PRACA ORYGINALNA
ORIGINAL ARTICLE

THE RELATIONSHIP BETWEEN HOMOCYSTEINE LEVEL AND VITAMINS B_{12}, B_9 AND B_6 STATUS IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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ABSTRACT

Introduction: According to present knowledge, hyperhomocysteinemia is one of the risk factors of cardio-vascular pathology. Patients with chronic kidney disease are known to develop hyperhomocysteinemia more often than those in general population. Important cause of hyperhomocysteinemia is the deficiency of vitamins B_6, B_9 and B_{12} that are involved in homocysteine metabolism. Vitamins deficiency, we believe, can be one of the causes of hyperhomocysteinemia in the patients with chronic renal failure.

The aim: To analyze the plasma homocysteine level in patients with chronic kidney disease and its assosiation with the levels of vitamins B_6, B_9, B_{12} in Ukraine.

Materials and methods: The study involved 148 persons with different stagesis of chronic kidney disease who underwent immunoenzyme determination of total plasma homocysteine, B_9, cobalamin and vitamin B_6 status.

Results: It was found that in ukrainian patient population with chronic kidney disease 58.7% of patients have hyperhomocysteinemia. Homocysteine level was shown to increase with the increase of chronic kidney disease stage. Supply of vitamins B_6, B_9 та B_{12} in the patients with chronic kidney disease was lower than in apparently healthy persons, but there was significant decrease of folic acid level proportionally to the increase of chronic kidney disease stage. There was close relationship between homocysteine level and folic acid status in the patients with chronic kidney disease, but it appeared to be independent on cobalamin and pyridoxin status.

Conclusions: The obtained data are promising for finding effective means of correction of hyperhomocysteinemia in patients with chronic kidney disease by normalizing the vitamin status of such patients.

KEY WORDS: hyperhomocysteinemia, cobalamin, pyridoxine, folic acid, renal failure

Wiad Lek 2019, 72, 4, 532-538

INTRODUCTION

According to present knowledge, hyperhomocysteinemia (HHC) is one of the risk factors of cardio-vascular pathology [1, 2, 3]. Patients with chronic kidney disease (CKD) are known to develop HHC more often than those in general population [4, 5]. Today it is proved that in general population total homocysteine (HC) levels depend on age, sex, race and ethnic factors as well as on the rate of enzyme genetic polymorphism, involved in HC metabolism [6]. Equelly important cause of HHC development is the deficiency of vitamins B_6, B_9 and B_{12}, involved in HC exchange, providing enzymes with cofactors involved in HC exchange and degradation [7, 8]. Taking into consideration rather high prevalance of vitamin deficiency even among people with rather high material status [9, 10], it is suggested to be one of the major reasons of HHC both in normal population and in the patients with chronic renal failure (CRF). It should be noted that in Ukraine neither the supply of those vitamins in the patients with CRF nor the relationship between their status and the level of HC in blood plasma have been previously studied.

THE AIM

In view of this, the aim of the study was to study homocystein contents in blood plasma of the patients with chronic kidney disease and to evaluate its association with vitamins B_6, B_9 та B_{12} levels.

MATERIALS AND METHODS

148 in-patients and/or outpatients with CKD were examined at Vinnytsia Regional Pirogov Memorial Clinical Hospital, the clinical basis of Vinnytsia National Pirogov Memorial Medical University. The patients gave an informed consent to participate in the study. Chronic glomerulonephritis was diagnosed in 99 (66.9 %) and

Table I. Total plasma homocysteine level in the patients with different stages of chronic kidney disease and in healthy individuals (M±m, P)

Studied individuals	Homocysteine level, mcmol/l M±m	Homocysteine level ranking , number of patients, %		
		Normal level <10.0 mcmol/l	Subnormal level 10-15 mcmol/l	Hyperhomo-cysteinemia ≥15 mcmol/l
Practically healthy, n=30	9.35±0,57	24 (80%)	4 (13.3 %)	2 (6.7%)
CKD-I, n=35	10.7±0,72	17 (48,6%)*	10 (28.6%)	8 (22.8%)*
CKD-II, n=31	15.4±1.45*#	6 (19,4)*#	16 (51.6%)*#	9 (29.0%)*
CKD-III, n=43	21.9±0.43*#$	3 (7%)*#	6 (14%)#$	34 (79.0%)*#$
CKD-IV, n=14	26.7±2.1*#$	0	2 (14.3%)#$	12 (85.7%)*#$
CKD-V, n=25	27.3±1.83*#	0	1 (4%)#	24 (96.0%)*#$^

Notes: * - significance of differences with the group of healthy individuals; # - significance of differences with the group of patients with CKD-I; $ - significance of differences with the group of patients with CKD-II; ^ - significance of differences with the group of patients with CKD-III. The mark is indicated only in case of significant differences (P <0.05).

Table II. Vitamin B_6 supply in the patients with various degrees of CKD and in healthy individuals (M±m)

GroupNo	Studied individuals	Erythrocytes ASAT, mcmol/h ml	PLP-effect, %	Pyridoxin supply		
				Normal	Marginal	Deficiency
				< 70%	70-80%	>80%
1	Practically healthy, n=30	27.2±0.49	65.8±1.17	22 73.3%	8 26.7%	0
2	CKD-I, n=35	26.1±0.34	67.8±1.02	25 71.4%	9 25.7%	1 2.9%
3	CKD-II, n=31	27.3±0.31	66.9± 1.0	23 74.2%	8 25.8%	0
4	CKD-III, n=43	24.8±0.30	67.3± 0.83	32 74.4%	11 25.6%	0
5	CKD-IV, n=14	24.2±0.96	64.3± 2.77	11 78.6%	3 21.4%	0

Note: P>0,05 in all cases.

chronic pyelonephritis - in 49 patients (33.1 %). There were 77 females (52%) and 71 males (48%). All the patients were divided into two groups: the first one included 113 patients in whom underlying disease was accompanied by decreased glomerular filtration rate (GFR), and the second group consisted of 35 patients with no GFR impairement (CKD-I). In the group of patients with impaired GFR the following stages of CKD were diagnosed: stage II - in 31patients with impaired GFR, stage III – in 43, stage IV – in 14, stage V (terminal) – in 25 patients. The age of patients in the group with decreased GFR ranged from 18 to 60 years, the average age being 39.6 ± 1.13 years. The average age of the patients was 40.3 ± 2.33 years in CKD-II group, 45.4 ± 2.0 years in CKD-III group, 45.5 ± 3.38 years in CKD-IVgroup and 37.8 ± 2.53 years in CKD-V group. Average age of the patients in CKD-I group was 36.9 ± 2.4 years. 30 apparently healthy individuals (14 men and 16 women) aged 21-57 years (average age 40.6 ± 2.38 years) served as representative control group.

The stage of CKD was determined according to the classification adopted by the Second Ukrainian Congress of Nephrologists (2005).

Total plasma HC level was determined by immunoenzyme method using "Axis-Shield" set (UK) on immunoenzyme analyzer "Santinaile". Plasma level of folic acid (FA) was determined by microbiological method using folate-deficient strain *Lactobacillus casei ATCC 7469*. Cobalamin status was established by quantitation of urinary methyl-malonic acid excretion, vitamin B_6 status – by pyridoxal-dependent enzymes ALAT and ASAT as well as by PLP-effect [11].

The study was carried out in compliance with the provisions of the Council of Europe Convention on Human Rights and Biomedicine, Declaration of Helsinki and recommendations of the Committee on Bioethics of the Presidium of National Academy of Medical Sciences of Ukraine.

Statistical analysis of obtained data was performed with application package STATISTICA (StatSoft, USA, v6.0). Nonparametric Mann-Whitney U-test was used to assess the difference between groups, Pearson correlation analysis - to determine the relationships between the indices, Fisher's test - to compare the frequency of changes. P <0.05 was considered to be significant difference.

Table III. Vitamin B_9 supply in the patients with various degrees of chronic kidney disease and in healthy individuals (M±m)

GroupNo	Studied individuals	Serum folate level, mcg/l	Folate supply		
			Normal	Marginal	Deficiency
			>6 mcg/l	3-6 mcg/l	<3 mcg/l
1	Practically healthy, n=30	7.67±0.25	26 86.7%	3 10%	1 3.33%
2	CKD-I, n=35	7.29±0.17	31 88.6%	4 11.4%	0
3	CKD-II, n=31	6.88±0.17*	26 83.9%	5 16.1%	0
4	CKD-III, n=43	6.42±0.13*#	28 65.1%	15 34.9%*#	0
5	CKD- IV, n=14	6.1±0.29*#	9 64.3%	5 35.7%*#	0

Notes: * - significance of differences with the group of healthy individuals; # - significance of differences with the group of patients with chronic glomerulo- and pyelonephritis without CKD. The mark is indicated only in case of significant differences ($P < 0.05$).

Table IV. Vitamin B_{12} supply in the patients with chronic renal failure and in healthy individuals by urine excretion of methyl-malonic acid (M±m)

GroupNo	Studied individuals	Creatinine MMA, mcg/g	Cobalamin supply		
			Normal	Marginal	Deficiency
			<20 mcg/g	20-25 mcg/g	>25 mcg/g
1	Practically healthy, n=30	18.0±0.29	26 86.7%	4 13.3%	0
2	CKD-I, n=35	17.8±0.26	31 88.6%	4 11.4%	0
3	CKD-II, n=31	18.2±0.36	25 80.6%	6 19.4%	0
4	CKD-III, n=43	18.3±0.25	36 83.7%	7 16.3%	0
5	CKD-IV, n=14	18.6±0.51	10 71.4%	4 28.6%	0

Note: $P > 0.05$ in all cases.

RESULTS

The first stage of the study was devoted to evaluation of HC level in the patients with CRF and comparison of the data received with those in apparently healthy persons (Table I). Only 6.7% of practically healthy persons appeared to have increased HC level (above 15 mcmol/l). Increase of HC level in blood plasma was proportional to the severity of CKD which, in its turn, lead to the increase of HHC cases with higher HC concentrations. Among the patients with CRF the following HC levels were determined: normal – in 26 patients (17.6%), subnormal – in 35 patients (23.6%), and HHC – in 87 persons (58.7%).

The level of vitamin B_6 in the studied patients was assessed indirectly by PLP-effect value related to aspartat transaminase (ASAT) activity (Table II). Decreased level of ASAT in erythrocytes by 15% with simultaneous increase of PLP-effect (by 15%) was considered to be a significant sign of vitamin B_6 deficiency as compared to the control group. As no distinct relationship between ASAT activity value and PLP-effect rate was detected in the patients with various degrees of CKD, Table II gives the data on vitamin B_6 stores according to enzyme activation by pyridoxal phosphate. Average indices of ASAT activity as well as those of PLP-effect were found to be normal with no differences between them in all studied groups.

Vitamin B_6 deficiency was found in only one patient with CKD-I, while marginal deficiency (PLP-effect – 70-80%) was observed in all studied groups with equal frequency. Overall 32 cases of vitamin B_6 deficiency or marginal deficiency were diagnosed in the patients with CKD-I - CKD-IV (26%). The data obtained suggested that the level of vitamin B_6 stores

Table V. Vitamin B_6, B_9, B_{12} supply depending on plasma homocysteine level in studied individuals (M ±m)

Groups	n	Indices of vitamins supply		
		PLP-effect, %	Serum folate, mcg/l	MMA, urine excretion, mcg/g of creatinine
1 Patients with HC<10 mcmol/l	50	68.0±0.96	7.82±0.12	18.1±0.20
2 Patients with HC 10-15 mcmol/l	38	67.6±1.22	7.06±0.13*	18.0±0.27
3 Patients with HC 15-25 mcmol/l	31	67.8±1.28	6.51±0.15*#	17.7±0.32
4 Patients with HC >25 mcmol/l	29	68.7±1.6	5.92± 0.08*#$	18.8±0.34

Notes: * - significance of differences with group 1, # – significance of differences with group 2, $ – significance of differences with group 3.

Table VI. Correlation relationship between total plasma homocysteine level and vitamins B_6, B_9, B_{12} status in the patients with chronic kidney disease of various degrees and in apparently healthy individuals of the control group (r)

Group No	HC level, mcmol/l	Vitamin supply indices		
		PLP-effect, %	Serum folate, mcg/l	MMA, urine excretion, mcg/g of creatinine
Apparently healthy individuals, n=30				
1	9.35±0.57	0.23	-0.41*	-0.22
Patients with CKD-I, n=35				
2	10.7±0.72	0.18	-0.38*	0.16
Patients with CKD -II, n=31				
3	15.4±1.45	0.13	-0.48*	0.19
Patients with CKD -III, n=43				
4	21.9±0,43	-0.10	-0.43*	-0.02
Patients with CKD -IV, n=14				
5	26.7±2.1	0.05	-0.4*	0.12

Note: * - significance of correlation relationship.

was equal in the studied healthy persons and in the patients with CKD and was not influenced by CKD degree.

Somewhat different data were obtained after evaluation of vitamin B_9 status determining its serum level by direct (microbiologic) method. The test with high diagnostic value for detecting vitamin B_9 deficiency proved to be serum folic acid contents and that for vitamin B_{12} deficiency – excretion of methyl-malonic acid [12]. The data received, presented in Table III, are indicative of the fact that folic acid level gradually decreased insignificantly in the patients with CKD proportionally to the degree of renal insufficiency.

Significant decrease of folic acid concertration was revealed in CKD-III and CKD-IV patients. Those patients had higher frequency of marginal folate deficiency – in 34.9% and 35.7% of cases, respectively (P <0.05 according to Chi-squre test when compared to groups 1 and 2). Folate deficiency was found only in one person of the control group. A total of 29 cases of folate deficiency or marginal deficiency (23.6%) were diagnosed in the patients of groups 2-5 (123 individuals).

Supply of vitamin B_{12} was determined by methyl-malonic acid (MMA), its urine excretetion increased in inverse proportion to concentration of that vitamin in blood. The MMA excretion indices were not found to vary among all the patients, in no occasion deficiency was revealed (Table IV). Higher proportion of persons with marginal deficiency was found only in CKD-IV patients. The total number of patients having marginal deficiency of vitamin B_{12} was 21 (17.1%).

Additional statistical analysis found no relationship between HC level in blood plasma and indices of vitamins B_6 and B_{12} supply (Table V), unlike folate – its level appeared to be the least in the persons with higher HC level.

Table VII. Vitamin B_9 supply in dialysis patients, the control and in the patients with no signs of renal failure (M±m, P)

Studied individuals	Serum folate level, mcg/l	Folate supply		
		Normal	Marginal	Deficiency
		>6 mcg/l	3-6 mcg/l	<3 mcg/l
Practically healthy individuals, n=30	7.67±0.25	26 86.7%	3 10%	1 3.33%
CKD-I, n=35	7.29±0.17	31 88.6%	4 11.4%	0
CKD-V, n=25	6.0±0.24*#	11 44%*#	14 56%*#	0

Notes: * – significance of differences with the group of healthy individuals; # – significance of differences with the group of patients with chronic glomerulo- and pyelonephritis with no CKD.

In addition, potential correlation relationship between three factors – plasma HC level (factor 1), vitamin status (separately by vitamins B_6, B_9 and B_{12} – factor 2), and degree of CKD (factor 3) - was studied in comparison with apparently healthy individuals. The data received are given in Table VI, they are indicative of the absence of correlation between all three factors concerning vitamins B_6 and B_{12} (in all cases index t was less than 2.2, P>0.05). But there was significant inverse relashionship between plasma levels of HC and folic acid even in healthy individuals. Similar relationship between those indices by its direction and intensity, was observed in CKD-I, CKD -II and CKD –III groups of patients (t=2.38, 2.36, 2.95 and 2.56, respectively; P<0.05 in all cases). Only in group 5 (CKD-IV) the tendency or weak correlation between them was revealed (r=0.4; t=1.51), possibly because of a small number of patients in the group (14 persons). Even in the same index r=0.4 the result would have been significant if the group had consisted of 28 persons (n=28, t=2.23, P<0.05).

Significant inverse relashionship between plasma levels of HC and folic acid detected in studied patients made it possible to calculate the role of folate in HC concentration decrease. Actually, with augmentation of renal failure signs, plasma HC level in the patients with CKD increased in the group as a whole, but in some individuals it was partially dependent on folic acid level, and its high concentration inhibited the indicated action of CKD. After absolute difference between folate and HC concentrations had been determined in each group as compared to the next one with higher degree of CKD, relative percentage concentration of folic acid and its specific gravity were calculated. Hypohomocysteinemic contribution of folic acid was found to be 15.8%.

Because of direct assosiation of HC metabolism with folate status, Table VII presents the data on the level of that vitamin supply in dialysis patients.

Folate supply in dialysis patients appeared to be 22% lower than in the control group and 18% lower than in the patients with CKD-I. It is noteworthy that more than a half dialysis patients (56%) had marginal folate deficiency, while there were only 10% of such persons in the control group.

DISCUSSION

Thus, the study of plasma HC concentration first conducted in Ukrainian population of patients with CKD revealed nomal HC level in 26 (17.6%), subnormal – in 35 (23.6%), and HHC - in 87 patients (58.7%). HHC was found to increase together with the increase of CKD stage. For example, an average HC contents in the patients with CKD-IV was significantly higher by 21.9% and 73.4% than in those with CKD-III and CKD-II, respectively, and the number of persons with HHC among the patients with CKD-IV significantly exceeded the proportion of those with HHC among the patients with CKD-II and CKD-I in 2.9 and 3.8 times, respectively.

According to the data from literature, homocystein level is closely correlated to the severity of kidney damage, and it is significantly higher in the patients with terminal than initial stage of renal failure. An important role of kidneys in elimination of HC from blood plasma has been shown in other studies as well [13].

The study of vitamins B_6, B_9, B_{12} status revealed unsatisfactory supply of those vitamins in both practically healthy individuals and in the patients with CKD. Deficiency, or marginal supply of vitamins B_6, B_9, B_{12} was found in 26.7% - 13.3% of apparently healthy individuals and in 26%, 23.5% and 17.1% of patients with CKD, respectively. The deficiency of those nutrients (except folate) proved to be independent of renal insufficiency stage. There were no significant differences in average indices of pyridoxin and cobalamin as well as in proportion of persons with marginal supply of those vitamins among the patients with various stages of renal failure. Only the level of folic acid significantly decreased proportionally to the increase of renal failure. While marginal folate supply occurred in one of ten patients among those with CKD-I, it was detected in one of two dialysis patients.

Literature data indicate the deficiency of B vitamins to be a common occurrence among the patients with CKD [14]. Glomerular filtration rate in the patients with CRF was shown to be assosiated with low folic acid level [15] while vitamin B_{12} supply is not assosiated with microalbuminuria [16]. It is noteworthy that some authors showed an addition-

al administration of folate and vitamin B_{12} to prevent the progression of CKD in a high proportion of patients [17, 18].

At the second stage of the study we tried to find the relationship between the changes in vitamin B_6, B_9, B_{12} status and plasma homocystein level. Plasma homocystein level in CKD patients was proved to be closely assosiated with folic acid status but not with cobalamin and pirydoxin ones. Among the patients with optimal supply of vitamin B_9 and B_{12} hyperhomocysteinemia occurred in 30.6% and 26.4% of patients, respectively, while in the patients with deficiency of one of the vitamins - in 63.6% and 75.8% of cases. Pathogenetic role of vitamin B_9 in HHC formation among CKD patients was additionally confirmed by correlation analysis (r=-0.38 - -0.48). Therefore, a large proportion of studied patients with CRF was believed to have marginal, i.e. virtually moderate folate deficiency which can be partially the reason of HHC syndrome development. So, folate-independent and folate-dependent ways of HC metabolism were suggested in renal insufficiency.

CONCLUSIONS

1. In the patients with chronic renal failure normal homocysteine level was revealed in 26 patients (17.6%), subnormal – in 35 (23.6%), and hyperhomocysteinemia - in 87 persons (58.7%). Hyperhomocysteinemia was found to increase together with the increase of chronic kidney disease stage.
2. Supply of vitamins B_6, B_9, B_{12} was lower in the patients with chronic kidney disease than in apparently healthy individuals. Deficiency, or marginal supply of vitamins B_6, B_9, B_{12} was detected in 26.7% (B_6) and13.3% (B_9) of apparently healthy individuals and in 26%, 23.6% and 17.1%, respectively, of chronic kidney disease patients. At the same time only the level of folic acid significantly decreased proportionally to the increase of chronic kidney disease stage.
3. In the patients with chronic kidney disease homocystein level was found to be closely associated with folic acid status but it was independent of pyridoxin and cobalamin status.

Directions for future research involve the search for effective means of hypercysteinemia correction in the patients with chronic kidney disease by normalization of vitamin status in such patients.

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The work was done as part of the research work of Scientific and Research Institute of Invalid Rehabilitation (Educational Scientific Treatment Complex) of National Pirogov Memorial Medical University: "To substantiate scientific approaches to definition of components of rehabilitation potential in

patients with chronic kidney disease I-V D, T", state registration number 0116U00142. Financing - own funds.

Authors' contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.

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Received: 18.11.2018
Accepted: 08.03.2019