correlations of serum Hcy with HbA1c and eGFR, this research aims to clarify its utility in the early detection and management of DN.

METHODS

Study design

This cross-sectional study was conducted at G.S.V.M. medical college, Kanpur, Uttar Pradesh, India, from January 2023 to April 2024. The objective of the study was to assess the correlation between serum Hcy levels, HbA1c, and eGFR in patients with T2DM.

The study design was chosen to provide a snapshot of the population at a specific point in time to explore the relationships between these clinical markers.

Setting

Participants were recruited from the outpatient and inpatient wards of G.S.V.M. medical college, Kanpur, Uttar Pradesh, India. The study period spanned from January 2023 to April 2024.

Data collection included demographic information, clinical history, and biochemical analyses.

Participants

Adult patients diagnosed with T2DM based on American diabetes association (ADA) criteria were included in the study. Exclusion criteria included patients with severe renal impairment (eGFR<30 mL/min/1.73 m²), cerebrovascular disease, pregnancy, intake of folate or methotrexate, coronary artery disease, thyroid disease, psychiatric disorders, or urinary tract infection. Patients receiving treatment that might affect Hcy levels, such as folate supplements, were also excluded.

Variables

The primary variables of interest were serum Hcy levels, HbA1c, and eGFR. The relationship between serum Hcy and HbA1c was assessed to determine the role of Hcy in glycemic control, while the correlation between serum Hcy and eGFR was explored to understand its impact on kidney function. Other variables included age, gender, duration of diabetes, blood pressure, and lipid profile, which were adjusted for in the analysis.

Data sources/measurement

Blood samples were collected after an overnight fast to measure serum Hcy, HbA1c, and serum creatinine levels. Serum Hcy levels were determined using high-performance liquid chromatography (HPLC) (Agilent technologies, Santa Clara, CA, USA). HbA1c was measured using the immunoturbidimetric method, while eGFR was calculated using the CKD-EPI equation based on serum creatinine levels. All biochemical analyses were performed at the central laboratory of G.S.V.M. medical college, following standardized protocols.

Bias

Efforts to minimize selection bias were made by including a broad range of participants from both outpatient and inpatient settings. Measurement bias was addressed by using standardized and validated methods for all laboratory analyses. Confounding was controlled through multivariate statistical adjustments for factors such as age, gender, and duration of diabetes**.**

Study size

The sample size was calculated based on preliminary data suggesting a correlation between serum Hcy, HbA1c, and eGFR. A total of 156 participants were required to achieve a statistical power of 80% with a significance level of 0.05, assuming a moderate correlation between the variables.

Quantitative variables

Serum Hcy, HbA1c, and eGFR were analyzed as continuous variables to allow detailed examination of their relationships. Correlation analyses were conducted to

explore how variations in serum Hcy levels related to both glycemic control and kidney function.

Statistical methods

Data analysis was performed using SPSS software (version 25.0, IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to assess the normality of the data. Due to non-normal distribution, Spearman's rank correlation coefficient was used to analyze the relationship between serum Hcy, HbA1c, and eGFR. Multiple linear regression models were used to evaluate the independent effect of serum Hcy on HbA1c and eGFR, adjusting for potential confounders such as age, duration of diabetes, and lipid profile. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Participant characteristics

The study evaluated 156 patients diagnosed with T2DM at G.S.V.M. medical college, Kanpur. Participants' mean age was 55.4 years, predominantly male (68%). The average duration of diabetes was 7.3 years. Most individuals managed their condition using oral hypoglycemic agents, with a smaller subset requiring insulin therapy. Table 1 summarizes the baseline characteristics of the 156 T2DM patients included in the study, highlighting the demographic and clinical parameters relevant to our analysis.

Table 1: Baseline characteristics of participants.

Variables	Mean	Standard deviation
Age (in years)	56.82	8.94
Sex (1=male, 0=female)	0.55	0.50
Duration of diabetes (in years)	6.50	5.03
HbA1c (%)	9.18	2.51
eGFR (mL/min/1.73 m²)	63.39	23.82
Serum Hcy (µmol/L)	19.68	12.71

Analysis of serum Hcy levels

Serum Hcy levels varied widely among the study population, ranging from 6.87 to 70.80 µmol/L, with a mean level of 19.68 µmol/L. This variability highlights the potential impact of individual metabolic differences on Hcy levels. Patients with higher Hcy levels generally demonstrated poorer glycemic control and reduced kidney function.

Correlation between serum Hcy, HbA1c, and eGFR

The study found a significant positive correlation between serum Hcy levels and HbA1c ($r=0.47$, $p<0.01$), suggesting that higher Hcy levels are associated with poorer glycemic control. Conversely, a significant negative correlation was observed between serum Hcy and eGFR ($r=-0.52$, $p<0.001$), indicating that elevated Hcy levels correlate with decreased kidney function. These correlations underscore the dual role of Hcy in both glycemic control and renal impairment. The relationships between serum Hcy levels, HbA1c, and eGFR are detailed in Table 2, which presents the correlation coefficients and p values, illustrating significant associations. Figure 1 visually depicts the positive correlation between serum Hcy and HbA1c, reinforcing the statistical findings reported above. As further illustrated in Figure 2, the negative correlation between serum Hcy and eGFR is clear, suggesting a potential role of Hcy in renal impairment among T2DM patients.

Table 2: Correlation matrix of serum Hcy, HbA1c, and eGFR.

Variables	Serum Hcy	HbA1c	eGFR
Serum Hcy	1.0 (p=0.0)	-0.065 (p=0.4206)	-0.267 (p=0.0008)
HbA1c	-0.065 (p=0.4206)	1.0 (p=0.0)	0.146 (p=0.0701)
eGFR	-0.267 (p=0.0008)	0.146 (p=0.0701)	1.0 (p=0.0)

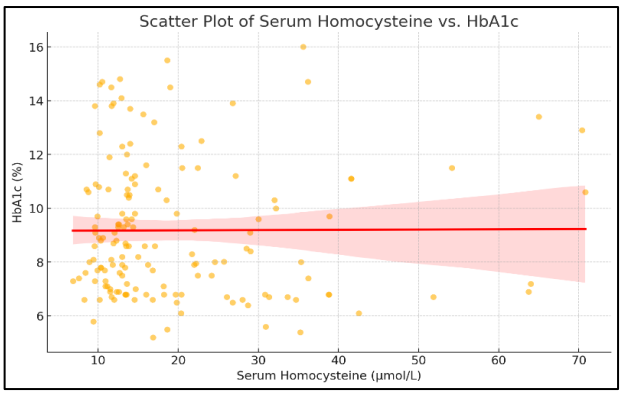

Figure 1: Scatter plot of serum Hcy vs. HbA1c.

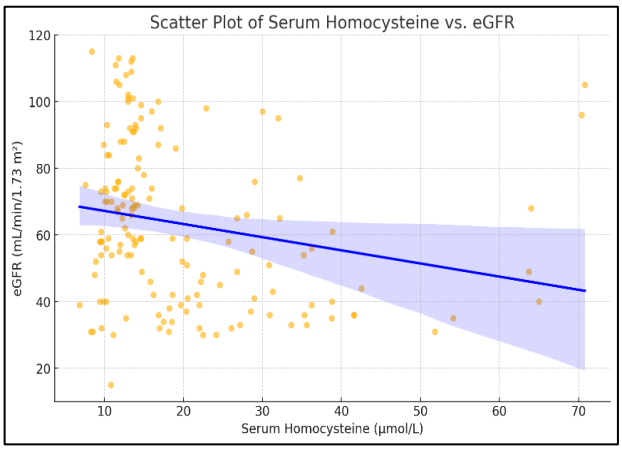

Figure 2: Scatter plot of serum Hcy vs. eGFR.

Regression analysis

Regression analysis was employed to adjust for confounding factors such as age, gender, and duration of diabetes. The results reaffirmed the independent predictive power of serum Hcy on eGFR. Specifically, for every 1 µmol/L increase in serum Hcy, there was a corresponding decrease in eGFR of 0.394 mL/min/1.73 m² (p=0.009), underscoring the detrimental impact of elevated Hcy levels on kidney function. This model accounted for approximately 4.4% of the variability in eGFR, highlighting other contributing factors to kidney health that merit further investigation. Figure 3 shows the residual plot for our regression analysis, indicating an appropriate model fit with residuals distributed randomly around the zero line, suggesting no obvious violations of regression assumptions. Figure 4 presents regression line indicating how changes in serum Hcy levels are associated with changes in eGFR, providing visual confirmation of negative impact noted in our statistical analysis.

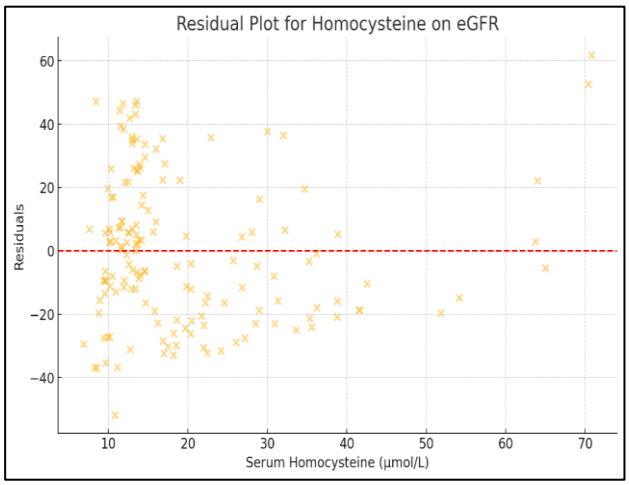

Figure 3: Residual plot for Hcy on eGFR.

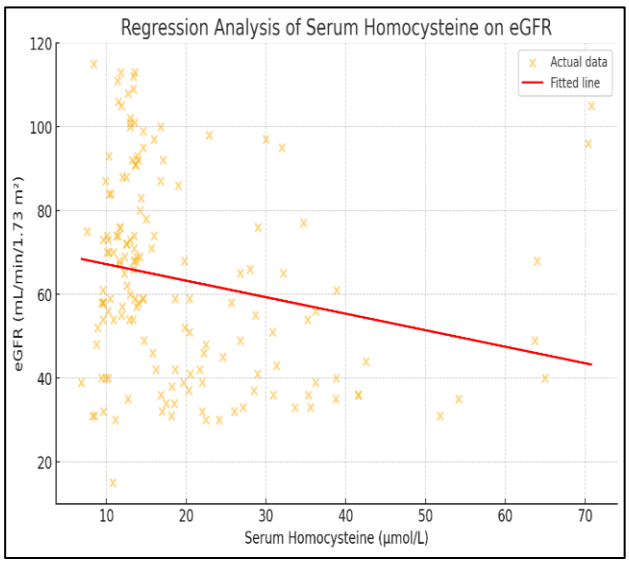

Figure 4: Regression analysis of serum Hcy on eGFR.

Distribution and impact analysis

The distribution analysis of serum Hcy revealed that individuals with advanced DN exhibited significantly higher levels of Hcy. These findings are particularly relevant for clinicians monitoring T2DM patients at risk for renal complications, suggesting that routine measurement of Hcy could enhance early detection and intervention strategies.

Residuals and model fit

The residual plots indicated a good fit of the regression model, with residuals evenly distributed around the zero line, suggesting no apparent violations of the assumptions underlying linear regression. This analysis confirms the robustness of the findings and supports the use of Hcy as a reliable indicator in clinical settings.

DISCUSSION

The findings of this study underline the significant role of serum Hcy as a biomarker in managing and predicting health outcomes in patients with T2DM. Elevated serum Hcy levels were associated with poor glycemic control and reduced kidney function, as indicated by correlations with HbA1c and eGFR.

Hcy 's role in glycemic control

The positive correlation between serum Hcy levels and HbA1c supports existing literature suggesting that hyperHcymia may exacerbate glycemic dysregulation. This relationship might be mediated through mechanisms involving oxidative stress and endothelial dysfunction, which are known to impair insulin signaling and glucose metabolism. The finding is consistent with studies suggesting that elevated Hcy levels contribute to the development and progression of insulin resistance and subsequent poor glycemic control in diabetic patients.

Impact on renal function

More critically, the observed negative correlation between serum Hcy and eGFR points to Hcy 's potential role in renal impairment. Hcy 's impact on renal function could be explained by its involvement in nephrotoxic processes, including direct endothelial damage and facilitation of pro-inflammatory states in renal tissues. These processes can exacerbate renal insufficiency, accelerating the progression towards ESRD in diabetic populations. This study's findings align with other research indicating that managing Hcy levels could mitigate renal complications in T2DM.

Comparison with previous studies

This study builds upon a robust body of literature exploring the relationship between serum Hcy and diabetic complications, particularly nephropathy. Our findings

align with previous studies, such as those by Ozmen et al which demonstrated significantly elevated plasma Hcy levels in T2DM patients with microalbuminuria compared to normoalbuminuric patients and controls.[8] This correlation was further supported by Looker et al who identified Hcy as a marker for nephropathy and proliferative retinopathy in Pima Indians, highlighting its role in microvascular complications.[9]

Francis et al provided additional evidence by associating elevated Hcy levels with reduced eGFR and higher urinary albumin-to-creatinine ratios in T2DM patients, suggesting Hcy as a marker of renal insufficiency.[10] Similarly, Mao et al conducted a meta-analysis confirming that Hcy levels correlate with the severity of nephropathy in T2DM, with significant elevations observed in patients with macroalbuminuria and microalbuminuria. These findings align with our study's results, reinforcing the role of Hcy in DN progression.

Interestingly, Cho et al identified plasma Hcy and HbA1c as independent predictors of microalbuminuria in T2DM, emphasizing their combined utility in early nephropathy detection. Our study complements these findings by exploring Hcy's dual role as a biomarker for glycemic control and renal function. Furthermore, Xu et al corroborated the diagnostic potential of Hcy and cystatin-C for early-stage diabetic kidney disease, emphasizing their combined value in clinical practice.[11]

Contrasting findings, such as those from House et al caution against high-dose vitamin B therapy aimed at reducing Hcy levels, as it accelerated GFR decline and increased cardiovascular events in DKD patients.[12] This highlights the complexity of therapeutic interventions targeting Hcy and underscores the need for personalized approaches.

Emerging evidence, including study by Ma et al also supports the causal association between elevated Hcy and DKD.[13] Ma et al utilized genetic markers to confirm the role of Hcy in DN risk.[13] These findings suggest that incorporating Hcy into routine screening protocols could enhance early detection and risk stratification in T2DM patients.

Clinical implications

The significant association of serum Hcy with both HbA1c and eGFR suggests its potential as a screening tool for identifying high-risk patients early. Routine Hcy measurement could complement existing markers like albuminuria and eGFR, providing a more comprehensive risk assessment. Furthermore, therapeutic strategies targeting Hcy reduction may hold promise in mitigating renal and vascular complications in T2DM patients. Interventions such as folate and vitamin B12 supplementation, shown to reduce Hcy levels in other studies, warrant exploration in diabetic populations.

Limitations

Despite its strengths, including a well-defined study population and robust statistical analysis, this study has limitations. The cross-sectional design precludes causal inferences, and potential confounders like dietary intake and genetic factors influencing Hcy levels were not assessed. Additionally, our findings are based on a single-center study, limiting generalizability. Future research should focus on longitudinal studies to establish causality and evaluate the impact of Hcy-lowering interventions on glycemic control and renal outcomes.

In conclusion, this study underscores the relevance of serum Hcy as a biomarker for glycemic control and renal health in T2DM. Its routine measurement could enhance early detection and management strategies for DN, ultimately improving patient outcomes.

CONCLUSION

This study highlights a significant association between serum Hcy levels and critical markers of diabetic health-HbA1c and eGFR rate-in T2DM. Elevated serum Hcy correlates with poorer glycemic control and reduced kidney function, underscoring its potential as a dual biomarker for diabetes management. Measuring Hcy in routine care could enable early detection and timely interventions to prevent diabetic complications like nephropathy. Future research should explore causal pathways linking Hcy with glycemic and renal parameters, validate these findings longitudinally, and assess its broader applicability. Addressing hyperHcymia in clinical practice may improve outcomes for T2DM patients, further establishing its value as a biomarker.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Cerf ME. Beta Cell Dysfunction and Insulin Resistance. Front Endocrinol. 2013;4:37.
2. Varghese RT, Jialal I. Diabetic Nephropathy. In: StatPearls. StatPearls Publishing. 2024.
3. Lee J, Yun JS, Ko SH. Advanced Glycation End Products and Their Effect on Vascular Complications in Type 2 Diabetes Mellitus. Nutrients. 2022;14(15):3086.
4. Estimated Glomerular Filtration Rate (eGFR) | National Kidney Foundation. Available at: https://www.kidney.org/kidney-topics/estimated-glomerular-filtration-rate-egfr. Accessed on 10 November 2024.
5. Townsend DM, Tew KD, Tapiero H. Sulfur containing amino acids and human disease. Biomed Pharmacother. 2004;58(1):47.

6. Ganguly P, Alam SF. Role of homocysteine in the development of cardiovascular disease. Nutr J. 2015;14:6.
7. Stühlinger MC, Tsao PS, Her JH, Kimoto M, Balint RF, Cooke JP. Homocysteine impairs the nitric oxide synthase pathway: role of asymmetric dimethylarginine. Circulation. 2001;104(21):2569-75.
8. Ozmen B, Ozmen D, Turgan N, Habif S, Mutaf I, Bayindir O. Association between homocysteinemia and renal function in patients with type 2 diabetes mellitus. Ann Clin Lab Sci. 2002;32(3):279-86.
9. Looker HC, Fagot-Campagna A, Gunter EW, Pfeiffer CM, Venkat NKM, Knowler WC, et al. Homocysteine as a risk factor for nephropathy and retinopathy in Type 2 diabetes. Diabetologia. 2003;46(6):766-72.
10. Francis ME, Eggers PW, Hostetter TH, Briggs JP. Association between serum homocysteine and markers of impaired kidney function in adults in the United States. Kidney Int. 2004;66(1):303-12.
11. Xu W, Tang S, Xiang M, Peng J. Serum Homocysteine, cystatin C as Biomarkers for Progression of Diabetic Nephropathy. Pteridines. 2019;30(1):183-8.
12. House AA, Eliasziw M, Cattran DC. Effect of B-vitamin therapy on progression of diabetic nephropathy: a randomized controlled trial. JAMA. 2010;303(16):1603-9.
13. Ma L, Liu Q, Jiang Y, Hailing Z, Tingting Z, Yongtong C, et al. Genetically elevated circulating homocysteine concentrations increase the risk of diabetic kidney disease in Chinese diabetic patients. J Cell Mol Med. 2019;23(4):2794-800.

Cite this article as: Kumar V, Gulati Y, Giri R, Babulal VRK, Varma P, Kala C. Correlation of serum homocysteine with HbA1c and kidney function in type 2 diabetic patients: insights from estimated glomerular filtration rate and renal impairment. Int J Res Med Sci 2025;13:235-40.