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Relationship between homocysteine and cognitive impairment in elderly patients with chronic kidney disease

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ABSTRACT

Aim: To investigate the association of serum homocysteine levels with cognitive function in elderly patients with chronic kidney disease (CKD).

Methods: A case-control study on 200 elderlies >60 years who were distributed into two groups: group 1 (cases): 100 patients with CKD and group 2 (controls): 100 subjects who do not have CKD. All subjects undergo comprehensive geriatric assessment, cognitive assessment, and biochemical investigations including serum homocysteine.

Results: The odds ratio of having impaired clinical dementia rating scores is 3.1 for CKD cases compared to controls. CKD patients have almost 3 times the risk of having cognitive impairment [OR=3.1; 95% CI (1.6-6.0)]. The mean serum homocysteine (18.2 µmol/L) among CKD showed a highly statistically significance compared to controls (10.1 µmol/L). Performance of multiple cognitive domains was reduced in association with elevated homocysteine levels. By using linear regression model for the factors independently related to cognitive performance among studied CKD cases, it was found that diabetes mellitus, educational level, age, and serum homocysteine level were strongly associated with consortium to establish a registry for Alzheimer's disease neuropsychological battery total scores. Respecting the percentage variance explained by each significant variable (R^2), serum homocysteine level is an independent significant variable predictor with the total scores.

Conclusion: The main features of cognitive impairment in CKD patients are executive dysfunction and memory impairment. Poor cognitive function in CKD patients was related with a higher homocysteine level independently.

Keywords: chronic kidney disease, clinical dementia rating, cognitive function, consortium to establish a registry for Alzheimer's disease neuropsychological battery, homocysteine

INTRODUCTION

Chronic kidney disease (CKD) patients have serum homocysteine levels higher than non CKD subjects. Homocysteine is primarily transsulfurated in the kidney and deficiency of this renal transsulfuration contributes to its elevation in the plasma [1].

Cognitive function may be affected by homocysteine by impairing myelin sheath methylation or toxic effect of its metabolites on N-methyl-D-aspartate glutamate receptors, which markedly increase the sensitivity of neurons to injury and oxidative stress [2], which has raised as an independent risk factor for multiple neurodegenerative diseases e.g., stroke, Alzheimer's disease (AD), and vascular dementia [3].

Atrophic changes in the brain were associated with higher serum homocysteine, which is considered a marker for lower levels of serum folate and vitamin B12 leading to histological changes of AD [4].

Our aim was to investigate the association of serum homocysteine levels with cognitive function in elderly patients with CKD.

SUBJECTS AND METHODS

Study Population

We performed a case-control study on 200 elderlies above 60 years who were distributed into two age and sex-matched groups: group 1 (cases): 100 patients with CKD and group 2 (controls): 100 subjects who do not have clinical history of CKD. The two groups were recruited from Ain Shams University hospitals' outpatient clinics. Informed consent was given for all participants before recruitment in the study.

Exclusion Criteria

We excluded patients who had received hemodialysis, renal transplantation, delirium, mini-mental state examination (MMSE) score <24, geriatric depression scale–Arabic version (GDS-15) score ≥5 [5], history of psychiatric diseases,

neurological disorders (e.g., cerebrovascular stroke, epilepsy, Parkinson disease, head trauma), thyroid disease, alcohol or drug abuse, visual or auditory impairment and patients on medications that affect homocysteine metabolism e.g., methotrexate, carbamazepine, phenytoin, vitamin supplements.

All subjects were subjected to the followings:

Comprehensive geriatric assessment

It includes detailed medical history, clinical examination and functional assessment by activity of daily living (ADL) [6], which is essential for assessment of elderly persons. Basic activities of daily living assess the ability of the patient to do basic self-care tasks such as feeding, continence, toileting, bathing, dressing, and transfer.

If an elderly is independent in the above six items so he is able to function at home without assistance and said to be independent. If there is a disability in any one of these six items, this means the need of at least part-time caregiver and said to be assisted. If he is completely unable to do basic activities of daily living, he is said to be dependent and needs a 24-hour caregiver. An Arabic version of the test was created. Design, validity, and reliability were assessed by [7].

Cognitive assessment

Cognitive function was assessed using the consortium to establish a registry for Alzheimer's disease neuropsychological battery (CERAD-NB) [8]. It is widely clinically used nowadays for cognitive impairment. Arabic version of the battery was applied [9]. The cognitive tests in the CERAD battery takes about half an hour to apply and consist of clinical dementia rating (CDR) [10], and eight subtests (J1-J8) to assess different levels and domains of cognitive and executive function.

CDR was used to assess cognitive impairment in 6 areas: orientation, memory, problem solving, judgment, home, personal care, hobbies and community affairs. Each domain is rated on a 5-point scale, as follows: 0: no impairment, 0.5: mild cognitive impairment, 1: mild dementia, 2: moderate dementia, and 3: severe dementia [11].

The global CDR score was calculated using the Washington University web algorithm (http://www.biostat.wustl.edu/~adrc/cdrpgm/index.html).

Verbal fluency (VF; animal category) (J1) tests language, semantic memory, verbal productivity, and cognitive flexibility by requesting subjects to name many animals in 60 seconds (maximum score=24) [12].

15 items modified Boston's naming test (BNT) (J2) tests gnosis, language ability, word finding and visual perception by requesting subjects to identify and name 15 drawn objects that represent words of high, medium, and low frequency (maximum score=15) [8].

MMSE (J3) is a brief screening test of cognitive function: orientation, attention, memory, language, and constructive praxis (maximum score=30) [13].

Word list memory task (WLM) (J4) tests delayed and immediate memory and ability of learning non-associated verbal material by recalling as many of 10 words as possible, immediately after having read them at the frequency of one every two seconds. Three trials are done with arrangement of the 10 words in new random order in each trial (maximum score=30) [14].

Because less educated/illiterate participants might be unable to read, the word list learning test can be given by reading each word in clear voice and on constant rate to the participants then ask them to repeat it.

Constructional praxis (CP) (J5) tests visuo-constructive abilities by requesting subjects to copy a diamond, a circle, three-dimensional cube, and a intersecting rectangles (maximum score=11) [15].

Word list recall (WLR) (J6) tests delayed recall, subjects are requested again to recall as many of the 10 words presented before in form J4 as possible within 90 seconds (maximum score=10) [14].

Word list recognition (WLRc) (J7) subjects have to recognize 10 words among a list of 20 words: 10 novel words and 10 original words (maximum score=10) [14].

Constructional praxis recall (CPR) (J8) subjects are requested to copy many of drawings as possible without seeing them (maximum score=11). Subjects are also asked about the pentagons of the MMSE [15].

Then, memory consolidation (savings scores in delayed recall of wordlist and delayed recall of the four geometric figures, the savings scores represent the percentage of items that were initially learned/copied that were retained at the delayed recall) and two CERAD-NP total scores: total score-I (TS-I) and total score-II (TS-II), were determined [16]. TS-I is calculated by summing the scores of 6 tests: VF (maximum score 24), BNT (15), WLM (30), CP (11), WLR (10), and WLRc (10). The maximum score of TS-I is 100 points. TS-II is calculated by adding CDR score (maximum score 11) to TS-I. Therefore, the maximum score of TS-II is 111 points.

Biochemical investigation

The Fasting serum homocysteine levels: three ml venous blood was aspirated in a serum separator tube and after samples were clotted at room temperature (10-20 minutes), centrifugation at approximately 2,000-3,000 RPM for 15 minutes was done. Then aliquot samples were stored at -20°C. serum homocysteine was assessed with enzyme linked immunosorbent assay (ELISA) using Bioassay Technology Laboratory Kit Cat. NO E3292Hu. High homocysteine was defined as a concentration of 13.7 µmol/L or greater [17].

The serum level of creatinine was measured and estimated GFR (eGFR) was calculated for diagnosis of CKD (eGFR <60 mL/min/1.73m^2) by using the modification of diet in renal disease (MDRD) formula (http://mdrd.com) using the patients' age, gender, racial origin and serum creatinine level. CKD stages were defined according to the clinical practice guideline for the evaluation and management of CKD, as follows: stage 1 and stage 2 CKD, decreased GFR alone does not determine the diagnosis, because the GFR may in fact be normal or borderline normal. Stage 3a: mild to moderate decrease in GFR (45-59 mL/min/1.73 m^2), stage 3b: moderate reduction in GFR (30-44 mL/min/1.73 m^2), stage 4: severe impairment (15-29 mL/min/1.73 m^2), stage 5: established renal failure with GFR (<15 mL/min/1.73 m^2 or pre-dialysis) [18].

Statistical Methods

Data were analyzed by IBM SPSS statistics for windows program version 23 (IBM Corp., Armonk, NY, USA). Qualitative data was totalized by frequencies and percentages while quantitative data was totalized by mean, standard deviation. Chi-square test, student t test, one-way ANOVA test and

Table 1. Comparison between CKD cases & control regarding socio-demographic, co-morbidities, & clinical dementia rating

Variables	Cases n=100	Control n=100	p-value
Age (mean±standard deviation)	68.0±6.1	69.4±6.6	0.100
Gender (No. [%])			
Male	61 (61%)	55 (55%)	0.300
Female	39 (39%)	45 (45%)	
Education (No. [%])			
Illiterate	30 (30%)	20 (20%)	0.100
Read & write	44 (44%)	45 (45%)	
Below high school (primary education)	10 (10%)	21 (21%)	
High school (secondary education)	9 (9%)	8 (8%)	
College	7 (7%)	6 (6%)	
Marital status (No. [%])			
Married	85 (85%)	76 (76%)	0.200
Widow	13 (13%)	22 (22%)	
Divorced	2 (2%)	2 (2%)	
Working status (No. [%])			
Not working	77 (77%)	88 (88%)	0.040
Working	23 (23%)	12 (12%)	
Living arrangement (No. [%])			
With spouse	77 (77%)	85 (85%)	0.200
With children	18 (18%)	13 (13%)	
Alone	5 (5%)	2 (2%)	
Smoking (No. [%])			
Non-smoker	48 (48%)	74 (74%)	0.001
Ex-smoker	20 (20%)	8 (8%)	
Current smoker	32 (32%)	18 (18%)	
Activities of daily living (No. [%])			
Independent	73 (73%)	89 (89%)	0.002
Assisted	18 (18%)	11 (11%)	
Dependent	9 (9%)	0 (0%)	
Comorbidities (No. [%])			
Diabetes mellitus	80 (80%)	45 (45%)	0.001
Hypertension	70 (70%)	48 (48%)	0.002
Heart disease	28 (28%)	17 (17%)	0.060
Liver disease	2 (2%)	5 (5%)	0.200
Chronic lung disease	17 (17%)	14 (14%)	0.500
Cancer	0 (0%)	1 (1%)	0.300
Others (Osteoarthritis, Benign Prostatic Hyperplasia)	5 (5%)	2 (2%)	0.200
Clinical dementia rating (No. [%])			
0.5	27 (27%)	14 (14%)	0.001
1	7 (7%)	3 (3%)	
2	4 (4%)	0 (0%)	
3	1 (1%)	0 (0%)	
Total impaired cognition	39 (39%)	17 (17%)	

Pearson correlation coefficient were utilized in analysis of this study. Multiple linear regressions were done to explore the significant predictors of the CERAD scores. “p-value” less than 0.05 was considered statistically significant.

RESULTS

100 patients with CKD were enrolled in the study after completing the inclusion and exclusion criteria and 100 gender and age matched subjects participated as control group.

The mean CKD duration among studied cases was 3.71±1.48 years, 17% were in stage 3a (mild), 32% in stage 3b (moderate) and 30% in stage 4 (advanced) while 21% were in stage 5 (ESRD).

The socio-demographic data, co-morbidities and CDR of the patients were compared to the control group in **Table 1**.

It showed a higher statistical significance of ex-smokers, current smokers and working subjects in CKD cases in comparison to controls. Also, it showed a higher statistical significance of assisted and functionally dependency in CKD cases in comparison to controls. Also, it showed a higher statistical significance of diabetics and hypertensive patients among CKD cases compared to control group. It showed a higher statistically significant percentage of impaired CDR among CKD cases compared to controls. The odds ratio of having impaired CDR scores is 3.1 for CKD cases compared to controls. CKD patients have almost 3 times the risk of having cognitive impairment (OR= 3.1; 95% CI [1.6-6.0]).

The mean serum homocysteine (18.2 µmol/L) among CKD showed a highly statistically significance compared to controls (10.1 µmol/L). **Table 2** showed that stage 5 (ESRD) has higher serum homocysteine level than stage 4 (advanced CKD) and stage 3 (mild to moderate CKD).

Table 2 showed a highly statistically significant lower mean VF among CKD cases compared to controls. There were lower statistically significant means for WLM, WLR, and WLRc subtests, among CKD cases compared to controls. Word List saving and constructional praxis saving means among CKD

Table 2. Comparison between CKD cases of different stages & controls regarding laboratory results & CERAD-NB subtests scores

	CKD stage 3 (n=49)	CKD stage 4 (n=30)	CKD stage 5 (n=21)	Control (n=100)	p-value
Laboratory results (mean±standard deviation)					
Creatinine (mg/dL)	1.69±0.31	3.22±0.52	4.48±0.50	0.80±0.10	0.001
eGFR (mL/min/1.73m^2)	37.88±7.01	19.54±3.77	13.36±1.15	85.80±16.60	0.001
Homocysteine (µmol/L)	16.50±2.91	19.88±2.32	20.18±2.43	10.10±2.00	0.001
CERAD-NB subtests scores (mean±standard deviation)					
Verbal fluency (24)	8.29±2.51	7.03±2.74	7.76±3.16	9.70±0.60	0.145
Boston naming test (15)	15.00±0.00	15.00±0.00	15.00±0.00	14.90±0.10	-
Mini-mental state examination (30)	26.57±1.32	25.93±1.20	26.52±1.60	26.10±1.30	0.111
Word list memory (30)	14.18±3.55	12.03±3.78	14.05±4.12	17.20±3.40	0.039
Constructional praxis (11)	7.65±2.03	6.83±1.91	7.38±2.18	7.10±1.70	0.223
Word list recall (10)	5.24±1.84	4.13±1.81	4.90±2.17	6.50±1.30	0.046
Word list recall saving (%)	85.89±17.39	80.07±15.27	78.45±22.38	95.70±11.60	0.192
Word list recognition (10)	7.37±2.15	6.20±1.86	6.90±2.62	8.50±1.10	0.074
Constructional praxis recall (11)	5.88±2.23	4.63±1.79	5.57±2.01	6.50±1.80	0.036
Constructional praxis recall saving (%)	74.91±13.65	67.34±14.65	74.44±11.18	91.70±12.80	0.046
Total score I	57.73±11.23	51.23±11.23	56.00±13.67	64.10±10.30	0.062
Total score II	63.61±13.23	55.87±12.87	61.57±15.50	70.70±11.90	0.052

Note. CERAD-NB: Consortium to establish a registry for Alzheimer's disease neuropsychological battery; CKD: Chronic kidney disease (stage 3 includes both stage 3a and 3b); & eGFR: Estimated glomerular filtration rate

Table 3. Comparison between mean serum homocysteine level & different parameters among CKD cases

CKD cases	Homocysteine		
	M	SD	p-value
Gender			
Male (n=61)	18.3	3.0	0.600
Female (n=39)	18.1	3.3	
Education			
Illiterate/read (n=74)	18.8	3.2	0.003
Education (n=26)	16.7	2.4	
Working status			
Not working (n=77)	18.7	3.1	0.010
Working (n=23)	16.8	2.6	
Smoking			
Non-smoker (n=48)	18.1	3.2	0.500
Ex-smoker/current smoker (n=52)	18.4	3.0	
Activities of daily living			
Independent (n=73)	17.1	2.4	0.001
Assisted/dependent (n=27)	21.3	2.7	
Diabetes mellitus			
Negative (n=20)	17.1	1.9	0.010
Positive (n=80)	18.5	3.3	
Hypertension			
Negative (n=30)	17.0	3.0	0.010
Positive (n=70)	18.8	3.1	
Heart disease			
Negative (n=72)	18.1	3.2	0.700
Positive (n=28)	18.4	3.3	

Note. CKD: Chronic kidney disease; M: mean; & SD: Standard deviation

cases were lower in comparison to control with highly statistically significance. Also, it showed that lower mean CERAD total score-I and total score-II among CKD cases in comparison to control with high statistical significance. Also, this table demonstrated significant differences in cognitive subtests scores (WLM, WLR, and CPR) in different stages of CKD. It showed that CKD cases have impaired learning abilities, delayed memory, and memory consolidation. The kidney disease severity was directly related to cognitive impairment severity, so more renal impairment was associated with delayed recall and poorer verbal learning.

Table 3 shows statistically significant higher serum homocysteine levels among CKD cases with diabetes, hypertension, less educational level, functionally dependent and not working. While there is no significant difference in serum homocysteine level and CKD cases as regarding gender, smoking or cardiac disease.

Table 4. Correlation coefficient between serum homocysteine level and CERAD-NB subtests performance in CKD cases

Cognitive domains & CERAD-NB subtests performance in CKD cases	Homocysteine 18.2±3.1 µmol/L	
	r	p-value
Executive function: Verbal fluency (J1)	-0.565	0.001
Global cognitive function: Mini-mental state examination (J3)	-0.483	0.001
Verbal learning: Word list memory (J4)	-0.567	0.001
Visuospatial function: Construction praxis (J5)	-0.469	0.001
Delayed recall: Word list recall (J6)	-0.542	0.001
Delayed recall: Construction praxis recall (J8)	-0.543	0.001
Recognition memory: Word list recognition (J7)	-0.614	0.001
Total score-I	-0.592	0.001
Total score-II	-0.593	0.001

Note. CERAD-NB: Consortium to establish a registry for Alzheimer's disease neuropsychological battery; CKD: Chronic kidney disease; & r: Correlation coefficient

In univariate analysis, serum homocysteine level was inversely correlated with CERAD-NB subtests scores. Elevated homocysteine levels associated with reduced performance in multiple cognitive domains. **Table 4** shows a highly statistically significant negative correlation between serum homocysteine level and the VF, MMSE, WLM, CP, WLR, WLRc, CPR scores, and CERAD total scores. Seven out of eight subtests in CERAD were significantly correlated to homocysteine level; except BNT as all CKD cases had score of 15 so the correlation coefficient couldn't be applied.

By using linear regression model for the factors independently related to cognitive performance among studied CKD cases, it was found the following factors were strongly associated with CERAD-NB total scores: presence of diabetes mellitus, educational level, age and serum homocysteine level (**Table 5**). With respect to the percentage variance explained by each significant variable (R^2), serum homocysteine level is an independent significant variable predictor with the total scores (with the entire remaining variable constant).

Table 5. Backward linear regression model for CERAD-NB total scores & significant predictors of the score

	B	t	p-value
CERAD-NB total score-I			
Constant	119.10		
Education	4.03	6.4	0.001
Diabetes	-3.90	2.3	0.020
Homocysteine	-0.83	3.2	0.002
Age	-0.79	5.7	0.001
CERAD-NB total score-II			
Constant	131.70		
Education	4.96	7.0	0.001
Diabetes	-4.50	2.3	0.020
Homocysteine	-0.98	3.3	0.001
Age	-0.88	5.6	0.001

Note. CERAD-NB: Consortium to establish a registry for Alzheimer's disease neuropsychological battery; F=59.2; R^2=0.715; The R^2 value: Reflecting the percentage of dependent variable (CERAD total score-I) variance explained by the independent demographic variables; R^2=71.5%; F=62.9; R^2=0.726; The R^2 value: Reflecting the percentage of dependent variable (CERAD total score-II) variance explained by the independent demographic variables; & R^2=72.6%

The final model of CERAD total score-I for the CKD patients is computed with this regression equation: CERAD-NB total score-I (predicted score)=119.1+4.03X education -3.9X diabetes -0.83X homocysteine value -0.79X age.

The final model of CERAD total score-II for the CKD patients is computed with this regression equation: CERAD-NB total score-II (predicted score)=131.7+4.96X education -4.5X diabetes -0.98X homocysteine value -0.88X age. For example, male patient 70 years old educated, diabetic and homocysteine (18 µmol/L)=131.7+4.95-17-61-4.5=53.9.

DISCUSSION

CKD leads to different changes in elderly such as decrease physical function, increases of frailty, vascular calcification and dysfunction, increases oxidative stress and inflammation, and cognitive impairment [19].

Cognitive impairment in CKD patients is due to different factors and many academics and clinicians are neglecting it in spite of its negative consequences [20].

Kidney is responsible for the production and metabolism of different amino acids including homocysteine. An increased level of homocysteine is present in individuals with declining kidney function; and this alteration of homocysteine metabolism can be considered a major factor in the progression and deterioration of kidney diseases [21].

However, the association between cognitive function in CKD elderly patients and serum levels of homocysteine was little studied, so the aim of this study was to investigate this association.

Regarding correlation between serum homocysteine levels and cognition performance test scores, the current study showed highly significant negative correlation. The mean of homocysteine level was higher in patients with CKD than controls, and it was inversely correlated with the CERAD-NB subtests and total scores. The study results showed a highly statistically significant difference between serum homocysteine levels among different stages of CKD. Stage 5 (ESRD) has higher serum homocysteine level than stage 4 (advanced CKD) and stage 3 (mild to moderate CKD). Significant correlations were demonstrated between serum homocysteine level and CERAD-NB subtests in different stages of CKD, so that in mild to moderate CKD cases (stage 3); there was negative correlation between executive function, verbal learning, delayed recall, and memory consolidation with serum homocysteine level. While in ESRD cases (stage 5); there was negative correlation between executive function, MMSE, verbal learning, visuospatial function, delayed recall, and memory consolidation with serum homocysteine level.

These results are in accordance with [22, 23], which are observational studies found that homocysteine had a role in cognitive impairment and dementia especially in CKD patients.

A study, which proposed that homocysteine, could have a role in vascular diseases of CKD patients leading to cognitive impairment without clear affected domains [24]. It was determined that executive function was inversely correlated with homocysteine level in CKD patients [25]. Higher levels of serum homocysteine were found to increase the development of brain infarction and hyperintensities of white matter through vascular factors [23].

Many studies confirmed that homocysteine has deleterious effect on cognitive functions by non-vascular mechanisms [26, 27]. In structural neuroimaging studies, it was found that higher serum homocysteine was associated with frontal lobe atrophy affecting the executive functions [28]. It was also found that elevated homocysteine levels in healthy adults were associated with decreased volume of cerebral white matter and lower cognitive scores [29]. Cognitive dysfunction can be explained by direct neurotoxic effect of homocysteine by activation N-methyl-D-aspartate receptor, which leads to cell death [30].

This was opposite to what was found in [31]. Their results showed that high levels of serum homocysteine in geriatric patients with multiple comorbidities with normal serum levels of vitamin B12 and folate were not significant among different short cognitive performance test score groups. They explained their results that cognitive assessment done using short cognitive performance test, which is a brief test evaluates only a certain degree of memory and attention impairment especially speed and execution time [31].

In this study, there was a statistically significant higher serum homocysteine level in CKD cases with diabetes and hypertension, while there was no statistical significance between serum homocysteine level and CKD cases with cardiac disease.

It was found that higher homocysteine levels in type 2 diabetics is involved in its cardiovascular complications and diabetic nephropathy with microalbuminuria and deteriorating renal function [32]. Also, a previous study by *Sonoda et al.,* confirmed the presence of higher homocysteine levels in diabetic patients with cerebral vascular disease and renal impairment suggesting its role in cognitive impairment by vascular and non-vascular mechanisms [33]. It was found that homocysteine is an independent risk factor for cardiovascular diseases by enhancing inflammation, endothelial injury and progressive vascular damage in CKD patients [34].

No correlation between plasma homocysteine and cognitive impairment was found [35]. Education and age of the subjects were significantly associated with cognitive impairment [35].

The current study results can construct that age, serum homocysteine level, diabetes mellitus and educational level can be considered as predictors of cognition test performance and the CERAD total scores in elderly patients with CKD. Each of them can be an independent significant variable predictor (with all the remaining variables constant).

This study has limitations with future recommendations. Brain-imaging and screening laboratory tests should be introduced to study the population with cognitive impairment. Further controlled studies with larger sample size are needed to confirm the relationship of several factors with cognitive impairment such as anemia, C-reactive protein, albuminuria, parathyroid hormone and vitamin D. Also, future studies should take into consideration other non-cognitive factors that affect quality of life in CKD patients such as frailty and physical disability. Further broader studies are recommended to include CKD patients with renal replacement therapy (either hemodialysis or transplantation), which may affect cognitive function.

CONSLUSION

The main features of cognitive impairment in CKD patients are executive dysfunction and memory impairment. Poor cognitive function in CKD patients was related to a higher homocysteine level independently.

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Declaration of interest: No conflict of interest is declared by authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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