Original Article

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Distribution of Homocysteine Levels in Type 2 Diabetes Patients and Its Association with Urine Albumin Creatinine Ratio: A Cross-sectional Study

Biochemistry Section

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ABSTRACT

Introduction: Homocysteine (Hcy) is a metabolite whose level increases with age, in patients with Vitamin B12 deficiency, and is associated with increased risk of Cardiovascular Disease (CVD). Diabetes patients have been reported to have an increased prevalence of B12 deficiency and have a higher than baseline risk for CVD.

Aim: To assess the distribution of serum Hcy levels in type 2 diabetes patients and to study its association with Urine Albumin:Creatinine Ratio (UACR).

Materials and Methods: This cross-sectional study was conducted at the Diabetes Clinic, Department of Medicine (OPD), Gujarat Medical Education and Research Society (GMERS) Medical College and General Hospital, Gotri, Vadodara, India, from February 2025 to July 2025. Demographic data were collected along with testing for eGFR, serum Hcy and UACR. The study participant data were sub-grouped into Group 1 (n=55): participants with UACR <300 mg/g creatinine and Group 2 (n=25) UACR >300 mg/g creatinine. The distribution of Hcy was described as mean and Standard Deviation (SD). Pearson's and Spearman's correlations were used to assess the correlation of serum Hcy with FBS, eGFR and UACR. Participants were further sub-grouped based on UACR values, and Hcy levels were compared between these groups using a t-test.

Results: The study cohort had 31 males and 49 females, with a mean age of 49.3±11.5 years, and the median duration of diabetes was two years. The serum Hcy level was found to be 16.68±8.01 µmol/L among type 2 diabetic patients. The sub-group of diabetic patients with UACR >300 mg/g creatinine had higher serum Hcy levels of 19.09±11.21 µmol/L, when compared to the sub-group with UACR <300 mg/g creatinine, in whom the distribution was 15.58±5.84 µmol/L.

Conclusion: The distribution of serum Hcy among diabetic individuals was higher than the normal reference range. It is not influenced by age, gender or duration of diabetes. It increases further as renal damage gets established with UACR >300 mg/g creatinine.

Keywords: Cardiovascular disease, Diabetic nephropathy, Fasting glucose, Metabolites, Microalbuminuria

INTRODUCTION

Diabetes is a lifestyle disease, with high prevalence in India and worldwide. Based on the Global Burden of Disease Data from 1990 to 2021, the incidence of diabetes in India has been reported to have increased from 162.74 to 264.53 per 100,000, during this period [1]. Diabetes can lead to multiorgan complications broadly divided into microvascular and macrovascular complications, including increased risk of CVD [2]. Diabetic retinopathy, diabetic neuropathy and diabetic nephropathy are microvascular complications, with microalbuminuria being the earliest clinical indicator of diabetic nephropathy [2,3]. Microalbuminuria is also found to increase the risk of development of macrovascular complications, including CVD, in diabetic individuals [4].

The Hcy is a biological metabolite and intermediate of the methionine and cysteine biosynthesis pathway. A variety of factors can influence serum Hcy levels, ranging from polymorphisms of the genes encoding enzymes of the remethylation and trans-sulphuration pathways of Methionine-Cysteine metabolism, to deficiency of the vitamins B12, folic acid and B6, involved in the same pathway. High levels of Hcy cause damage to the endothelium, which in conjunction with inflammation and hypercoagulability, promote atherosclerosis and therefore increased risk of CVD [5].

Since, high Hcy levels and increased urine albumin excretion are independently associated with damage to the endothelium, and can contribute to complications of diabetes [5,6], the study was planned to assess the distribution of Hcy in Indian diabetic patients and evaluate its association with UACR levels. Plasma Hcy has been previously studied in Indians but is often studied in association with hypertension, CVD and Chronic Kidney Disease (CKD) [7-9]. There are few studies on Hcy levels in Indian diabetics, and they focus on correlation with diabetic nephropathy and therefore include study populations with low GFR [10,11].

Decline in GFR to less than 60 mL/min is a precursor for hyperhomocystinaemia, defined as plasma levels more than 12 µmol/l [12]. So, low GFR is a confounding factor, and such patients with raised Hcy levels could actually be an effect of low renal function itself [13,14]. To get a clear assessment of the distribution of serum Hcy in diabetics, this study includes type 2 diabetes individuals with eGFR >60 mL/min only. Among this study population with eGFR >60 mL/min, the correlation between serum Hcy and UACR was also assessed, independent of the influence of decline in glomerular function below 60 mL/min, observed in previous studies [10,11]. The objective of the study is to evaluate the distribution of serum Hcy in Diabetic patients and assess its association with UACR.

MATERIALS AND METHODS

This cross-sectional study was conducted at the Diabetes Clinic, Department of Medicine (OPD), Gujarat Medical Education and Research Society (GMERS) Medical College and General Hospital, Gotri, Vadodara, India, from February 2025 to July 2025. The hospital and associated medical college are funded by the government, and therefore all individuals with diabetes attending the diabetes OPD at

the hospital receive free-of-cost care. Approval of the Institutional Human Ethics Committee was obtained before beginning the research project (letter no. IHEC/25/OUT/FR0025, dated 10/02/25). Informed consent was obtained from the patient and from an impartial witness, in the case of illiterate patients. Patient's confidentiality was maintained by assigning IDs to them. All data were de-identified during entry into Excel sheets for data analysis.

Inclusion criteria: Individuals in the age group 18 to 70 years, with a type 2 diabetes diagnosis, with a duration of diabetes less than 25 years, were included in the study. Patients on oral hypoglycaemic agents and/or Insulin were also included in the study. Diabetes patients with controlled as well as uncontrolled diabetes were included in the study.

Exclusion criteria: Individuals with a history of alcoholism and smoking were excluded. Individuals aged more than 70 years and with eGFR <60 mL/min/1.73m2, were also excluded because advanced age and decline in renal function are known to be associated with nutritional deficiencies, which lead to increased serum Hcy levels [11]. Individuals with additional co-morbid conditions such as CVD, Chronic Renal Failure (CRF) and hypothyroidism were excluded. Individuals on medications known to elevate Hcy levels (e.g., methotrexate) were also excluded.

Sample size calculation: The primary objective of the study was to evaluate the distribution of Hcy in type 2 diabetes patients. The sample size was calculated by using the following formula-

$n=Z1-\alpha/2\ SD2/d2$.

The sample size obtained was 56, with an SD of 3.7 [10] and absolute error (d)=1, for 95% Confidence Interval (CI). Convenience sampling was used to sample the study population. A total of 80 study subjects were enrolled.

Study Procedure

The information collected from the study participants included age, gender, duration of diabetes and a detailed medical and drug history, to exclude the co-morbid conditions listed in the exclusion criteria. A blood sample of 4 mL was collected in a plain vacutainer and 2 mL in a fluoride vacutainer to estimate serum creatinine, Hcy and fasting plasma glucose, respectively. A random urine sample (10 to 25 mL) was collected in sterile containers to estimate UACR.

Serum creatinine estimation was performed by Jaffe's method on a Roche c311 analyser, with a reference range for males of 0.7 to 1.2 mg/dL and females 0.5 to 0.9 mg/dL [11]. Serum Hcy estimation was performed by the immunoturbidimetry method, with Diasys Hcy reagent on EM 200 analyser. The reference range in the kit is mentioned as 6 to 14 µmol/L for females and 6 to 17 µmol/L for males [12]. Fasting plasma glucose was estimated by the hexokinase method on a Roche C311 analyser. Interpretation of blood glucose values was done as per ADA guidelines [13]. Urinary albumin was quantitatively estimated by an immunoturbidimetric method using the DiaSys Albumin in Urine/CSF FS (Microalbumin) reagent kit on an EM 200 analyser.

Urine creatinine was also estimated by the Jaffe method on the EM 200 analyser, with suitable sample dilution. Urine microalbumin concentration was expressed as mg/g creatinine by dividing the microalbumin concentration (mg/dL), by creatinine conc (mg/dL), and multiplying by 1000. The UACR of <30 mg/g creatinine was interpreted as normal; 30-300 mg/g creatinine is microalbuminuria, and >300 mg/g creatinine is macroalbuminuria or frank albuminuria [14]. The study participant data were sub-grouped into group 1 (n=55): participants with UACR <300 mg/g creatinine and group 2 (n=25) UACR >300 mg/g creatinine. eGFR was calculated using the CKD-EPI equation, with serum creatinine estimated using the ID-MS traceable method [15]. All the information collected was entered in case record forms. The information was then transferred to an Excel sheet for data analysis.

The individuals with type 2 diabetes attending the diabetes OPD were screened using the exclusion criteria for suitability to enroll in the study. Such individuals were then given details of the study procedure using a hard copy of the patient information sheet. Individuals who consented to participate in the study were included after signing the informed consent sheet. After collection of demographic and clinical details in the case record form, they were referred to the sample collection centre for collection of blood and urine samples. All the laboratory tests were performed in the biochemistry laboratory, using reagents and equipment mentioned under study variables.

STATISTICAL ANALYSIS

The data collected were manually entered into Excel sheets. All study variables were tested for normality of distribution. Mean ± SD or median-IQR was calculated within the Excel sheet, as per the distribution of the study variable. To assess correlation of Hcy with different patient demographic, clinical and laboratory variables, Pearson's correlation or Spearman's correlation was used for continuous variables. When comparing the Hcy levels between sub-groups defined based on gender or UACR sub-classifications, a t-test was used. All statistical testing was performed using statistical calculators available at https://www.socscistatistics.com/. The calculation of CIs was done using relevant calculators available at https://www.statskingdom.com/.

RESULTS

The study participants (N=80) were predominantly middle-aged, with more female participants than male participants. Most study participants 57 (71.3%) had diabetes for less than five years, with a median duration of two years [Table/Fig-1].

S. No.	Study population characteristic	Distribution
1.	Age	49.3±11.5 years*
2.	Gender (M:F Ratio)	31:49
3.	Duration of diabetes	Median 2 years, IQR 0.5 - 5 years

[Table/Fig-1]: Distribution of the demographic variables in the study participants (N=80).
Foot note: The distribution of parametric data (*) is expressed as mean (SD) and that of nonparametric data is expressed as median and Interquartile range (IQR).

There were 17 individuals with UACR in the normal range (<30 mg/g creatinine), 38 individuals with microalbuminuria (UACR 30 – 300 mg/g creatinine) and 25 individuals with albuminuria (UACR >300 mg/g creatinine). A total of 43 of the study participants were found to have elevated Hcy levels [Table/Fig-2]. The 95% CI for the mean of serum Hcy was found to be 16.68±1.78 (14.9 - 18.46) µmol/L.

S. No.	Study population characteristic	Distribution
1.	Fasting Plasma Glucose (FPG)	150.4 (87.8) mg/dL*
2.	Serum creatinine	0.78 (0.18) mg/dL*
3.	eGFR	100.1 (17.3) mL/min*
4.	Urine Albumin: Creatinine Ratio (UACR)	Median 138.1 mg/g creatinine IQR: 49.5 to 412.6 mg/g creatinine
5.	Normoalbuminuria subjects Microalbuminuria subjects Macroalbuminuria subjects (%)	21.25% 47.5% 31.25%
6.	Serum Homocysteine (Hcy)	16.68 (8.01) µmol/L*
7.	Participants with normal Hcy	46.25 %

[Table/Fig-2]: Distribution of the laboratory variables in the study participants (n=80).
Footnote: The distribution of parametric data (*) is expressed as mean (SD), and that of nonparametric data is expressed as median and Interquartile range (IQR).

The correlation of Hcy levels with other study variables was assessed to identify any participant variable which may be a determinant of Hcy distribution in diabetic individuals. None of the study variables

was found to correlate with Hcy levels observed in the study participants [Table/Fig-3].

S. No.	Study variables	Correlation with Serum Homocysteine (Hcy)	
		r-value	p-value
1.	Age* (in years)	-0.01	0.96
2.	Gender†	0.07	0.54
3.	Duration of diabetes‡	-0.16	0.16
4.	Fasting Plasma Glucose (FPG)*	0.06	0.58
5.	Serum creatinine*	-0.11	0.34
6.	eGFR*	0.14	0.22
7.	Urine Albumin:Creatinine Ratio (UACR) ‡	0.06	0.60

[Table/Fig-3]: Results of statistical analysis of correlation between distribution of serum Homocysteine (Hcy) with study variables (characteristics of the study population).
Footnotes: *Pearson's correlation test was used for variables with normal distribution. †Point Biserial Correlation test was used for categorical variable. ‡Spearman correlation test was used for variables with non-normal distribution.

The study participant data were sub-grouped into group 1 (n=55): participants with UACR <300 mg/g creatinine and group 2 (n=25) UACR >300 mg/g creatinine. UACR distribution in both subgroups was non normal, with a median of 79.8 (IQR 11.8 - 141.1) mg/g creatinine in group 1 and a median 1031 (IQR 505.5 - 1551.2) mg/g creatinine in group 2. In group 1, mean serum Hcy was 15.58 µmol/L, and in group 2 the mean value was 19.09 µmol/L [Table/Fig-4].

S. No.	Parameters	Group 1 n=55	Group 2 n=25	Results of statistical tests of significance
1.	Age*	48.99 (10.56)	49.84 (13.44)	t(78)=-0.31, p=0.760, Cohen's d=0.07
2.	Gender† (M:F Ratio)	18:37	13:12	$\chi^2(1)$=2.69, p=0.101, Cramér's V=0.18
3.	Duration of diabetes ‡ (in years)	2 (IQR 0.5-4.5)	3 (IQR 1 – 6.5)	U=574.50, p=0.241.
4.	Fasting Plasma Glucose (FPG)*	136.2 (75.8)	181.7 (104.7)	t(78)=-2.20, p=0.031, Cohen's d=0.53
5.	Serum Creatinine*	0.78(0.18)	0.78 (0.18)	t(78)=-0.01, p=0.990, Cohen's d=0.00
6.	eGFR*	99.71 (15.93)	100.96 (20.26)	t(78)=-0.30, p=0.766, Cohen's d=0.07
7.	Serum Homocysteine (Hcy)*	15.58 (5.84)	19.09 (11.21)	t(78)=-1.85, p=0.034, Cohen's d=0.45 (with single tail hypothesis) (t(78)=-1.85, p=0.069, Cohen's d=0.45 (with two tailed hypothesis)

[Table/Fig-4]: Distributions of study variables in Group 1: individuals with UACR <300 mg/g creatinine and Group 2: UACR >300 mg/g creatinine.
Footnotes: *Parameters with normal distribution; significance of difference of means was tested with an Independent-samples t-test. †Nominal parameter; significance of difference of proportions was tested with Chi-square test. ‡Parameter with non normal distribution, Mann-Whitney U test was used to test for significance of difference of distribution; In order to analyse whether macroalbuminuria had a significant effect on serum Hcy level, the participants were grouped into UACR <300 mg/g creatinine and UACR >300 mg/g creatinine. The reason for merging participants with normoalbuminuria and microalbuminuria is that microalbuminuria is reversible.

Since moderate significance in the difference in mean FPG and mean Hcy was found between the two subgroups, the 95% CI for the mean difference was calculated. In the case of serum Hcy, the 95% CI was (-1.34, 8.36) µmol/L and for FPG, it was (-1.77, 92.73) mg/dL, calculated via Welch's method for unequal variances.

DISCUSSION

In the current study, the distribution of serum Hcy levels in type 2 diabetes individuals was found to be 16.68±8.01 µmol/L. This is higher than the commonly used reference interval for plasma Hcy, which is 5 to 15 µmol/L. There is only one Hcy reference interval study in apparently healthy Indians, where they reported mean plasma Hcy levels as 11.46±2.56 µmol/L in males and 11.41±2.48 µmol/L in females [16]). The 2.5th percentile was 6.5 (0.90 CI=6.3–6.7) µmol/L and the 97.5th percentile was 16.38 (0.90 CI=16.2-16.6) µmol/L.

A comparison of serum Hcy levels reported in various studies among Indian diabetic patients is shown in [Table/Fig-5] [10,17,18]. It is observed that the distribution of serum Hcy in diabetic patients is generally higher than the reference range and increases in patients with diabetic nephropathy and reduced eGFR. Only the study by Singla H et al., reports normal Hcy levels in diabetics without microalbuminuria [10]. The microalbumin testing in this study was performed using NYCocard, which generally exhibits lower precision and higher variability at low and medium concentration ranges of microalbumin. The PPV is 38-62 %, indicating that the positive microalbumin results obtained should be confirmed with other quantitative laboratory tests [19]. The mean FPG of 150.4 mg/dL (observed in the current study) corresponds to HbA1c of 7.97%, as per the linear regression equation developed by Barua A et al., [20]. This is likely the reason for the higher Hcy levels observed in the current study.

Study and year	Population/ region	Sample size (n)	Study design	Key parameters	Main clinical finding
Junaidi AA et al., 2020 [17]	Indians/ Nanded, Maharashtra	120	Case control study	BP and Hcy levels	Hcy level 17.13±7.11 µmol/L in Diabetics without HT and 20.51±6.92 µmol/L, in Diabetics with Hypertension
Singla H et al., 2015 [10]	Indians/ Faridkot, Punjab	120	Case control study	FBS, Glycated Haemo-globin, Hcy and UACR	Hcy level 10.8±3.7 µmol/L in diabetics without microalbuminuria, 19.3±6.5 µmol/L in Diabetics with microalbuminuria.
Kumar V et al., 2024 [18]	Indians/ Kanpur, Uttar Pradesh	156	Cross sectional study	Hcy, eGFR, UACR	Mean Hcy levels 21.69 µmol/L in patients with Diabetic nephropathy and 13.1 µmol/L, in Diabetics without nephropathy. (SD not reported)
Current study (2026)	Indians/ Vadodara, Gujarat	80	Cross sectional study	FBS, Hcy, eGFR, UACR	Distribution of serum Hcy in Diabetics 16.68±8.01µmol/L. Sub-group evaluation shows 19.09±11.21 µmol/L among Diabetics with UACR >300 mg/g creatinine

[Table/Fig-5]: Comparison of Serum Homocysteine (Hcy) levels reported in other research studies on Indian diabetic patients [10,17,18].

Studies from outside India: The distribution of Hcy in diabetic individuals of European descent is similar to the distribution in the present study. A 2014 study by Malaguarnera G et al., on 175 consecutive diabetic patients, compared the distribution of Hcy in diabetic individuals without retinopathy (12.1±6.8 µmol/L), with non proliferative retinopathy (14.4±6.7 µmol/L) and proliferative retinopathy (18.2±5.6 µmol/L) [21]. They reported that all sub-groups of diabetic individuals had serum Hcy distribution higher than levels observed in apparently healthy individuals, which was 7.8±6.4 µmol/L.

The elevation of serum Hcy with impairment in glycaemic control is reported in hypertensives too. Fu D et al., studied the association of comorbidity of diabetes with an increase in Hcy level in hypertensives and found an OR of 1.17 (95% CI, 1.01-1.35), per interquartile range

increment in Hcy level [22]. The overall Mean±SD of total Hcy for the study population was 18.45±12.15 µmol/L.

Surprisingly, the distribution of Hcy among Japanese diabetics is different from the values discussed above. The study by Masuda Y et al., reports the concentration of total Hcy as 12.28±7.23 µmol/L among diabetic males and 9.99±4.39 µmol/L among diabetic females [23]. Even though these values are lower than values commonly reported among diabetics, even in this population group the association with hyperglycaemia is evident, as the healthy Japanese controls had Hcy distributions of 10.75±3.39 µmol/L among males and 8.41±2.40 µmol/L among females [23].

The distribution of serum Hcy was found to have high dispersion in the current study population, with SD of 8.01 µmol/L. This is possibly due to larger variation in FPG distribution (FPG 150.4±87.8 mg/dL) and UACR distribution (138.1; IQR 49.5- 412.6) mg/g creatinine among the study participants.

There was no association of serum Hcy levels with UACR in the current study population, when assessed with Spearman's Correlation test. Since the studies by Singla H et al., and Kumar V et al., have reported an association with Diabetic nephropathy, we analysed the possible reasons for the lack of association in our study [10,18]. The foremost reason could be the exclusion of diabetics with eGFR <60 mL/min. This decision was taken to remove the effect of increased Hcy due to renal failure. Since the above studies used eGFR <30 mL/min as a cut-off for exclusion, their study participants may have included individuals with CRF.

The second reason for the lack of association could be the wide range of UACR values in this study population. When sub-grouping of data was done based on UACR levels, as "Patients with normal-to-moderate albuminuria", that is UACR <300 mg/g creatinine (n=55), and "Patients with macroalbuminuria", that is UACR >300 mg/g creatinine (n=25) [Table/Fig-4], the association of serum Hcy elevation with UACR increase could be identified. Serum Hcy level was 19.09±11.21 µmol/L among "Patients with macroalbuminuria", numerically higher, but not statistically significant in the two-sided analysis than the level of 15.58±5.84 µmol/L in "Patients with normal-to-moderate albuminuria". The difference in Hcy levels corresponded to a small-to-medium effect size (Cohen's d=0.42), indicating moderate practical importance. This association, however, became "not significant" if a two-tailed hypothesis was assumed. Further, the two subgroups have a difference in the distribution of FPG, which is statistically significant. These observations indicate the necessity of a larger sample size to make the association of UACR with serum Hcy explicit.

The current study consolidates the finding of increased Hcy levels in diabetic individuals. This finding is of importance as increased Hcy levels increase the risk of cardiovascular as well as all-cause mortality, in the general population as well as in diabetics [24,25]. Since diabetic individuals are at increased risk of elevated Hcy levels even at baseline, which may be aggravated by nephropathy and vitamin B12 deficiency, which is common in Diabetic patients [26,27], regular monitoring of serum or plasma Hcy is necessary.

Serum Hcy level can be brought down in diabetics, comparable to the control group, by increased consumption of fish, fruit and vegetables. Such a modified diet, along with high plasma folate levels, has been reported to be associated with normal Hcy levels in Mediterranean diabetic individuals [28].

Limitation(s)

The current study population included a significant proportion of patients with microalbuminuria, which could have increased the overall Hcy levels. The FPG distribution also shows a higher proportion of patients with poorly controlled diabetes, which could have also contributed to higher Hcy distribution in the study population.

CONCLUSION(S)

The mean serum homocysteine concentration was elevated relative to commonly cited reference values in this cohort of patients with type 2 diabetes mellitus. Serum homocysteine was not significantly correlated with UACR in the overall study population. Exploratory subgroup analysis demonstrated a higher mean homocysteine concentration among participants with UACR >300 mg/g creatinine; however, this difference was not statistically significant in the two-sided analysis. Larger, adequately powered prospective studies incorporating serum levels of vitamin B12, folate and other potential confounding factors are warranted to clarify the relationship between homocysteine and albuminuria in type 2 diabetes mellitus.

Authors' contribution: LA, AC and HJ: Contributed equally to conceptualisation, methodology, data analysis, and writing of the original draft; PP: Contributed to data acquisition, data analysis and report writing. All authors contributed to the review and editing of the original and revised manuscript, and approved the final manuscript submitted.

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