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ORIGINAL ARTICLES

The Influence of the Cooperation of Hyperhomocysteinemia and Arterial Hypertension. A Risk Factor on the Acceleration of the Progress of Chronic Renal Diseases

Art Zylbeari [1, 3], Elita Masha [3], Zamira Bexheti [2], Gazmend Zylbeari [1],
Milka Zdravkovska [4], Lutfi Zylbeari [1*]

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Abstract

Introduction: Chronic kidney disease (CKD) is a heterogeneous group of disorders that manifest differently with a multifactorial etiology. In addition to known factors such as diabetes, high blood pressure, genetic predisposition, age, gender, race, physical inactivity, obesity, and MIA, in recent years, high concentrations of homocysteine have also been considered as an independent risk factor in the acceleration of the progression of CKD, which, together with arterial hypertension, apparently affect the acceleration of the progress of chronic renal diseases.

Materials and Methods: In a cohort-prospective study, 100 patients were treated (40 women with an average age of 55.40±8.20 years and 60 men with an average age of 56.00±9.50 years) with CKD in the third stage (stage III and b b) with a GFR of 30- 59 ml/min/ 1.73m2 determined according to the formula modification of diet in renal disease (MDRD- GFR in ml/min for 1.73 m2=175 x Serum creatinine (Cr) -1.154 x age-0.203x1.212 (if the patient is black) x 0.742 (if female) treated in the internal medicine clinic at the Clinical Hospital in Tetovo, in the period January-2023-December-2023 randomized according to gender, age, nationality, primary kidney disease…

Results: The results obtained at the beginning of the study for all the examined parameters and those obtained after 12 months, both from the patients with Chronic disease and the control group of healthy individuals, are presented in the text below.

A significant difference was observed between the patients and the control group with $p<0.0001$.

Conclusion: CKD is a frequent occurrence worldwide (1 in 10 inhabitants or 10 of the world's population suffers from CKD; therefore, it is necessary to implement preventive and therapeutic measures aimed at early detection, prevention, and treatment of that disease as a conclusion of our paper, we can confirm that there is a strong connection between HHcy and high blood pressure and that together they contribute to the acceleration and progression of CKD; therefore their treatment with folate, vitamin B12, vitamin B6 should be started at an early stage of the disease to prevent the rapid progression of CKD.

Keywords: chronic kidney disease, hyperhomocysteinemia, arterial hypertension

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* ***Corresponding author:***
Prof. Dr. Ord. Lutfi Zylbeari, MD, PhD
✉ *dr-luti@hotmail.com*

1 Faculty of Medical Sciences, University of Tetovo, Republic of North MACEDONIA
2 Southeast European University-Tetovo, Republic of North MACEDONIA
3 Clinical Hospital, Tetovo, Republic of North MACEDONIA
4 Faculty of Medical Sciences, Goce Delçev University-Stip, Republic of North MACEDONIA

Introduction

Chronic kidney disease (CKD) presents a progressive impairment of all renal functions over several months (three months) months) to several years. CKD is a serious clinical and public health challenge globally. Despite the options contemporary for the treatment of CKD are not sufficient, and they have an increasing incidence and prevalence worldwide with a high cost. Therefore, it is more necessary to identify the risk factors responsible for the progression towards end-stage renal disease (ESRD), such as the balance of diabetes, the reduction of high blood pressure, the reduction of high

concentrations of lipids (triglycerides and cholesterol, LDL-ch, apolipoprotein-B100) and the reduction of high levels of Hcy, adiposity, tobacco consumption, which are among the most critical factors in the acceleration of CKD with a decrease in GFR and towards uremia. The reduction of the Glomerular Filtration Rate (GFR) and the ratio between albumin to creatinine (Urine albumin to creatinine ratio ACR) >30 mg/ CKD is manifested by five stages of the disease [1, 2]. The etiology of CKD is multifactorial, born or acquired from various diseases [3, 4]. In addition to the known factors, high concentrations of homocysteine (hyper-homocysteinemia-HHcy) coexist with arterial hypertension (AHT), apparently influence the acceleration of the progress of SKR towards the stage of uremia when treatment with chronic intermittent hemodialysis (HD) is imposed. CKD has reached a worldwide prevalence of 11.0-16.0% and is the leading cause of 15-18% of mortality in the year 2020. Hcy is a sulfur-containing amino acid, and the entire amount of Hcy in the body is formed through the methylation cycle from the essential amino acid methionine and cysteines, as the primary and only source of Hcy and is an essential mediator of the pathway of Hcy formation.

Hcy is not found in the proteins humans consume through food, so there is no DNA code for it. Only 1% of Hcy is free in plasma, while 70% is bound to albumin. The metabolism of Hcy includes methionine synthase (MS), methylene-tetrahydrofolate reductase (MTHFR), cystathionine B synthetase (CBS), vitamins B6, B12, and folic acid, as cofactors of these enzymes [5, 6]. In case of disruption of Hcy metabolism due to any enzymatic defect or due to the lack of an intercellular cofactor, an accumulation of Hcy in the cells occurs, and then a reduction in its excretion and an increase in circulating Hcy levels-Hyperhomocysteine. Hcy is eliminated through its catabolism in the kidneys and only 1% through urine due to glomerular filtration. Reference values of Hcy vary between 5-15 **μmol** /l. Hcy values between 15-30 **μmol** /l are considered elevated, 30-10 **μmol**/l represent moderate HHcy, and values >100 μmol/l are considered severe HHcy [7-9]. Several factors affect the increase in Hcy levels. Most of them are related to lifestyle, food, i.e., does the diet contain methionine, vitamins B6, B12, folates of acidic, animal or plant origin), age (Hcy concentrations increase with age), race (Indians and Pakistanis have lower levels), alcohol consumption (Eleva-ted values due to inhibition of the enzyme methionine synthase), smoking (elevated values due to the direct influence of toxic components on the process of methylation), the influence of hormones (pregnancy, menopause, and delayed age-senescence) as well as polymorphism of the methylene-tetrahydrofolate reductase (MTHFR) gene as a result of cystathionine B synthase and vitamin B6 deficiency, diseases (gastrointestinal, renal, autoimmune diseases, hypothyroidism, malignancies and diabetes mellitus), drugs (anticonvulsants, antilipemic, antibiotics, antidiabetics). Patients with kidney disease also have HHcy. HHcy affects the damage of renal parenchyma, renal tubules, and blood vessels. High homocysteine values are in high positive correlation with increased concentrations of creatinine and urea in serum and decreased GFR, accelerating the course of the disease because, in conditions of HHcy, the physiological path of filtration and reabsorption of Hcy in the glomeruli-tubular system of kidney is damaged [10-14].

The relationship between Hcy and the kidneys was first discovered in 1962 by Carson and Neill [15, 16] when they proved that HHcy is closely related to high serum creatinine and urea values. In recent years, several studies have proven that HHcy is also a risk factor in the progression of CKD due to high blood pressure. Elevated plasma homocysteine (Hcy) levels, termed hyperhomocysteinemia (HHcy), is a pathological condition characterized by elevated Hcy concentrations>15 μmol/L in the blood. HHcy begins to appear in the early stages of CKD and increases with the deterioration of renal function [8, 9]. The mechanisms by which the level of Hcy in plasma increases in patients with chronic kidney disease have not been fully discovered. Reducing renal excretion due to the weakening of renal functions is assumed to contribute to increasing homocysteine values in patients with CKD.

The decrease in GFR and the increase in nitrogen degradative products have a high positive correlation with HHcy and AHT.

The purpose of the work was to document the relationship between HHcy and high blood pressure and their impact on accelerating the progression of CKD in patients in the third stages a and b) to conclude the role of HHcy and hypertension in the progression of CKD.

Materials and Methods:

In a cohort-prospective study, 100 patients were treated (40 women with an average age of 55.40±8.20 years and 60 men with an average age of 56.00±9.50 years) with CKD in the third stage (stage III a and III b) with GFR=30-59 ml/min/1.73m^2 determined according to the formula Modification of Diet in Renal Disease (MDRD- GFR in mL/min for 1.73 m^2=175 x SerumCr-1.154 x age-0.203 x 1.212 (if patient is black) x 0.742 (if female), treated in the internal medicine clinic at the Clinical Center-Tetovo, randomized according to gender, age, nationality, primary kidney disease.

In the study, we also had a group of 70 healthy individuals: 30 females with an average age of 57.40±8.20 and 40 men with an identical average age of 56.00±9.40 years. As a reference value for total homocysteine (tHcy), 5-15 μmol/l was taken. High blood pressure was considered the average systolic blood pressure≥130mm Hg and mean diastolic pressure≥90mm Hg. The following parameters were examined in all individuals in the study (both patients with CVD and the control group): tHcy, blood count (Er, Hb, Htc), iron (sFe), lipid profile (TL, tHol. TG, HDL-ch, LDL-ch (Total Lipids-TL, Total cholesterol-TCh, Triglycerides-TG, HDL-ch (High-Density Lipoprotein cholesterol), LDL-ch (Low-Density Lipoprotein cholesterol), blood sugar, total albumin, microalbuminuria, serum urea, creatinine, uric

acid, BUN, and C-reactive protein (CRP). Venous blood and urine from patients with CKD and healthy individuals were always taken in the morning (after 12 hours of fasting) from 8-9 o'clock. They were analyzed in the clinical laboratory at the Clinical Hospital-Tetovo every four months within 12 months (January 2023-December 2023) with three measurements. The patients' results were compared with those obtained by the control group.

Table 1 shows the patients with CKD=100 (stage III a and stage III b) and the control group (F+M=70) according to gender and average age.

Table 2 shows the patients with CKD (stage III a and stage III b) according to the underlying disease (Diabetes mellitus-DM, arterial hypertension (AHT), chronic glomerulonephritis (ChrGMN), Chronic Pyelonephritis (ChrP), Adult polycystic kidney disease (APCKD) and by gender.

Statistical processing of the results: The obtained results from the examined patients with CKD and the control group were statistically processed with arithmetic mean value, standard deviation X±SD, with student "t" test, Mann-Whitney, and Wilcoxon test. The results were processed with the appropriate state-of-the-art statistical program, SPSS V26.

Results:

The results of the examined parameters (also of patients with CKD and the control group randomized by gender) at the study's beginning and end are presented in Tables 3-6. The tables show that the percentages of the parameters examined at the beginning and after 12 months are presented with a significant statistical difference for p=0.0001.

Over time, concentrations of Hcy, hypertension, urea, creatinine, uric acid, and proteinuria are observed in BUN, as well as the lipid fraction and decrease in GFR. This is another piece of evidence of the role of HHcy and blood pressure in the acceleration of chronic renal disease.

Table 3 shows the results of patients with CKD (F-40, M-60) and control group-70 (F-30, M-40) for tHcy, GFR, Urea (serum), Creatinine (serum), uric acid (serum), proteinuria (r.v=<3.4-33.9mg/mmol), BUN (Blood Urea Nitrogen (RV=2.4-6.4 mmol/L) and arterial pressure at the beginning of the study.

Table 4 shows the results of patients with CKD (F-40, M-60) and the control group-70 (F-30, M-40) from the parameters obtained for tHcy, lipid fractions, and blood pressure at the beginning of the study

From table 3 and 4, according to the statistical analysis performed with the Mann-Whitney U inversion test, a statistically significant difference in the average values of

Total no. of patients with CKD=100	*mean age ±SD*	*Cont.gr=70(F-30, M-40), mean age ±SD*
Female = 40	**55.00±8.20 years**	**57.40±8.20**
Males = 60	**56.00±9.50 years**	**56.00±9.40**

Table 1 Presentation of patients with CKD

Total nr. of pat. with CKD=100	*Females-40*	*Males-60*
DM	14 (35%)	24 (40%)
ART	11 (27,5%)	16 (26,6%)
Chr GMN	8 (20%)	12 (20%)
Chronic Pyelonephritis	4 (10%)	6 (10%)
APCKD	3 (7,5%)	2 (3,4%)

Table 2 Distribution of patients with CKD according to the underlying disease by gender

Total number of patients with CKD=100				*Control group=70*		
Param. examined	*number*	*Females-40*	*Males-60*	*Femalee-30*	*Males-40*	*p*
tHcy (µmol/l	100	24,30±9,00	38,60±8,60	7,00±3,60	9,50±4,80	0.0001
GFR(ml/min/1.73m^2)	100	56,50±2,00	58,00±1,00	110,00±3,20	112,00±3,50	0.0001
Urea(mmol/l)	100	17,30±4,60	20,50±2,00	6,00±2,00	7,20±3,00	0.0001
Kreatinin(µmol/l)	100	160,00±6,40	175,±4,00	80,00±5,00	92,00±4,20	0.0001
Ac.urik(µmol/l)	100	385,00±8,00	410,50±6,50	280±18,00	320±26,00	0.0001
Proteinuria/24 h	100	>47,00 ↑	>49,60 ↑	<16,50	<18,00	0.0001
BUN	100	>9,8↑	>11.00 ↑	4.5	5.7	0.0001
TA mmHg	100	175/95	180/95	116/75	118/80	0.0001

Table 3 Results of patients with CKD according to the control group

Total number of patients with CKD=100				Control group=70		
Param. examined	number	Females-40	Males-60	Female-30	Males-40	p
tHcy	100	24,30±9,00	38,60±8,60	7,00±3,60	9,50±4,80	0.0001
TL (g/l)	100	8,50±1,40	8,70±1.20	6,00±2,00	7,20±3,00	0.0001
TCh(mmol/l)	100	4,80±1,50	4,90±1,70	5,90±1,50	6,00±1,80	0.0001
TG(mmol/l)	100	2,90±1,80	3,20±1,30	1,26±0,40	1,35±0,80	0.0001
HDLch(mmol/l	100	1,06±0,40	1,10±0,20	1,40±1,00	1,30±0,90	0.0001
LDL-ch(mmol/l)	100	3,6±0,50	3,90±0,90	3,40±0,50	3,50±0,80	0.0001
TA mmHg	100	175/95	180/90	116/75	118/80	0.0001

Table 4. Results of patients with CKD according to the parameters

Total number of patients with CKD=100				_Control group=70		
Param. examined	number	Female-40	Males-60	Females-30	Males-40	p
tHcy	100	43,40±3,00	49,70±10,50	7,00±3,60	9,50±4,80	0.0001
Urea	100	20,00±6,80	26,00±5,00	6,00±2,00	7,20±3,00	0.0001
Kreatinin	100	190.00±20,50	230,00±12,00	80,00±5,00	92,00±4,20	0.0001
Acidi urik	100	410.00±10,00	430.0±8,00	280±18,00	320±26,00	0.0001
GFR	100	30,20±1,60	32,800±1,50	110,00±3,20	112,00±3,50	0.0001
Proteinuria/24 h	100	>35,40	>38.00	<16,50	<18,00	0.0001
BUN	100	>7,50	>8.20	4,5	5,7	0.0001
TA	100	175/95	180/95	116/75	118/80	0.0001

Table 5. Results of patients with CKD according to the control group after 12 months.

Total number of patients with CKD=100				Control group=70		
Param. examined	No.of the patient.	Females-40	Males-60	Females-30	Males-40	p
tHcy	100	43,40±3,00	49,70±10,50	7,00±3,60	9,50±4,80	0.0001
TL	100	8,00±1,00	8,70±1.20	6,00±2,00	7,20±3,00	0.0001
TCh	100	4,90±2,00	5,00±1,70	5,90±1,50	6,00±1,80	0.0001
TG	100	3,20±1,00	3,60±0,90	1,26±0,40	1,35±0,80	0.0001
HDL-ch	100	1,03±0,40	1,04±0,20	1,40±1,00	1,30±0,90	0.0001
LDL-ch	100	4,30±0,90	4,50±0,70	3,40±0,50	3,50±0,80	0.0001
TA	100	175/95	180/90	116/75	118/80	0.0001

Table 6. Results of patients with CKD according to the parameters after 12 months.

the examined parameters between the two studied groups (females+males) for Hcy, UACR, BUN, and lipid profile where a significant statistical difference was observed for p<0.0001 between the control group and patients with CKD.

Table 5 shows the results of patients with SKR (F-40, M-60) and control group-70 (F-30, M-40) for tHcy, GFR, Urea, Creatinine, uric acid in serum, and arterial pressure after 12 months.

From the table, we evident significant correlation between the examined parameters, gender, and the control group; a significant statistical difference was observed for p<0.0001 of all the examined parameters.

Table 6 shows the results of patients with CKD (F-40, M-60) and the control group-70 (F-30, M-40) from the parameters obtained for tHcy, lipid profile, GFR, and blood pressure after 12 months.

From the table, we evident significant correlation between the examined parameters, gender, and the control group; a significant statistical difference was observed for p<0.0001 of all the examined parameters.

Discussion

The main finding in our study was the positive correlation between HHcy and arterial hypertension (systolic and diastolic pressure) as well as their effects on the deterioration and progression of CKD, which consisted of a decrease in GFR and an increase in nitrogen degradation products (urea, creatinine, acid uric), BUN, proteinuria, results that are compatible with studies cited in the text. CKD represents

the progressive and irreversible decrease in the ability of the kidneys to perform their physiological functions. In the deterioration and rapid progression of CKD, in addition to diabetes and hypertension in recent years, concentrations of increased homocysteines (hyperhomocysteinemia (HHcy). HHcy is an increase in the plasma level of total Hcy (tHcy)>15 μmol/l.

The level of tHcy in patients with CKD is 3-5 times higher than average values, with a prevalence of HHcy of 85-100%. There is a significant correlation between creatinine and urea concentrations and the reduction of GFR. This argument proves that HHcy affects the acceleration of the progression of CKD. The connection between the metabolism of Hcy and the kidneys was discovered for the first time in 1962 by scientists Carson and Neill, who found that high concentrations of Hcy are closely correlated with increased concentrations of urea and creatinine in serum and decreased GFR. Studies on Hcy have verified that Hcy affects the vascular endothelium, causing arteriolar vasoconstriction, arterial wall hardening, increased sodium reabsorption, and kidney damage. Disease regardless of their underlying disease.

The main mechanisms by which Hcy, together with AHT, can result in kidney damage include oxidative stress (leading to oxidative damage to the vascular endothelium), reduced nitric oxide action to cause vasodilation, stimulation of vascular smooth muscle proliferation, and changing the elastic properties of the blood vessel wall.

Hcy is a non-proteinogenic amino acid produced during the methionine metabolism pathway, containing sulfur, which is formed as an intermediate between the transsulfuration and remethylation pathway of methionine and cysteine.

The role of Hcy is to serve as an intermediate in methionine metabolism.

Many studies on HHCy have verified that Hcy levels are reduced with folate and cyanocobalamin supplementation. This argument proves a close relationship between Hcy and folate and cyanocobalamin metabolism. In one study, it was verified that 80% of patients with CKD who also suffer from hypertension had high levels of Hcy compared to healthy participants (17). The results obtained from our work verified that there is a high positive correlation between AHT with HHcy and the decrease in glomerular filtration rate (GFR) with increasing concentrations of urea, creatinine, uric acid and proteinuria, results that also correspond with the findings of the studies cited in the text (18). The findings suggest that combining AHT and HHcy can increase the impact and generate a more aggravating and worsening effect on kidney function.

The coexistence of AHT and HHcy in patients with CKD affects the appearance of premature atherosclerosis of the vessels, blood pressure, and acceleration of the disease. Arterial hypertension (HTA) is one of the most critical risk factors for CKD. Early studies found that the prevalence of HTA was inversely correlated with the estimated glomerular filtration rate (eGFR) and that lowering blood pressure may slow the progression of CKD. At the same time, HHcy and AHT may impair the autoregulatory capacity of the renal arterioles, resulting in increased glomerular pressure, glomerulosclerosis, and tubulosclerosis [8, 15].

AHT and diabetes are traditionally considered a typical marker of CKD and are an important and independent risk factor for their progression; therefore, early intervention in balancing and normalizing HTA, diabetes, and HHcy to prevent the progression of renal damage in individuals with CKD is a challenge and obligation of health professionals [19-23].

Patients with AHT and HHCy, called H-type hypertension, are at high risk for early presentation of cardiovascular disease (CVD) (24). A multivariate multivariate logistic regression analysis showed that type H hypertension was associated with high concentrations of Hcy, proteinuria, urea, creatinine, uric acid, low glomerular filtration rate (GFR), and hypertension. They documented that patients with type H and HHcy hypertension had poorer kidney function and left ventricular hypertrophy with carotid intima-media thickening (cIMT) compared to individuals with normotension and normal homocysteinemia [24].

HHcy is a crucial independent biomarker for endothelial dysfunction. It leads to an imbalance between blood endothelin and nitric oxide (NO) levels, causing subclinical inflammation with increased vascular endothelial damage, glomerulosclerosis with nephrology-arteriosclerosis with impaired GFR in patients with CKD and AHT [20].

In our study, patients had a high increase in Hcy and AHT with a statistically significant difference for $p<0.0001$ with all parameters examined (total cholesterol, total lipids, TG, HDL-Ch, LDL-ch Ch, urea, creatinine uric acid, proteinuria, BUN and with GFR) compared to the control group of healthy individuals—the increase in Hcy concentrations with reduced bioavailability of NO leads to the proliferation of myocytes. Excessive growth of smooth muscle cells in the vascular wall increases peripheral resistance and induces hypertension [25, 26].

HHcy leads to oxidative stress, and free radicals cause excessive damage to structural proteins and enzymes of the vascular wall, including endothelial damage [27, 28].

The excess of Hcy builds thiolactone, which, as a highly reactive ester, chemically reacts with the protein component of LDL-lipoproteins, forming thiolactone LDL-homocysteine aggregates.

These LDL-homocysteine molecules represent an attractive material for cellular macrophages, which turn them into foam cells ("foam cells") and deposit them easily and quickly in the endothelium of the arteries.

Deposited in this form, LDL lipoproteins and Hcy initiate the process of hyperplasia and fibrosis of smooth muscle cells and facilitate the accumulation of free oxygen radicals. The critical effects of HHcy on endothelial function are mediated through the inhibition of oxide synthase.

Endothelial nitric (NO) produces endoplasmic reticulum stress, further increasing oxidative stress and inflammation. Genetic factors such as methylenetetrahydrofolate

reductase (MTHFR), a key enzyme in folic acid and vitamin metabolism, also affect the appearance of HHcy. Recent studies have shown that HHcy can also appear as a result of reduced excretion of Hcy, which is also manifested by an extrarenal increase in Hcy concentrations, manifesting with HHCy, which, in the presence of AHT, apparently affects the acceleration of the progression of CKD and premature arteriosclerotic manifestations of the renal arteries.

Treatment of HHcy with folate, vitamin B12, vitamin B6, and antioxidant supplements, dietary compliance, AHT normalization with ACE inhibitors or ARBs, and balancing diabetes management of uremic dyslipidemia has shown highly positive effects in preventing the rapid progression of disease in patients with CKD. Accumulation of homocysteine eventually damages glomerular cells and causes glomerular sclerosis [29]. Oxidation caused by homocysteine causes the primary pathogenesis of hyperhomocysteinemia [30, 31].

Homocysteine and glutathione are primary thiol-containing amino acids in the human body. Thiols are readily catabolized to thiol radicals (RS), which interact with other thiols to produce disulfide anions (the joining of two thiol-urea disulfide groups) and other oxygen species (ROS), including superoxide anion radicals (O_2) and hydrogen peroxide (H_2O_2). Hcy can also produce reactive oxygen species (ROS) by activating nicotinamide adenine dinucleotide phosphate oxidase (NADPH).

These ROS disrupt normal cellular function and lead to kidney damage and the acceleration of CKD.HHcy, together with AHT, compromises the normal microvascular physiological function in many organs with microvascular systems, including the kidney, which accelerates CKD [32-35].

Conclusion:

In conclusion, we propose that the examination of the level of Hcy be included in the protocols of nephrological examinations in the initial stages of CKD to prevent adverse effects and the rapid progress of CKD, especially in patients who also suffer from HTA. Our study proves that the joint influence of hypertension and HHCy play an essential role in renal damage and acceleration of SKR. HHcy associated with AHT is considered an independent risk factor for CKD. In conclusion, substitution with preparations of folate, vitamin B (B12 and B6), and other antioxidants affect the reduction of Hcy concentrations, which also significantly affects the slowing down of CKD progress in patients with HHcy and HTA.

COI Statement: This paper has yet to be submitted in parallel, presented fully or partially at a meeting, podium, or congress, published, or submitted for consideration beforehand.

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Abbreviations;

Chronic Kidney Disease - CKD; end-stage renal disease - ESRD; Hemodialysis - HD; Methionine Synthase – MS; methylene-tetrahydrofolate reductase – MTHFR; cystathionine B synthetase – CBS; Malnutritio-Inflammatio-Atherosclerosis – MIA; hyper-homo-cysteinemia - HHcy; Arterial Hypertension – AHT; creatinine – Cr; Glomerular Filtration Rate – GFR; total homocysteine – tHcy; serum iron – sFe; total Lipid – tL; triglyceride -TG; total cholesterol – Tchol; high-density lipoprotein- cholesterol – HDL- ch; Low-density lipoprotein - cholesterol – LDL-ch; blood urea nitrogen – BUN; c-Reactive Protein – CRP; Diabetes mellitus -DM; chronic glomerulonephritis - ChrGMN; Chronic Pyelonephritis – ChrP; Adult polycystic kidney disease – APCKD; Blood Urea Nitrogen – BUN; Endothelial nitric – NO; Nicotinamide Adenine Dinucleotide Phosphate Oxidase – NADPH; Reactive Oxygen Species – ROS;

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