Evaluation of serum homocysteine level and its relation with carotid intima-media thickness in patients of chronic kidney disease

Ocena stężenia homocysteiny w surowicy i jego zależności od wskaźnika intima-media tętnicy szyjnej u pacjentów z przewlekłą chorobą nerek

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Key words: chronic kidney disease, cardiovascular disease, haemodialysis, homocysteine, carotid intima-media thickness.

Słowa kluczowe: przewlekła choroba nerek, choroba sercowo-naczyniowa, hemodializa, homocysteina, wskaźnik *intima-media* tętnicy szyjnej.

Abstract

Introduction: Patients with chronic kidney disease (CKD) are at high risk for the development of cardiovascular disease (CVD). The intima-media thickness (IMT) is the best-studied sonographic marker for early atherosclerotic vascular wall lesions. Homocysteine is an important non-traditional risk factor for CVD in CKD patients.
Aim of the research: To explore the relationship between elevated serum homocysteine level and its relationship with carotid intima-media thickness in patients with CKD.
Material and methods: The study was undertaken in 60 adult patients with chronic renal failure. The patients were divided into three groups: group I had subjects with CKD (stage 3); group II had subjects with CKD (stage 4) on conservative therapy; and group III had subjects with CKD (stage 5) on regular haemodialysis at least 3–4 times per week. Carotid sonography was done in all patients at the time of inclusion in the study. The patients in all the groups were then followed for 3 months and the relevant investigations were carried out, initially at the time of presentation, and then at 3 months in group III patients. The patients were monitored for various renal parameters along with serum homocysteine.
Results: The value of carotid intima-media thickness (CA-IMT) was increased in groups II and III as compared to group I. Patients in group III had higher levels of serum homocysteine as compared to patients in groups I and group II. The comparison of homocysteine levels between three groups was also highly statistically significant. No correlation was observed between serum homocysteine levels and carotid artery IMT in all the three groups.
Conclusions: The present observations show that baseline serum homocysteine levels and carotid artery IMT levels were elevated at baseline in all the three groups, with progressive increase in their values with decline in renal function.

Streszczenie

Wprowadzenie: Pacjenci z przewlekłą chorobą nerek (CKD) stanowią grupę wysokiego ryzyka choroby sercowo-naczyniowej (CVD). Wskaźnik *intima-media* jest najlepiej zbadanym markerem ultrasonograficznym wczesnych zmian miażdżycowych naczyń. Homocysteina jest ważnym, innym niż tradycyjny, czynnikiem ryzyka wystąpienia choroby sercowo-naczyniowej u chorych na CKD.
Cel pracy: Zbadanie zależności między podwyższonym stężeniem homocysteiny w surowicy a wskaźnikiem *intima-media* u chorych na CKD.
Materiał i metody: W badaniu wzięło udział 60 dorosłych chorych na przewlekłą niewydolność nerek. Zostali oni podzieleni na trzy grupy: grupę I stanowili chorzy na CKD (stadium 3), grupę II – chorzy na CKD (stadium 4) leczeni zachowawczo, a grupę III – chorzy na CKD (stadium 5) poddawani regularnej hemodializie co najmniej 3–4 razy tygodniowo. W chwili włączenia do badania u wszystkich chorych przeprowadzono badanie ultrasonograficzne naczyń. Chorzy z wszystkich grup byli następnie monitorowani przez 3 miesiące oraz przeprowadzano u nich odpowiednie badania – wstępnie w chwili włączenia, a następnie po 3 miesiącach u chorych z grupy III. U pacjentów monitorowano różne parametry nerek wraz ze stężeniem homocysteiny w surowicy.
Wyniki: Wartość wskaźnika *intima-media* tętnicy szyjnej (CA-IMT) była podwyższona w grupie II i III w stosunku do grupy I. U chorych z grupy III stwierdzono większe stężenie homocysteiny w surowicy w stosunku do chorych z grupy I i II. Różnice stężenia homocysteiny między trzema grupami były również statystycznie istotne. Nie wykazano współzależności między stężeniem homocysteiny w surowicy i wskaźnikiem *intima-media* tętnicy szyjnej we wszystkich trzech grupach.
Wnioski: Z obserwacji wynika, że stężenie homocysteiny w surowicy oraz poziom wskaźnika *intima-media* tętnicy szyjnej były wyjściowo zwiększone we wszystkich trzech grupach, z progresywnym wzrostem wartości wraz z utratą funkcji nerek.

Introduction

Patients of chronic kidney disease (CKD) are at a high risk of cardiovascular diseases, which is an important cause of mortality. The cardiovascular mortality is higher in patients of CKD than in individuals with normal renal function [1, 2]. Chronic kidney disease is an independent risk factor for cardiovascular disease (CVD), and most patients die prior to or after initiation of dialysis due to cardiovascular diseases. Coronary artery disease is present prior to initiation of dialysis in the majority of CKD patients [3]. Therefore, it is important to intervene in the earlier stages of CKD, to prevent and treat CVD [4].

There are both traditional and non-traditional risk factors for the development of CVD in CKD patients. Traditional risk factors are: older age, male sex, hypertension, higher low-density lipoprotein (LDL) cholesterol, lower high-density lipoprotein (HDL) cholesterol, diabetes, smoking, physical inactivity, menopause, family history of CVD, and left ventricular hypertrophy (LVH). The non-traditional risk factors or uraemia-specific risk factors for development of CVD are: albuminuria, hyperhomocysteinaemia, anaemia, abnormal calcium phosphate metabolism, extracellular fluid overload and electrolyte imbalance, oxidative stress, inflammation, malnutrition, thrombogenic factors, abnormal vascular calcification, and altered nitric oxide endothelin balance [5].

It is known that patients with chronic kidney disease show accelerated atherosclerosis and microangiopathic changes in their vessels [6]. The intima-media thickness (IMT) is the best-studied sonographic marker for early atherosclerotic vascular wall lesions, at present. A thickening of the intima-media complex reflects local alterations and also corresponds to generalised atherosclerosis. Advantages of IMT are that it is non-invasive, relatively inexpensive, and can be repeatedly performed with no adverse effects on the patient [7].

Homocysteine is a non-protein amino acid. It has been included in the non-traditional risk factors for CVD in CKD patients, but its precise role has not been defined as to how it causes increased risk of CVD. It is elevated in patients of CKD; the reasons for its elevation are not fully understood. It causes increased atherosclerosis by various mechanisms, of which increased lipoprotein oxidation, enhanced smooth muscle cell proliferation, endothelial dysfunction, activation of factor V, and reduced activation of protein C are important [8]. Increased homocysteine level and its relation with atherosclerosis has been shown in normal patients, but its relation in CKD patients has been an area of interest recently with inconsistent results.

Aim of the research

Hence, this study was carried out to explore the relationship between elevated serum homocysteine level and its relationship with carotid intima medial thickness in patients with CKD.

Material and methods

A total of 60 patients aged 18–70 years with CKD as per NKF/DOQI classification were included in the study protocol. The patients were divided into three groups: group I had subjects with CKD stage 3 on conservative therapy for 3 months; group II included subjects with CKD stage 4 on conservative therapy for 3 months; and group III had subjects with CKD stage 5 on regular haemodialysis for at least 3–4 weeks.

Inclusion criteria: Patients in stage 3–5 of CKD aged 18–70 years were included. The diagnosis of CKD was made on the basis of NKF/DOQI guidelines [9].

Exclusion criteria: stage 1 or 2 CKD patients, creatinine clearance > 90 ml/min, age ≥ 70 years and ≤ 18 years, any condition that precluded a patient from remaining in the study, such as drug abuse, alcohol, malignancy, psychiatric illness, pregnancy, etc.

Pre-informed written consent for enrolment in the study was obtained. The study was duly approved by the Ethical Committee of Pt. B. D. Sharma University of Health Sciences, Rohtak. Each patient was subjected to detailed general physical examination, and the following relevant renal and other biochemical investigations were carried out.

Routine renal and other biochemical investigations including: blood urea, serum creatinine, serum calcium levels, serum phosphorous levels, serum protein, serum sodium and potassium, blood sugar, and serum total homocysteine levels were carried out as per the standard methods used in the Department of Biochemistry, PGIMS, Rohtak. Glomerular filtration rate (GFR) was measured by Cockcroft-Gault formula.

The levels of serum homocysteine were measured by chemiluminescence method in the fasting state. Intima-media thickness for both the common carotid arteries was measured. Intima-media thickness was determined by a high-resolution B-mode system equipped with broad-band linear array transducer (5–10 MHz) with a footprint of 3 cm. The common carotid arteries were examined bilaterally up to the bifurcation and including the proximal part of the internal carotid artery and external carotid artery in the longitudinal and transverse projections. Intima-media thickness, plaque characterisation including echo texture, calcification, and cavitation was assessed by greyscale ultrasound, and further colour flow imaging and conventional duplex scanning was done. The final values were the average of three consecutive measurements. The same observer (a consultant radiologist) assessed the IMT in all the patients. During follow-up also the same consultant performed the tests but was not provided with the previous measurements, to avoid any bias.

In patients of groups I and II all the above investigations were carried out at baseline. Group III patients were subjected to haemodialysis three times a week for 3 months, and all the investigations were also carried out at the end of 3 months in this group.

Statistical analysis

At the end of the study, the data were expressed as mean ± SD or range. Probability values of < 0.05 were considered to be significant in all the analyses. The statistical analyses were performed using Kruskal-Willis one-way analysis of variance (ANOVA) between three different groups, paired samples *t*-test for before and after haemodialysis comparisons. The correlations were tested using Spearman's Rank order correlation analysis. All statistical calculations were carried out using SPSS 20.0 software.

Results

The present study was a prospective study of 3 months' duration. A total of 60 patients with age ranging from 18 to 70 years were enrolled. There were 36 males and 24 females. The mean age of the patients in group I was 54.7 ±13.91 years, in group II was 47.05 ±15.44 years, and in group III was 49.15 ±12.7 years.

Most common cause of CKD was chronic glomerulonephritis followed by diabetes mellitus and hypertension. Less frequent aetiologies included polycystic kidney disease and obstructive uropathy. The mean body mass indexes of the three groups were 19.90 ±2.99, 18.24 ±2.64, and 18.48 ±2.56, respectively. Overall, the patients with CKD had a low body mass index (BMI). Anaemia was present in all the patients, and more so in group II and group III. Group III patients had severe anaemia. In patients of group III, who were mostly on regular maintenance dialysis, the blood urea and serum creatinine remained persistently high throughout the study, indicating the severity of disease. Serum uric acid levels were high in group II and group III. The serum calcium levels were significantly lower in group II and group III when compared to group I. The serum phosphate levels were significantly higher in group III followed by group II and then group I (Table 1).

The CA-IMT in the left common carotid artery (CCA) at baseline was 0.68 ±0.12 mm in group I, it was 0.72 ±0.11 mm in group II, and in group III it was 0.78 ±0.12 mm. The value of IMT was higher in group II and group III as compared to group I and was statistically significant ($p < 0.05$) (Table 2). The values of IMT of bilateral internal carotid and left common carotid artery were higher in group III than in group II and were statistically significant ($p < 0.05$). The value of IMT of the left common carotid artery after 3 months of haemodialysis was reduced to 0.67 ±0.12 mm, which was highly significant ($p < 0.01$) (Table 3).

The basal value of serum homocysteine in group I was 22.66 ±9.17 μmol/l, in group II was 24.20 ±8.43 μmol/l, and in group III was 29.38 ±7.3 μmol/l. Thus, the values increased as the stage of CKD increased progressively. These values between groups were sta-

Table 1. Basal value of renal function tests

Parameter	Group I	Group II	Group III
GFR [ml/min]	35.67 ±4.29	18.66 ±3.31	7.36 ±2.45
Haemoglobin [gm%]	10.205 ±2.63	9.155 ±2.11	8.365 ±1.91
Blood urea [mg%]	98.35 ±34.28	114.215 ±33.12	239.15 ±85.6
Serum creatinine [mg%]	1.638 ±0.41	3.105 ±0.85	9.14 ±3.55
Serum uric acid [mg%]	5.47 ±1.58	8.159 ±2.79	8.49 ±3.01
Serum calcium [mg%]	8.72 ±0.96	8.49 ±1.00	7.78 ±1.18
Serum phosphate [mg%]	4.17 ±2.04	4.99 ±1.57	6.88 ±1.83
Serum homocysteine [μmol/l]	22.66 ±9.17	24.20 ±8.43	29.38 ±7.3

Table 2. Intima-media thickness of carotid arteries at baseline

Group	Common carotid artery		Internal crotid artery	
	Left	Right	Left	Right
I	0.68 ±0.12	0.71 ±0.09	0.69 ±0.08	0.69 ±0.11
II	0.72 ±0.11	0.72 ±0.11	0.72 ±0.08	0.72 ±0.06
III	0.78 ±0.12	0.80 ±0.09	0.80 ±0.17	0.80 ±0.16

Table 3. Effect of haemodialysis on various parameters (group III)

Parameter	Baseline	After dialysis	*P*-value
Serum homocysteine [μmol/l]	29.38 ±7.3	15.49 ±5.72	< 0.01
Left common carotid IMT [mm]	0.78 ±0.12	0.67 ±0.12	< 0.01
Right common carotid IMT [mm]	0.80 ±0.09	0.736 ±0.094	< 0.01
Left internal carotid IMT [mm]	0.80 ±0.17	0.71 ±0.13	< 0.01
Right internal carotid IMT [mm]	0.80 ±0.16	0.73 ±0.11	< 0.01

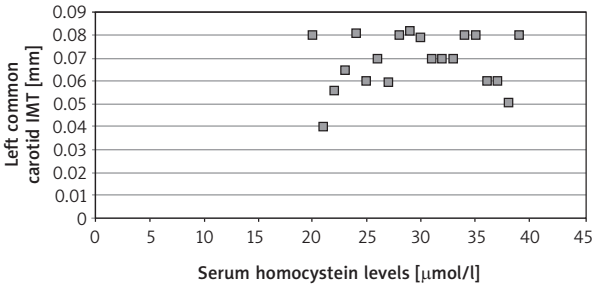

Figure 1. Correlation between serum homocystein levels and left CCA IMT in group I

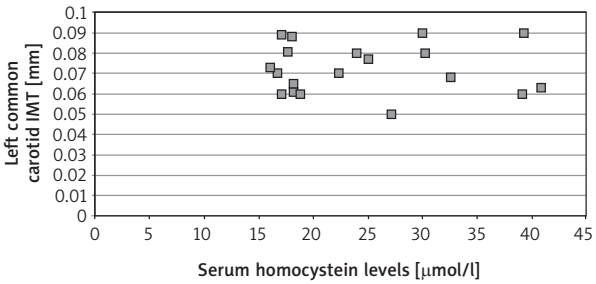

Figure 2. Correlation between serum homocystein levels and left CCA IMT in group II

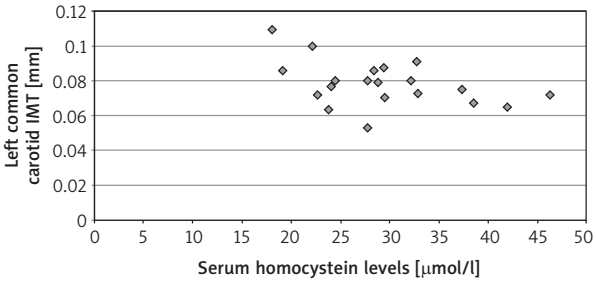

Figure 3. Correlation between serum homocystein levels and left CCA IMT in group III

tistically significant ($p < 0.05$). These values significantly reduced after 3 months of dialysis in group III to 15.49 ±5.72 μmol/l ($p < 0.01$) (Table 3).

On correlation analysis, there was no statistically significant association between serum homocysteine levels and carotid intima medial thickness in all the three groups ($p > 0.05$) (Figures 1–3).

Discussion

Patients with CKD experience a high rate of fatal and non-fatal cardiovascular events before reaching kidney failure [10]. Patients in all stages of CKD are considered to be in the high-risk group for development of cardiovascular diseases, and recent guidelines have defined CKD as cardiovascular disease risk equivalent [5[. These patients have high risk of developing cardiovascular disease, which develops in the early stages of CKD [11].

The two major outcomes of patients of CKD stages 1 to 4 are progression of kidney disease, including development of kidney failure, and development of cardiovascular disease. In a recent study, Keith *et al.* observed that in every stage of CKD death was a more likely outcome than progression to kidney failure, with 3.1% of patients with CKD stages 2 to 4 progressing to renal replacement therapy (dialysis or transplantation), whereas 24.9% died. There was greater baseline prevalence of CVD in patients who died compared with those who survived, suggesting that CVD accounted for a large proportion of deaths [12].

Herzog *et al.* examined outcomes of 34,189 long-term dialysis patients from the US Renal Data System, who were hospitalised between 1977 and 1995 with acute myocardial infarction. The prognosis of these patients was poor: at two years post infarction 73% patients had died. By year 5, the mortality was nearly 90%. Cardiac disease-related mortality rates were 51.8% at 2 years and 70.2% at 5 years. Cardiac disease was the single most important cause of death in long-term dialysis, accounting for 44% of overall mortality [13].

As a part of the National Kidney Foundation Task Force on CVD, cardiovascular mortality rates in the general population were approximately two million deaths when compared with CVD mortality rates in dialysis patients. These results showed that annual CVD mortality rates are much greater in dialysis patients despite stratification of sex, race, or age group. Younger dialysis patients have approximately 500-fold increased CVD mortality rates compared with their counterparts in the general population, and rates remain approximately five-times higher even among the oldest patients [12].

Homocysteine is a novel non-traditional risk factor for cardiovascular disease in CKD patients. The

data evaluating the role of elevated homocysteine levels and their relation to CVD in CKD patients has been sparse and only recently studied. The relationship between raised serum homocysteine and cardiovascular diseases is well established. Xu *et al.* in their study found the impact of raised serum homocysteine levels in CKD patients. It was also suggested that the raised homocysteine levels in chronic kidney disease lead to increased mortality and morbidity [14]. Studies have shown that elevated homocysteine levels are associated with unfavourable effects on left ventricular structure and function in haemodialysis patients, and also lead to microalbuminuria [15, 16]. It has also been shown that it is a powerful predictor of cardiovascular events in CKD patients.

Intima-media thickness, also called intimal medial thickness, is a measurement of the thickness of tunica intima and tunica media – the innermost two layers of the arterial wall. An increase in IMT is predictive of future cardiovascular disease [11]. Multiple studies have shown that the carotid artery IMT, as measured noninvasively by ultrasonography, is directly associated with an increased risk of cardiovascular disease in CKD patients, also. Therefore, the present study was conducted to evaluate the role of elevated homocysteine levels in CKD patients and its relationship with intima medial thickness in CKD patients.

The mean baseline values for serum homocysteine in group I, group II, and group III were 22.66 ±9.17, 24.20 ±8.43, and 29.38 ±7.3 μmol/l, respectively, reflecting their progressive increase with reduction in GFR. This finding was consistent with the observations of Guldener *et al.*, who noted raised homocysteine levels with declining kidney function [17]. Moustapha *et al.* found that homocysteine levels were higher in dialysis patients who had fatal and non-fatal cardiovascular events, and the high cardiovascular risk conferred by this hyperhomocysteinaemia was largely independent of traditional risk factors and unrelated to all-cause mortality [18]. Mallamaci *et al.* found a 20% increased risk of fatal cardiovascular complications for each 10 μmol/l increase in total plasma homocysteine levels [19]. After haemodialysis serum homocysteine levels decreased to 15.49 ±5.72 μmol/l, a decrease of 50% was observed. These findings were consistent with the findings of Arnadottir *et al.* and Hewitson *et al.*, who also noted a decrease in homocysteine levels with haemodialysis [20, 21].

Intima-media thickness in the bilateral common carotid arteries and internal carotid arteries at baseline increased significantly with decline in kidney function. Intima-media thickness is at present the best-studied sonographic marker for early atherosclerotic wall lesions. Measurement of carotid artery intima media thickness (CA-IMT) with ultrasonography is a reliable, reproducible, and non-invasive method for detecting and monitoring the progression of atherosclerosis in patients without clinical signs of CVD [22, 23]. Intima-media thickness is an important diagnostic tool to detect atherosclerotic plaque burden in patients with CKD. Kennedy *et al.*, in a study of 213 patients (69 on haemodialysis, 60 on peritoneal dialysis, and 82 non-uremic controls), observed that patients with CKD had higher IMT and the uremic milieu in these patients is an independent predictor of intima medial thickness [24]. Similarly, in a study by Sumil Kumar *et al.*, patients with end-stage renal disease (ESRD) at the time of initiation of dialysis were found to have significantly higher IMT as compared to controls [25]. The patients undergoing haemodialysis were found to have significantly higher values (group III) as compared to patients in non-haemodialysis groups (group I and group II). Paul *et al.* also observed similar findings. The authors found that haemodialysed patients had a higher IMT as compared to non-haemodialysed patients, and the medial thickness was independent of traditional risk factors for cardiovascular disease. It was also shown that ischaemic heart disease was positively correlated with carotid artery IMT and inversely correlated with GFR in CKD patients, and haemodialysis was an independent risk factor increased IMT [26]. Aggarwal *et al.* also showed higher values of IMT and increased calcification and plaque burden in the left common carotid artery as the stage of CKD progressed [27].

There was a 15% reduction in the mean baseline CA-IMT of left common carotid artery after haemodialysis. Similar reductions were noted in the values of CA-IMT of the right common carotid artery and bilateral internal carotid artery. These findings were consistent with findings of Duran *et al.*, who also noted a significant decrease in mean IMT values, but only after 2 years of haemodialysis [28].

The correlation coefficient for serum homocysteine levels and CA-IMT was non-significant in all the groups. These findings are consistent with the findings of other studies. Leskinen *et al.* found no correlation between serum homocysteine levels and CA-IMT [29]. This suggests that an elevation of serum homocysteine level may act simply as marker of CVD rather than being a significant risk factor in the pathogenesis of CVD. To study the effect of elevated serum homocysteine levels on atherothrombotic vascular diseases renal function has been considered an important confounding factor. This finding is further supported by the fact that similar factors are at play in development of CKD and CVD and an elevation in serum homocysteine levels. Randomised, placebo-controlled trials of the effect of serum homocysteine lowering on CVD events are required to resolve this issue. To date, results of such trials are not available [29].

Therefore, the present observations show that baseline serum homocysteine levels and carotid artery IMT levels were elevated at baseline in all the three groups, and progressively increasing values with declining renal function. Both serum homocys-

teine and CA-IMT were reduced significantly after haemodialysis, but the elevated levels of both did not correlate with each other.

This study is a single-centre study with no control group. Although the study clearly showed that carotid intima media thickness (CA-IMT) and homocysteine levels progressively increased with declining renal function, comparison with a normal control group would have been informative in this scenario. The further effect of haemodialysis on CA-IMT was seen only in a very small number of subjects with a shorter follow up of 3 months. Supportive studies in larger numbers of patients with longer follow-up are needed to strengthen the value of the study.

Conclusions

Both traditional and non-traditional risk factors play a role in the pathogenesis of cardiovascular diseases in patients of CKD. It is known that in CKD, uremic milieu accelerates the atherosclerotic process at an early stage, as is evident from increased serum homocysteine and CA-IMT levels. Based on consistent evidence, they should be included in routine investigations for risk evaluation and stratification of CVD in patients of ESRD. Long-term follow-up studies should be undertaken to analyse the influence of these factors on mortality in dialysis and pre-dialysis patients.

Conflict of interest

The authors declare no conflict of interest.

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