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Homocysteine levels and cardiovascular disease risk factors in chronic kidney disease (CKD), hypertensive and healthy Nigerian adults: a comparative retrospective study

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ABSTRACT

Objectives To investigate homocysteine (Hcy) levels in individuals with chronic kidney disease (CKD), hypertension and a healthy Nigerian population, and to assess their association with cardiovascular disease (CVD) risk.

Setting The study was conducted using data from the Ibadan CRECKID (Cardiovascular and Renal Event in People with Chronic Kidney Disease) study in Nigeria.

Participants A total of 420 adults (aged 18+) categorised into three groups: individuals with stage 2 CKD or higher, hypertensive non-CKD individuals and normotensive individuals.

Outcomes The primary outcome was the difference in serum Hcy levels across the groups; secondary outcomes included the prevalence of hyperhomocysteinaemia (HHcy) and correlation with fibroblast growth factor (FGF).

Results No significant difference in mean serum Hcy levels among the CKD, hypertensive and healthy groups (p=0.39) was observed. However, HHcy (≥15 µmol/L) prevalence was significantly higher in the hypertensive group (p<0.05). A strong positive correlation between Hcy levels and FGF was identified across all groups (p<0.001).

Conclusions The present study indicates that Hcy levels may not serve as a reliable predictor of CVD outcomes across populations with varying kidney function and CVD risk profiles.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study includes a diverse Nigerian sample with chronic kidney disease, hypertensive and healthy participants, enabling group comparisons.
⇒ Homocysteine (Hcy) levels were objectively measured, providing direct data for analysis.
⇒ Retrospective data limit the ability to infer causation between Hcy and cardiovascular disease outcomes.
⇒ Variability in participant age between groups could influence Hcy measurements.
⇒ Reliance on a single Hcy measurement does not capture longitudinal variation.

INTRODUCTION

Cardiovascular diseases (CVDs) continue to pose a substantial global health challenge, accounting for a considerable burden of morbidity and mortality, especially in low- and middle-income countries.[1] Various prevalence studies in Nigeria have demonstrated differences in the pattern and profile of CVDs, and according to the WHO, non-communicable diseases accounted for 30% of all deaths in Nigeria, with CVDs contributing to 11% of these cases.[2 3] Adedapo,[4] in a study in southwestern Nigeria, revealed a significant increase of 150% in CVD risk prevalence over 20 years, a finding consistent with several studies across the country.[5–7]

Among the various risk factors for CVD, homocysteine (Hcy), a sulfur-containing amino acid derived from methionine metabolism, has received considerable attention in recent decades.[8 9] Hcy is present in plasma in four different forms: free thiol, disulfide-bound to plasma proteins, Hcy dimer and mixed disulfides with other thiols, and its levels are influenced by genetic and environmental factors. These factors include the methylenetetrahydrofolate reductase gene polymorphism, dietary intake of B vitamins (folate, vitamin B_6 and B_{12}), smoking, alcohol consumption and renal function.[10–12] The recycling of Hcy involves its conversion back to methionine or its conversion to cysteine, facilitated by specific B vitamins (such as vitamin B_6, B_{12} and folic acid) (figure 1). Low levels of these vitamins can result in the accumulation of Hcy in the bloodstream, known as hyperhomocysteinaemia (HHcy). HHcy (>15 µmol/L)[13] has been associated with increased oxidative stress, endothelial dysfunction, inflammation, thrombosis and vascular smooth muscle cell proliferation,

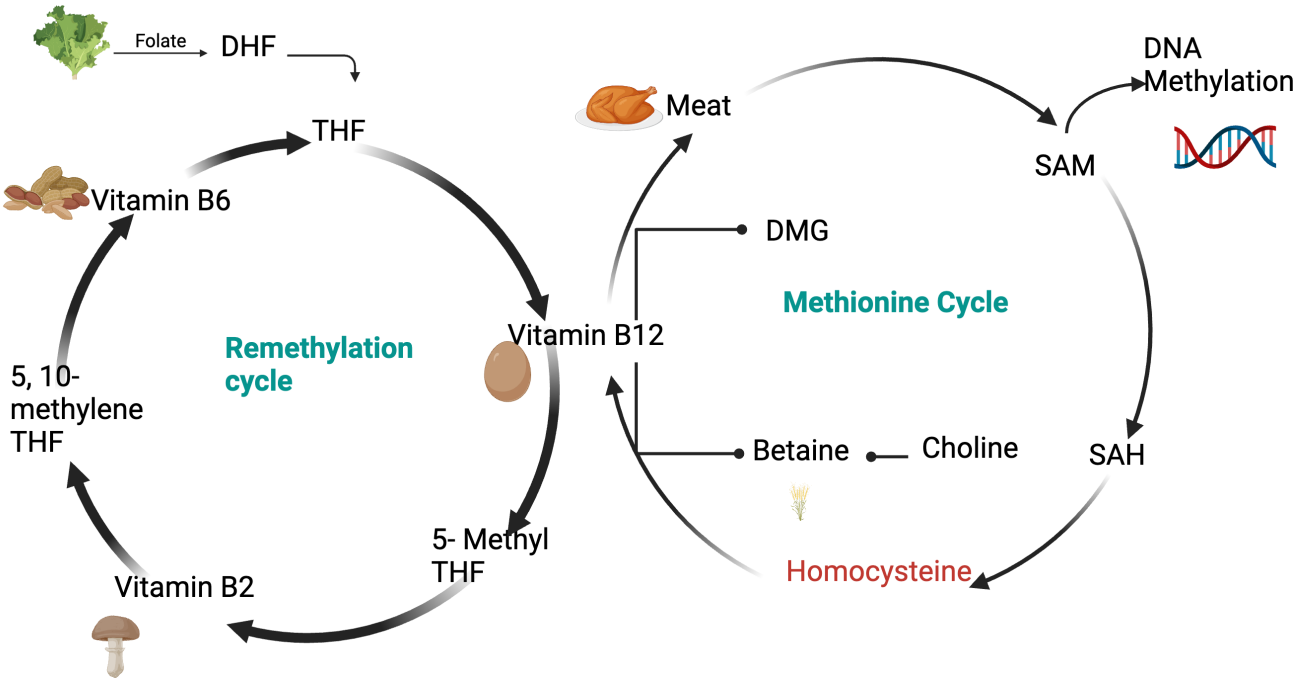

Figure 1 Diagram of the homocysteine metabolic pathway, showing the remethylation and trans-sulfuration pathways. Images of foods that are sources of key molecules in the pathway are also included. DHF, dihydrofolate; DMG, N,N-dimethylglycine betaine; Met, methionine; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine; THF, tetrahydrofolate.

which may contribute to the development and progression of atherosclerosis and CVD.[12 14]

One modifying factor that may influence the relationship between Hcy and CVD is chronic kidney disease (CKD).[15] CKD is a growing public health problem worldwide, affecting about 11%–13% of the adult population.[16] In a community-based study in China, high Hcy levels emerged as an independent predictor of renal function decline among patients with CKD. This is due to impaired renal clearance and reduced availability of cofactors for Hcy metabolism.[17 18] The relationship between Hcy and CVD in patients with CKD has been investigated in several studies, but the results are inconsistent and inconclusive.[15 18] Hcy concentrations surpassing 20.0 µmol/L are linked to a 4.5-fold surge in mortality rates.[19–21] The prevalent rise of HHcy in individuals with CKD has heightened curiosity regarding its potential role in influencing CKD advancement and CVD. While some studies suggest that therapies reducing Hcy levels using B vitamins can reduce CVD incidents or mortality in patients with CKD, others indicate no advantages or even potential detrimental effects.[21–23] In individuals with end-stage renal disease, prospective analyses have demonstrated that an increment of 5 µmol/L in Hcy concentration is concomitant with a 7% increase in the risk of total mortality and a 9% increase in the likelihood of cardiovascular incidents. Interventional studies employing B vitamin supplementation have evidenced a decrement in Hcy levels, ranging from 13 to 31 µmol/L, which is associated with a 27% reduction in cardiovascular event risk.[24] Conversely, in the meta-analysis conducted by Pan *et al*, which included 10 studies focusing on patients with CKD, Hcy-lowering therapy did not demonstrate an association with a reduction in CVD, stroke or all-cause mortality.[25]

Another important aspect that needs to be considered is the comparison of Hcy levels and CVD risk between patients with CKD and other populations with different degrees of kidney function or CVD risk. For example, hypertensive individuals are known to have higher Hcy levels than normotensive individuals and a higher risk of CVD.[26] Pertinent to the debate above, the relationship between Hcy levels and hypertension was found to be significantly higher among the hypertension group ($p<0.05$) in a study by Yang *et al*.[27] Additionally, healthy individuals may have lower Hcy levels and lower CVD risk than CKD or hypertensive individuals, but they may also have different genetic or environmental factors that affect their Hcy metabolism and CVD susceptibility.

In Nigeria, CKD and hypertension are prevalent,[28] and both conditions are known to exacerbate cardiovascular risk, yet the interplay between Hcy levels and these diseases remains poorly understood. Most research has predominantly centred on contrasting two specific groups: those with hypertension and healthy individuals. These studies have consistently shown a higher prevalence of Hcy in the hypertensive group compared with the healthy group.[29–31] However, this study aimed to broaden the scope by examining Hcy levels across three distinct groups. The study will explore the relationship between Hcy levels and conventional CVD risk in individuals with

CKD, hypertension and healthy populations, using data and insights obtained from the Ibadan Cardiovascular and Renal Event in People with Chronic Kidney Disease (CRECKID) study.[32 33] This study provides a unique opportunity to examine the relationship between Hcy and CVD in a population where few studies have been conducted.

METHODS

Subjects and methods

Data for this study were retrospectively collected from the CRECKID study, a prospective study conducted in Ibadan, Nigeria.[32 33] The CRECKID study's primary objective was to identify high-risk CKD individuals for serious cardiovascular events and ensure they receive timely treatment. Participants were adults aged 18 years and older, enrolled from the Cardiology and Nephrology outpatient department unit of the University College Hospital, Ibadan.

Inclusion and exclusion criteria

The study collected data for adult participants aged 18 years and above, diagnosed with at least stage 2 CKD (estimated glomerular filtration rate (eGFR)=60–89 mL/min) for a minimum of 3 months. Additionally, hypertensive non-CKD individuals, defined by anti-hypertensive medication usage or an average blood pressure (BP) reading of >140/90 mm Hg, and normotensive individuals who consented were included. Individuals below 18 years, those with a history of kidney transplantation or those who declined consent were excluded.

Sample size and power calculations

The sample size and power calculation were performed using G*Power software (V.3.1.9.7). The calculation aimed to estimate the required sample size to achieve a power of 80% while detecting a minimum effect size of 0.25 with a significance level of 0.05. An effect size of 0.25 was selected for power calculations based on previous studies reporting moderate associations between Hcy levels and cardiovascular outcomes, including findings from CKD and hypertensive populations.[34 35] Based on the provided parameters and using the analysis of covariance (ANCOVA) statistical test, G*Power computed a total sample size of 269 participants. The numerator df for the statistical test were set at 10. To allocate an equal number of participants to each group, the total sample size (269) was divided by the number of groups (3) to obtain an equal distribution. In this case, each group required approximately 89 participants.

Data collection

The following data were retrieved and analysed anonymously. It contained demographic information, CKD duration and cause, history of hypertension and diabetes mellitus, previous valvular heart disease, heart surgery, kidney transplant, social history, lifestyle factors, history of stroke or coronary artery disease, family history of hypertension or kidney disease, and current medications. Anthropometric measurements, BP readings, electrocardiography, echocardiography and laboratory parameters were also retrieved. Key laboratory parameters such as serum creatinine, urea, cholesterol, triglycerides, high-density lipoprotein (HDL), C reactive protein (CRP), fasting blood sugar (FBS), fibroblast growth factor (FGF), and notably, plasma Hcy concentration were included in the analysis. Although other CVD markers, such as low-density lipoprotein and inflammatory cytokines (eg, interleukin 6), are also relevant, they were excluded from this analysis due to limitations in data availability.

Laboratory measurements

Venous blood samples were collected from participants after an overnight fast. The collected blood samples were used to measure various components, including serum creatinine, lipid panel (total cholesterol, high-density cholesterol, low-density cholesterol and triglycerides), blood glucose levels and plasma Hcy concentration. Glucose levels were measured using the glucose oxidase method, while the lipid profile was determined using an enzymatic colourimetric method. Plasma Hcy concentration was quantified using the Human Homocysteine (HCY) ELISA kit from Fine Test, China (Catalogue No EH4011) as per the manufacturer's instructions. HHcy was defined as plasma Hcy levels of >15 µmol/L, consistent with thresholds established in previous studies.[13 36] For the analysis, Hcy levels were stratified into two categories: normal Hcy: ≤15 µmol and elevated Hcy (HHcy): >15 µmol/L. Mean Hcy levels among individuals with HHcy were further calculated and compared across the groups.

Blood pressure measurement

BP measurements were conducted using a standard Omron (HEM711DLX) device. The measurements were taken on the subject's left arm, positioned at heart level after a 5-min rest. A cuff of appropriate size was used, and the subject was in a seated position with their legs uncrossed. Following the guidelines set by the WHO, three BP readings were obtained with a minimum interval of 1 min. The average of the last two readings was used to determine hypertension. Office/clinical hypertension was defined as a systolic BP (SBP) exceeding 140 mm Hg and/or a diastolic BP (DBP) exceeding 90 mm Hg, or if the subject was on pharmacological treatment for hypertension. The Omron apparatus used for the measurements had been validated, with a sensitivity of 88.2% and specificity of 98.6% for detecting hypertension.[37] The BP measurements were carried out by well-trained research nurses and assistants who had their measurements validated by the investigators at the beginning of the study. This ensured that the individuals conducting the measurements were skilled and accurate in their technique.

Estimated glomerular filtration rate

The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)

creatinine equation. In this study, CKD was defined as an eGFR less than 60 mL/min/1.73 m². The CKD-EPI equation is commonly used in individuals aged 18 years and older and is considered more accurate than the Modification of Diet in Renal Disease equation, particularly in the subgroup of patients with eGFR values between 60 and 120 mL/min/1.73 m². Based on their eGFR values, participants were classified into different stages of CKD. Stage 1 represented normal or high GFR (GFR >90 mL/min), stage 2 indicated mild CKD (GFR=60–89 mL/min), stage 3A denoted moderate CKD (GFR=45–59 mL/min), stage 3B represented moderate CKD (GFR=30–44 mL/min), stage 4 indicated severe CKD (GFR=15–29 mL/min) and stage 5 represented end-stage CKD (GFR <15 mL/min).

Statistical analysis

The collected data were entered into Microsoft Excel for data cleaning and then transferred to Jamovi V.2.3.26 for analysis. Descriptive statistics for baseline sociodemographic and clinical variables were reported as proportions for categorical variables, mean (SD) for continuous variables and median (IQR) for non-parametric data. The 95% CIs were appropriately reported to indicate the precision of the estimates. The normality of the data was assessed using the Shapiro-Wilk test, which indicated a non-normal distribution for several variables (p<0.05).

To compare the means (SD) across the three groups, a one-way ANOVA (analysis of variance) test was performed, and post hoc analysis was conducted using the least significant difference method. For continuous variables that did not follow a normal distribution, the Kruskal-Wallis and Mann-Whitney U test, non-parametric tests, were used. The association between categorical variables was tested using the χ^2 analysis. Spearman's correlation analysis was used to examine the relationship between different parameters. This non-parametric method measures the strength and direction of monotonic associations between variables. Statistical significance was defined as a p value less than 0.05, indicating that the observed results are unlikely to occur by chance. Variables with p values below this threshold were considered statistically significant and potentially associated with CVD.

Patient and public involvement

Patients and members of the public contributed to the initial data collection by participating in the study design and providing feedback on the data collection process. However, no additional patient and public involvement was included in this secondary analysis.

RESULTS

A total of 420 subjects across the three groups were included in this study with a mean age of 54.0±13.0, 42.9±13.1 and 48.6±12.5, respectively. The hypertension group had a higher mean age, body mass index (BMI), SBP, DBP, creatinine, urea, total cholesterol, triglycerides, CRP and FBS than the healthy group (p<0.05 for all comparisons). The CKD group had a higher mean SBP, DBP, HDL cholesterol (HDL-C) and FBS than the healthy group (p<0.05 for all comparisons). The CKD group also had a higher mean creatinine, urea and CRP than the hypertension group (p<0.001) (table 1). The mean serum Hcy levels were not significantly different among the three groups (p=0.390). The hypertension group had a mean Hcy level of 17.5±16.2 µmol/L, the healthy group had a mean Hcy level of 17.4±14.8 µmol/L and the CKD group had a mean Hcy level of 14.1±9.88 µmol/L. Following stratification into normal and elevated Hcy groups, the prevalence of HHcy (plasma Hcy >15 µmol/L) was highest in the hypertensive group. The mean plasma Hcy levels within the subset of participants classified as having HHcy were significant across the three groups (p<0.05) (table 1).

The stratification of Hcy levels into high and normal, as depicted in figure 2, reveals differences in other biomarkers of endothelial damage. Notably, FGF levels were significantly high among the HHcy group across all three study populations (p<0.001). While no significant difference was observed in CRP levels, triglyceride levels were significantly different in the hypertension group and HDL levels were significantly different in the CKD group (p<0.05)

In the analysis presented in table 2, it is evident that the correlation between Hcy and FGF levels was the most robust among the variables examined, with correlation coefficients ranging from 0.538 to 0.871 across all three groups. These correlations were both positive and statistically significant (p<0.001). Conversely, other cardiovascular risk factors displayed either weak or non-existent correlations with Hcy levels in the respective groups. Also, the only deviation from this pattern was observed in the CKD group, where FBS showed a weak positive correlation with Hcy (r=0.239, p=0.088).

A χ^2 test of independence was conducted to examine the association between Hcy level (HCY_15) and mortality status in 113 patients at 12 months and 87 patients at 18 months. Hcy levels were divided into two categories: upper (>15 µmol/L) and normal (≤15 µmol/L). The results of the χ^2 tests are shown in table 3. Using a significance level of 0.05, the p values for both time points were not statistically significant (p=0.462 for 12 months and p = 0.255 for 18 months), indicating that there was no evidence of an association between Hcy level and mortality at either time point. The death rate of patients with high Hcy levels was slightly higher than that of patients with normal Hcy levels at both time points; however, the difference was not significant (38.6% vs 31.9% and 55.9% vs 43.4%).

DISCUSSION

This study aimed to investigate both the differences in Hcy levels among individuals with CKD, hypertension and a healthy population in Nigeria, as well as the association between these levels and conventional CVD risk. The results showed no significant difference in mean

Table 1 Comparison of demographic and clinical characteristics among HTN, healthy and CKD groups (n=420)

Variables	HTN (n=178)	Healthy (n=87)	CKD (n=155)	P values
Age (years)	54.0±13.0	42.9±13.1	48.6±12.5	<0.001
Females (%)	54.8	67.3	37.9	
BMI (kg/m^2)	27.1±4.8	25.4±5.9	23.9±4.6	<0.001
SBP (mm Hg)	148±22.7	119±7.5	144±25.0	<0.001
DBP (mm Hg)	95.4±14.4	80.2±11.6	94.3±17.0	<0.001
Hcy (µmol/L)	17.5±16.2	17.4±14.8	14.1±9.88	0.390
Creatinine (mg/dL)	1.06±0.6	0.891±0.2	7.0±6.95	<0.001
Urea (mg/dL)	24.7±14.4	18.8±5.65	97.9±76.6	<0.001
Cholesterol (mg/dL)	184±42.8	165±42.8	177±66.1	0.002
Triglycerides (mg/dL)	110±47.9	86.7±34.2	121±72.1	<0.001
HDL (mg/dL)	50.9±15.7	52.9±15.1	53.1±19.7	0.323
CRP (mg/L)	4.96±11.2	4.23±9.68	19.5±42.6	<0.001
FBS (mg/dL)	97.9±36.7	82.7±12.4	94.0±33.6	<0.001
FGF-23 (RU/mL)	378±347	357±316	325±263	0.890
HHcy (µmol/L)	32.4±20.8	31.3±18.3	22.9±12.3	0.03

Comparison of demographic and clinical characteristics among HTN (n=178), healthy (n=87) and CKD (n=155) groups. Values are expressed as mean±SD. Statistical analysis was conducted using one-way ANOVA or the Kruskal-Wallis test, based on data distribution.
HHcy values represent the mean Hcy concentration within the elevated Hcy subgroup.
ANOVA, analysis of variance; BMI, body mass index; CKD, chronic kidney disease; CRP, C reactive protein; DBP, diastolic blood pressure; FBS, fasting blood sugar; FGF, fibroblast growth factor; Hcy, homocysteine; HDL, high-density lipoprotein; HHcy, hyperhomocysteinaemia; HTN, hypertension; RU/mL, relative units; SBP, systolic blood pressure.

serum Hcy levels among the three groups. However, in a subgroup analysis, the prevalence of HHcy was found to be significant among them. A strong correlation was found between Hcy and FGF across all three groups, but no significant association was found between Hcy levels and mortality at 12 and 18 months. These findings provide insights on the understanding and management of Hcy and CVD in different populations with varying kidney function and CVD risk profiles.

In the current study, HHcy, typically defined as total Hcy levels greater than or equal to 15 µmol/L, was observed in less than half of all the patient groups examined. The levels of HHcy detected were in the moderate to intermediate range, falling between 15 and 100 µmol/L, which is consistent with the categorisation described in previous literature as moderate or intermediate severity.[29 38] The prevalence of HHcy in the current study aligns with previous findings, where this level of HHcy has been observed in approximately one-third of patients with vascular conditions or stroke.[10 39 40] Contrastingly, another study assessing the plasma Hcy levels in diverse CVDs in urban Africans revealed an elevation of fasting HHcy in 50% of its participants.[41] The implication of these high levels has been associated with high risk of mortality in different patient scenarios.[42]

Furthermore, this study revealed that the mean HHcy levels were significantly different among the three groups. Contrary to the hypothesis that patients with CKD would have higher Hcy levels than healthy individuals due to impaired renal clearance and reduced availability of cofactors for Hcy metabolism, findings showed the highest prevalence in the hypertensive group. This may indicate that other factors, such as dietary intake, genetic variations or medication use, may have a more substantial influence on Hcy levels.[21 43] Additionally, this could suggest that hypertension is a more critical determinant of Hcy levels than kidney function or health status.[44] This observation is consistent with previous studies that have reported higher Hcy levels in hypertensive individuals than in normotensive individuals.[45] It remains unclear whether Hcy levels are independently linked to hypertension or if they are influenced by other factors such as BP, renal function or vascular damage.[10 46] Additionally, the causal relationship between high Hcy levels and hypertension is uncertain. Some research has proposed that elevated Hcy levels might impair endothelial function, escalate oxidative stress, foster inflammation and trigger vascular remodelling, all of which could lead to increased BP.[46 47] Conversely, other studies have posited that hypertension itself might elevate Hcy levels by diminishing renal clearance, altering folate metabolism or enhancing platelet activation.[47] Consequently, further research is imperative to clarify the causal relationship between Hcy and hypertension, as well as to understand its subsequent influence on CVD risk.

This study revealed no correlation between Hcy and BMI, HDL-C, triglycerides or cholesterol. However, a strong positive correlation was observed between Hcy and FGF across all three groups (p<0.001), suggesting a potential connection between Hcy and endothelial dysfunction.

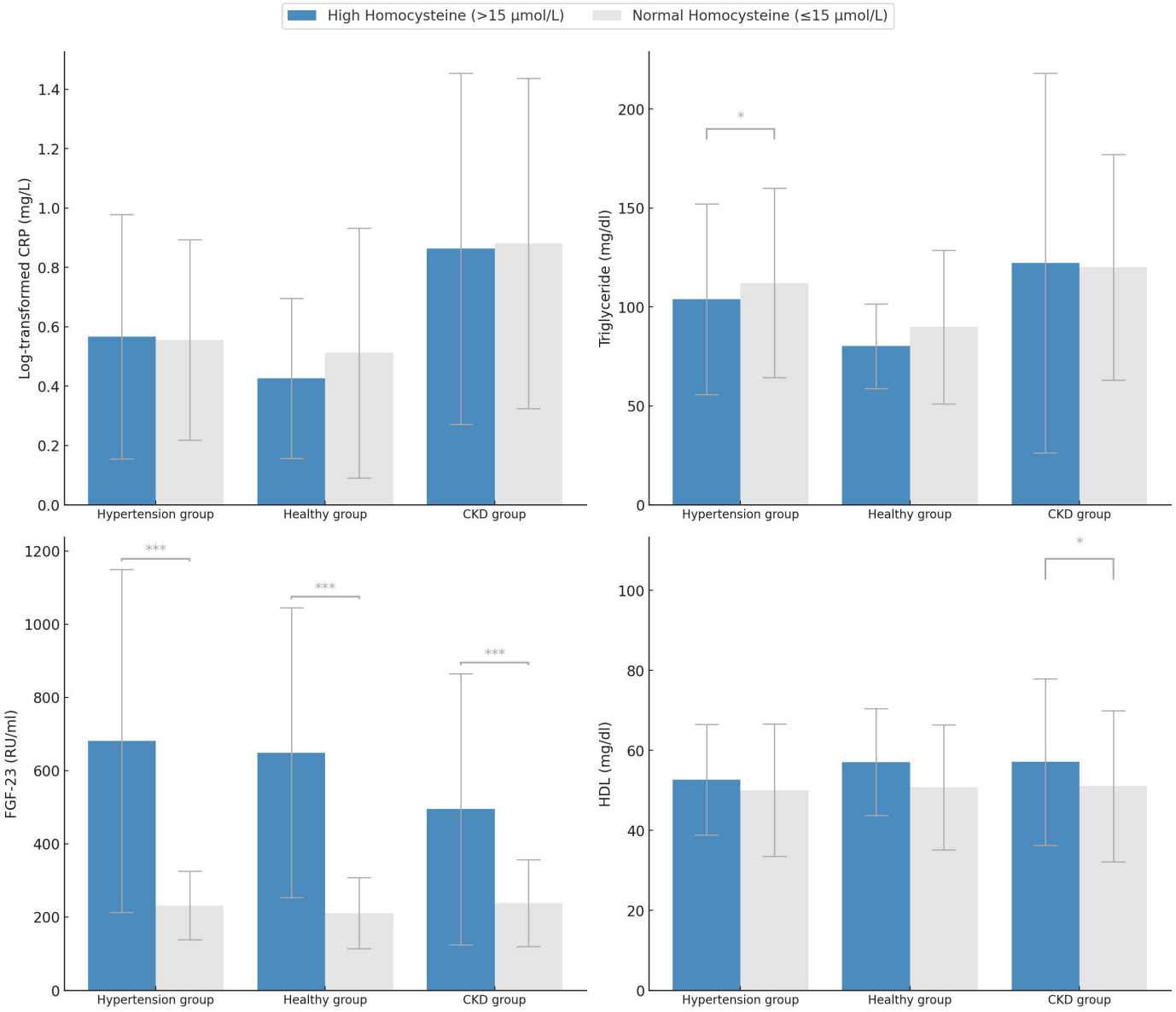

Figure 2 The bar chart shows mean differences in biomarkers of cardiovascular disease between high homocysteine (>15 µmol/L) and normal homocysteine (≤15 µmol/L) groups, analysed using the Mann-Whitney U test. Error bars denote SD, while significant differences between groups are indicated by horizontal lines and asterisks (*p<0.05, ***p<0.001). CKD, chronic kidney disease; CRP, C reactive protein; FGF, fibroblast growth factor; HDL, high density lipoprotein; RU/mL, relative units.

FGF is a marker of endothelial damage and a predictor of CVD events.[48–51] The association between Hcy and FGF suggests that elevated Hcy levels may adversely affect endothelial function by disrupting nitric oxide synthesis, increasing oxidative stress, inducing inflammation or stimulating smooth muscle cell proliferation.[52] This is consistent with previous studies that have reported a positive association between Hcy and FGF or other markers of endothelial dysfunction in various populations.[50 53] However, this correlation does not imply causation. It is possible that other factors may influence both Hcy and FGF levels independently or interactively.[53] For example, malnutrition, inflammation, oxidative stress, uraemic toxins, medication use and genetic variations may affect both Hcy and FGF levels in patients with CKD.[54–56]

The lack of association between Hcy levels and mortality at 12 or 18 months across the groups in the current study suggests that Hcy levels may not be a reliable predictor of CVD outcomes in populations with varying kidney function and CVD risk profiles. Similarly, a study by Menon *et al*[9] found no relationship between HCY and mortality in patients with CKD. However, a meta-analysis by Peng *et al*[57] concluded that elevated Hcy levels are an independent predictor for subsequent cardiovascular mortality or all-cause mortality, particularly among elderly individuals.

The role of Hcy in CVD has been a topic of interest for many years, especially given its potential modifiability. Elevated Hcy levels have been associated with endothelial dysfunction, oxidative stress and increased risk of thrombosis, all of which are critical pathways in the development

Table 2 Correlation between Hcy levels and cardiovascular risk factors across HTN, healthy and CKD groups

Study group	HTN		Healthy		CKD	
	Spearman's correlation	P value	Spearman's correlation	P value	Spearman's correlation	P value
HDL	−0.012	0.929	−0.030	0.875	−0.135	0.340
Total cholesterol	−0.128	0.333	−0.048	0.804	0.035	0.804
Triglycerides	0.111	0.409	0.008	0.968	0.136	0.338
FBS	0.025	0.853	−0.104	0.590	0.239	0.088
BMI	−0.033	0.813	0.078	0.688	0.114	0.491
CRP	0.179	0.176	−0.016	0.934	0.124	0.382
FGF	**0.801*** **	**<0.001**	**0.871*** **	**<0.001**	**0.538*** **	**<0.001**

This table presents the Spearman rank correlation analysis between Hcy levels and various cardiovascular risk factors for HTN (n=54–59), healthy (n=29–87) and CKD (n=39–52) groups. For each risk factor, the Spearman's correlation coefficient (r) and p value are provided. Values in bold depict a statistical significance at p<0.05.
***p<0.001.
BMI, body mass index; CKD, chronic kidney disease; CRP, C reactive protein; FBS, fasting blood sugar; FGF, fibroblast growth factor; Hcy, homocysteine; HDL, high-density lipoprotein; HTN, hypertension.

and progression of CVD. While our study did not establish a direct causal relationship between Hcy levels and CVD outcomes, the consistent associations observed in various studies suggest a potential therapeutic target. B vitamins, particularly folic acid, vitamin B_6 and vitamin B_{12}, play a crucial role in Hcy metabolism. In African populations, where dietary intake of these vitamins may vary, deficiencies could potentially exacerbate HHcy. Supplementation with these vitamins has been shown to effectively lower Hcy levels. However, the clinical benefits of Hcy-lowering therapy with B vitamins in preventing or treating CVD remain controversial. It is possible that the benefits of Hcy-lowering therapy may be more pronounced in specific subgroups of individuals. For instance, individuals with genetic polymorphisms affecting Hcy metabolism, those with extremely elevated Hcy levels, or those with certain comorbidities might derive more significant benefits from such interventions. Identifying these subgroups could allow for more targeted and effective therapeutic strategies.

Several limitations of the present study merit consideration. First, the retrospective nature of the study design precludes the establishment of causal relationships between Hcy levels and CVD risk factors or outcomes. A more robust approach to elucidate causality would involve a longitudinal or interventional study design. Second, the reliance on a single measurement of serum Hcy levels may not adequately capture long-term exposure or variability in Hcy levels. Future studies could benefit from repeated measurements or the utilisation of more stable markers of Hcy metabolism, such as S-adenosylmethionine or S-adenosylhomocysteine, to provide a more accurate assessment of the effects of Hcy on CVD.[58] Third, the present study did not account for potential confounding or modifying factors that could influence Hcy levels or CVD risk, including dietary intake, alcohol and genetic variations. Fourth, while power calculations were conducted to ensure an adequate sample size for primary outcomes, there was a significant difference in the mean age between groups, which could influence the results. To account for potential confounding factors, including age differences, future studies should consider employing multiple regression analysis to better elucidate the associations between Hcy levels and cardiovascular outcomes. Finally, the relatively small sample size and geographical constraints may limit the study findings' generalisability to other populations.

Table 3 Association between Hcy levels and mortality at 12 and 18 months

Time point	Hcy level	Death rate	χ^2 value	df	P value
12 months	Upper (>15 µmol/L)	38.6%	0.542	1	0.462
12 months	Normal (≤15 µmol/L)	31.9%			
18 months	Upper (>15 µmol/L)	55.9%	1.293	1	0.255
18 months	Normal (≤15 µmol/L)	43.4%			

This table presents the χ^2 comparison of mortality rates at 12 and 18 months based on Hcy levels. Hcy levels are categorised as 'Upper' (greater than 15 µmol/L) and 'Normal' (15 µmol/L or below). The death rate for each category at the respective time points is provided. The χ^2 value, df and p value are also listed to indicate the statistical significance of the observed differences between the groups.
Hcy, homocysteine.

Conclusion

The present study revealed no significant difference in mean serum Hcy levels among individuals with CKD, hypertension and those in the healthy population. However, a significant difference was observed in the mean HHcy among the three groups, with the highest prevalence noted in the hypertensive group. Additionally, a positive correlation was identified between Hcy levels and FGF across all three groups, suggesting a potential link between Hcy and endothelial dysfunction. No association was observed between Hcy levels and mortality at 12 or 18 months in any of the groups. These results indicate that Hcy levels may not serve as a reliable predictor of CVD outcomes across populations with varying kidney function and CVD risk profiles. Screening for elevated Hcy levels in hypertensive populations could serve as a valuable public health measure. Identifying and managing HHcy in hypertensive individuals may provide an opportunity to address cardiovascular risk factors early, particularly in low-resource settings where hypertension and related comorbidities are increasingly prevalent

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Contributors MA did the conceptualisation. MA, HH and AMA contributed to data acquisition and data analysis. MA wrote result interpretation, first and final draft of manuscript. HH and AMA conducted a critical review of the first manuscript draft. The final manuscript draft was approved by all authors. MA is the guarantor of the study, accepting full responsibility for the work.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design or conduct or reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study was conducted according to the international guideline on the declaration of Helsinki. The research protocol was approved by University of Ibadan/University College Hospital Research Ethics Committee, Ibadan, Nigeria (approval reference number UI/EC/15/0254). Written informed consents were obtained from study participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data is securely stored and protected by the Ibadan CRECKID study team to safeguard participant confidentiality. For additional details, please reach out to the corresponding author at 2225822@chester.ac.uk.

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