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Renalase, dopamine, and norepinephrine as markers for the development of hypertension in CKD patients

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Abstract

Introduction Chronic kidney disease (CKD) leads to irreversible changes in kidney function and structure, with over 90% of patients developing arterial hypertension (HT). Renalase, dopamine, and norepinephrine are believed to influence HT development and CKD progression.

Aim of the study This study aims to measure renalase, dopamine, and norepinephrine levels in CKD patients to evaluate their potential as markers for CKD progression, HT development, and cardiovascular event risk.

Materials and methods The study involved 117 CKD patients divided into four groups: 32 hemodialysis patients (before and after treatment), 31 peritoneal dialysis patients, 24 kidney transplant recipients (pre- and post-transplant), and 30 conservatively treated patients (CKD stages 2–5). A control group included 31 healthy volunteers. Levels of renalase, dopamine, and norepinephrine were measured using the ELISA method.

Results The study found that CKD significantly affected renalase, dopamine, and norepinephrine levels ($p=0.046$; $p=0.035$; $p=0.023$). The lowest renalase levels were in patients with ADPKD and HT, while the highest dopamine levels were in those with CKD due to glomerulonephritis. The lowest norepinephrine levels were observed in patients with HT and diabetes.

Conclusions Levels of renalase, dopamine, and norepinephrine may indicate CKD progression, cardiovascular event risk, and patient prognosis.

Keywords Renalase, Dopamine, Norepinephrine, Chronic kidney disease, Hypertension

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Summary table

What is known about the topic	What this study adds
1. Arterial hypertension (HT) develops in > 90% of patients with CKD. 2. Renalase dopamine and norepinephrine may be involved in the pathogenesis of HT and are factors in the progression of kidney disease	1. The influence of the cause of CKD on renalase, dopamine, and norepinephrine levels. 2. The type of renal replacement therapy affects the concentration of renalase, dopamine, and norepinephrine. 3. The concentration of renalase, dopamine, and norepinephrine may inform about the progression of CKD, the probability of cardiovascular events, the patient's prognosis

Introduction

Chronic kidney disease (CKD) develops due to various disease pathways that permanently change renal function and structure over months or years [1, 2]. The global annual incidence of CKD is around 150 million. In the United States, approximately 11% of adults have chronic kidney disease, with this percentage rising to 30% among people over the age of 65 (specifically in stages G3-G5, about 8%). In Poland, CKD in stages G3-G5 is already present in 21% of individuals older than 65, with an estimated prevalence of 4–5 million [1].

Chronic kidney disease (CKD) treatment involves addressing the underlying causes, slowing disease progression, managing complications and comorbidities, preventing cardiovascular disease, and preparing for and initiating renal replacement therapy [3].

Hypertension (HT) increases the risk of atherosclerotic cardiovascular disease, congestive heart failure, and end-stage kidney disease (ESKD) and is a significant contributor to morbidity and mortality worldwide. According to the 2010 National Health and Nutrition Examination Survey, 84% of adults with an estimated glomerular filtration rate (eGFR) less than 60 ml/min per 1.73 m2 had hypertension. Still, only 32% had well-controlled HT with blood pressure (BP) values below 140/90 mm Hg [4].

Cardiovascular disease is the leading cause of illness and death in patients with chronic kidney disease (CKD), even when they receive renal replacement therapy. Common heart-related issues in CKD include heart failure, coronary artery disease, and cardiac arrhythmias. Pulmonary hypertension (PH) is also increasingly recognized as a prevalent condition in CKD patients. More than 90% of CKD patients develop hypertension, which is linked to an increased risk of left ventricular hypertrophy, coronary artery disease, congestive heart failure, cerebrovascular complications, and mortality. Causes of hypertension in CKD include glomerulonephritis, diabetic kidney disease, kidney damage in systemic connective tissue diseases, inflammatory nephropathy, tubulointerstitial nephritis, polycystic kidney disease, and conditions following kidney injury, renal cysts, or renal cell carcinoma. The discovery of renalase has provided hope for understanding the pathogenesis of hypertension in cardiovascular disease. It is believed that renalase may break down catecholamines and regulate sympathetic tone and blood pressure [5–7].

The intricate relationship between renalase, dopamine, and norepinephrine in the context of chronic kidney disease and its associated cardiovascular complications has been the subject of numerous comprehensive studies [8–14]. Despite the wealth of research, our understanding of how these compounds specifically contribute to the pathogenesis of these diseases remains limited. Considering their potential impact on chronic kidney disease, hypertension, and the complex interplay between these conditions, delving further into the correlations and cause-and-effect relationships presents an exciting avenue for research. Exploring these connections could significantly enhance our comprehension of these diseases, refine patient prognosis accuracy, and potentially pave the way for innovative pathophysiological therapies. Ultimately, this line of inquiry holds promise for mitigating the considerably heightened cardiovascular risk faced by individuals with chronic kidney disease.

Materials and methods

Blood was drawn from the study group patients and healthy volunteers acting as controls to determine planned parameters. Blood was collected in two tubes: K_2EDTA (8 ml) for renalase, dopamine, and norepinephrine level determination and clot (8 ml) for biochemical tests. Before blood collection, patients were instructed to sit or lie down for 20–30 min to relax. This was important for accurately measuring dopamine and norepinephrine levels, as it helps reduce sympathetic nervous system tension. Blood was collected from the dialysis vascular access (a-v fistula or dialysis catheter) for hemodialysis patients. Blood was collected from a peripheral vein for other patients (peritoneal dialysis, renal transplant patients, conservative treatment) and healthy volunteers. Hemodialysis patients had blood collected twice: before (A) and after (B) the procedure. For renal transplant patients, blood was collected before and approximately 5–7 days after the transplantation. Blood samples collected in K_2EDTA and clot tubes were centrifuged at 2600 rpm, 10 min, and 20 °C to obtain plasma and serum, which were then frozen at -80 °C until further testing.

Determination of biochemical parameters in serum

Basic serum biochemical parameters such as creatinine, glucose, total cholesterol, triacylglycerols (TAG), HDL cholesterol, urea, albumin, and total protein were

determined using ready-made reagent kits (Biomaxima, Lublin).

Determination of renalase concentration

Using a ready-to-use ELISA reagent kit, ELISA determined renalase concentration in EDTA- plasma (Cloud-Cloune Corp, USA).

Determination of dopamine and norepinephrine concentration

ELISA determined Dopamine concentration in EDTA-plasma using a ready-to-use ELISA reagent kit (DLD Diagnostika GMBH, Germany).

Statistical analysis

The obtained results underwent statistical analysis. The Shapiro-Wilk test assessed the normality of distributions, indicating that some of the variables deviated from a normal distribution. Each factor was described by its mean, standard deviation, median, and lower and upper quartiles. Fisher's exact test and Chi-square were used to analyze the qualitative data. Student's t-test and ANOVA analysis were used to assess differences between related (paired) and unrelated (unpaired) variables for univariate systems. The F-test was used to analyze variance, and Levene's test was used to test the homogeneity of variance for multiple series. In some cases, the assumptions required for the analysis of variance were violated, but this did not affect the reliability of the F statistic in most cases. Kruskal-Wallis ANOVA analysis was used for non-parametric variables, the Whitney U-Mann test for unpaired data, and the Wilcoxon test for paired data. Spearman's rank correlation coefficient was used to measure the strength of the correlation between parameters. A multivariate regression model assessed the associations between the studied parameters. Renalase, dopamine, and norepinephrine concentrations were the dependent variables, while the age of patients, duration of dialysis, cause, and stage of chronic kidney disease were the independent variables. The G*Power software performed a sensitivity analysis for Kruskal-Wallis ANOVA. Based on our analysis, a Kruskal-Wallis ANOVA with 137 participants across 5 groups would be sensitive to the effects of $\eta^2 = 0.113$ with a power of 95% ($p = 0.05$). This indicates that our study would not be equipped to detect an impact smaller than $\eta^2 = 0.113$ reliably. For all analyses, an alpha level of 0.05 was applied. The results were processed using the StatSoft Statistica PL 13 Trial statistical program. Statistically significant results were considered when $p < 0.05$.

Results

Characteristics of the study group

The study group included 117 patients diagnosed with, who were treated at the Department of Nephrology, Transplantation, and Internal Medicine of the Pomeranian Medical University in Szczecin.

Based on the type of renal replacement therapy used, patients were divided into four groups: hemodialyzed (divided into 2 subgroups of determinations: HD A - before hemodialysis and HD B immediately after completion of hemodialysis on a given day in the same patients) – 32 patients, peritoneal dialysis (PD) – 31 patients, renal transplant patients – 24 patients (divided into 2 subgroups of determinations: TE A before kidney transplantation and TE B CKD – 5–7 days after kidney transplantation) and conservatively treated patients – 30 patients (stage CKD 2–5). Patients recruited into the TE group did not simultaneously belong to the group of hemodialysis or peritoneal dialysis patients. The control group included 31 healthy volunteers (GFR > 90). Persons belonging to the control group did not have any chronic diseases. To qualify for this group, was to show the basic blood tests such as blood count and biochemistry, including, in particular, the concentration of creatinine, albumin, total protein, cholesterol, triglyceride, and glucose levels. All participants in the study underwent a control ECG and had their blood pressure measured. The ECG results did not deviate from the norm at that time.

The conditions for exclusion from the study group were infections, serious infections (using antibiotics or other drugs that affect the results obtained), operations performed within six months, pregnancy, and contraceptives.

The conditions for exclusion from the control group were chronic diseases declared by the volunteers (e.g., diabetes, kidney disease), infections, operations performed within six months, pregnancy, and contraceptives.

Tables 1 and 2 provide details of age, gender, duration of dialysis, cause of chronic renal failure, creatinine, uric acid, albumin, phosphorus, CRP levels, blood pressure, and chronic kidney disease stage. All patients included in the study gave informed consent to participate. The study was approved by the Bioethics Committee at the Pomeranian Medical University in Szczecin (no KB-0012/36/11).

Renalase, dopamine, and norepinephrine levels in renal replacement therapy used

The concentrations of the factors studied (renalase, dopamine, and norepinephrine) are shown in Table 3. The effect of the type of renal replacement therapy on renalase, dopamine, and norepinephrine concentrations was demonstrated ($p < 0{,}001$; $p < 0{,}001$; $p = 0{,}002$). The highest renalase levels were observed in peritoneal

Table 1 General characteristics of Hemodialysis patients (HD), peritoneal dialysis (PD) treated conservatively (PNN) before and after kidney transplantation (TE), and control group (NK) participating in the study (mean ± OS)

Parameters	HD	PD	CKD	TE	NK	*p**	*p***
SEX [M- male; F – female]	M-19 F-13	M-17 F-14	M-18 F-12	M-12 F-12	M-18 F-13	NS	NS
Age [years]	61 ± 15	55 ± 14	66 ± 14	59 ± 11	50 ± 10	0,002	NS
Dialysis duration [months]	25 ± 19	33 ± 24	-	45 ± 34	-	-	0,003
Residual diuresis Yes/No	Y-24 *N* – 8	Y- 28 *N* – 3	-	-	-	NS	NS
Ultrafiltration [mL/h/mmHg]	45 ± 15	37 ± 10	-	-	-	-	NS
Causes of chronic kidney failure: 1 – DM	6 (19%)	5 (16%)	4 (13%)	1 (4%)	-	-	NS
2 – HT	13 (41%)	1 (3%)	6 (20%)	1 (4%)	-	-	NS
3 – KZN	4 (12,5%)	6 (19%)	7 (23%)	6 (25%)	-	-	NS
4 – ADPKD	2 (6%)	2 (6%)	6 (20%)	3 (13%)	-	-	NS
5 – other	4 (12,5%)	10 (32%)	5 (17%)	6 (25%)	-	-	NS
6 – unknown	3 (9%)	7 (31%)	2 (7%)	7 (29%)	-	-	NS

P* - statistical significance for differences between HD, PD, CKD, TE, and NK groups for quantitative variables - Kruskal Wallis rank ANOVA and Fisher's exact test for qualitative variables;

P** - statistical significance for differences between HD, PD CKD, and TE groups for quantitative variables -

Kruskal Wallis ranks ANOVA or Fisher's exact test for qualitative variables: DM—diabetic nephropathy; HT—hypertension; KZN—glomerulonephritis; ADPKD—autosomal dominantly inherited polycystic kidney disease

Table 2 General characteristics of hemodialyzed (A - before, B - after HD), peritoneal dialysis (PD) treated Conservative (PNN) patients before and after kidney transplantation (TEA and TE B) and control group (NK) participating in the study (mean ± OS)

Parameters	HD A	HD B	PD	CKD	TE A	TE B	NK	*P**	*P***
Kt/V	1,34 ± 0,2	1,34 ± 0,2	2,94 ± 0,7	-	-	-	-	NS	NS
Concentration of creatinine [mg/dl	6,5 ± 2,6	3,14 ± 0,2	4,78 ± 2,3	2,64 ± 1,05	6,36 ± 2,5	2,1 ± 2,37	0,82 ± 0,18	< 0,001	< 0,001
GFR [ml/min./1,73m^2]	12 ± 11	24 ± 11	20 ± 11	37 ± 25	11 ± 9	71 ± 44	116 ± 24	< 0,001	< 0,001
Concentration of uric acid [mg/dl]	5 ± 2,38	3,49 ± 1,2	5,69 ± 1,03	6,29 ± 1,24	5,5 ± 1,1	5,55 ± 1,95	6,34 ± 1,07	< 0,001	< 0,001
Concentration of albumin [g/dl]	5,65 ± 2,4	3,56 ± 0,78	5,67 ± 4,2	3,66 ± 0,84	3,7 ± 0,6	3,15 ± 1,95	5,75 ± 0,7	0,0006	0,0131
Concentration of phosphorus [mg/dl]	1,52 ± 0,44	1,8 ± 0,58	1,55 ± 0,3	1,31 ± 0,3	1,23 ± 0,38	1,81 ± 0,51	–	–	NS
CRP [mg/L]	0,9 ± 0,4	1,1 ± 0,6	1,4 ± 0,6	0,7 ± 0,5	2,3 ± 1,2	25 ± 4,0	0,3 ± 0,1	0,01	0,01
Systolic BP, [mmHg]	142 ± 12	134 ± 7	145 ± 20	142 ± 10	137 ± 9	119 ± 4	115 ± 8	NS	NS
Diastolic BP, [mmHg]	87 BP ± 5	78 ± 5	90 ± 5	80 ± 6	83 ± 7	75 ± 5	72 ± 4	NS	NS
BMI [BMI index]	25,9 ± 3,9	–	27,2 ± 2,1	31 ± 2,9	26,3 ± 3,8	-	25,1 ± 3,6	NS	NS
Diabetes	N – 24 Y – 8	–	N – 25 Y – 6	N – 20 Y – 10	N – 23 Y – 1	-	N – 31 Y – 0	0,01	NS
Dyslipidemia	N – 26 Y – 6	–	N – 25 Y – 6	N – 14 Y – 16	N – 8 Y – 16	-	N – 31 Y – 0	0,01	NS
Hypertension	N – 7 Y – 25	–	N – 13 Y – 18	N – 15 Y – 15	N – 3 Y – 21	-	N – 31 Y – 0	NS	NS

P* - statistical significance for differences between HD, PD, CKD, TE, and NK groups for quantitative variables - Kruskal Wallis rank ANOVA and Fisher's exact test for qualitative variables;

P** - statistical significance for differences between HD, PD CKD, and TE groups for quantitative variables -

Y-Yes; N-No

BMI-Body mass index is the ratio of weight to height, expressed in one value - the BMI index

Dyslipidemia- The diagnosis was confirmed by testing lipid parameters if one or more abnormalities were present, such as blood cholesterol level > 5.2 mmol/l (200 mg/dl); triglycerides > 1.7 mmol/l (150 mg/dl); LDL cholesterol > 2.58 mmol/l (100 mg/dl) and/or HDL cholesterol < 1.03 nmol/l (40 mmol/l)

GFR -glomerular filtration rate- **Cl = U × V/P**

Cl – clearance of the tested substance (ml/min), U – concentration of the substance in urine (mg/dl or mmol/l), V – urine volume (ml/min), P – concentration of the substance in serum (mg/dl or mmol/l)

Table 3 Plasma Renalase, dopamine, and norepinephrine levels in patients with chronic kidney disease - hemodialyzed (before and after treatment - HD A, HD B), peritoneal dialysis (PD) treated conservatively (CKD), before and after kidney transplantation (TE A TE B), and in the control group (NK) (mean ± OS, median - lower and upper quartile). P* Kruskal-Wallis rank ANOVA analysis of Renalase concentration across study groups

Parameters	Group of patients	Descriptive statistics	*p**
Renalase [ng/mL]	Before Hemodialysis (HD A)	5709 ± 7930 1459 (865; 11 045)	<0,001
	After Hemodialysis (HD B)	7944 ± 7285 5340 (2085; 13 930)	
	Peritoneal dialysis (PD)	9946 ± 7858 6720 (3558; 14 595)	
	Conservative treatment (CKD)	8224 ± 7526 6123 (2854; 10 495)	
	Before kidney transplant (TE A)	11 331 ± 9872 6157 (5118; 14 013)	
	After kidney transplant (TE B)	9464 ± 8291 6057 (4320; 14 043)	
	Control Group (NK)	5658 ± 5264 4155 (347; 9675)	
Dopamine [ng/mL]	Before Hemodialysis (HD A)	0,059 ± 0,114 0,022 (0,008; 0,05)	<0,001
	After Hemodialysis (HD B)	0,375 ± 1,424 0,091 (0,044; 0,19)	
	Peritoneal dialysis (PD)	0,008 ± 0,007 0,055 (0,04; 0,16)	
	Conservative treatment (CKD)	0,093 ± 0,107 0,076 (0,47; 0,11)	
	Before kidney transplant (TE A)	0,06 ± 0,038 0,051 (0,035; 0,09)	
	After kidney transplant (TE B)	0,077 ± 0,054 0,059 (0,037; 0,11)	
	Control Group (NK)	0,057 ± 0,036 0,05 (0,033; 0,072)	
Norepinephrine [nmol/L]	Before Hemodialysis (HD A)	0,225 ± 0,583 0,015 (0,002; 0,05)	0,002
	After Hemodialysis (HD B)	0,261 ± 0,298 0,149 (0,031; 0,36)	
	Peritoneal dialysis (PD)	0,396 ± 0,833 0,232 (0,004; 0,44)	
	Conservative treatment (CKD)	0,321 ± 0,518 0,228 (0,037; 0,34)	
	Before kidney transplant (TE A)	0,2 ± 0,166 0,187 (0,013; 0,34)	
	After kidney transplant (TE B)	0,517 ± 1,435 0,224 (0,037; 0,39)	
	Control Group (NK)	0,7 ± 1,935 0,135 (0,003; 0,436)	

P* Kruskal-Wallis rank ANOVA analysis of renalase concentration across study groups

dialysis patients, while the lowest levels were observed among patients before hemodialysis (Fig. 1). Statistically significant differences were observed between the renalase levels of patients before hemodialysis and the HD B, PD, TE A, TE B, and CKD groups, as well as between the control group (NK) and the peritoneal dialysis (PD) and TE B groups.

The effect of renal replacement therapy on plasma dopamine concentrations was demonstrated ($p < 0{,}001$). The highest dopamine concentrations were found in patients treated conservatively and the lowest in patients before hemodialysis. Also, high concentrations were present after hemodialysis (HD B) and kidney transplantation (Fig. 2). Statistically significant differences were observed between dopamine levels in patients before hemodialysis, the HD B, PD, TE A, TE B, and CKD and NK groups, and between the control (NK) group and the HD B group.

The effect of renal replacement therapy on plasma norepinephrine concentrations was demonstrated ($p = 0{,}002$). The highest NE concentrations were found in patients treated conservatively and after kidney transplantation and the lowest in patients before hemodialysis (Fig. 3). Also, high mean norepinephrine concentrations were found in the control group. Significant differences were observed between NE concentrations in patients before hemodialysis and the HD B, PD, TE A, TE B, and CKD groups. A difference in NE concentrations on the verge of statistical significance was shown between the HD A and NK groups ($p = 0.051$).

The influence of the cause of chronic kidney disease on the concentration of renalase dopamine and norepinephrine

The influence of the cause of chronic kidney disease on the concentration of renalase and dopamine has been demonstrated as norepinephrine ($p = 0{,}046$; $p = 0{,}035$; $p = 0{,}023$). The highest concentration of renalase was shown in patients whose cause of CKD was other than diabetic nephropathy, hypertension, glomerulonephritis, and polycystic kidney disease. The lowest concentration was found in patients whose CKD was caused by ADPKD (autosomal dominantly inherited polycystic kidney disease) and arterial hypertension (Fig. 4).

The highest dopamine concentration was found in patients with CKD caused by glomerulonephritis. Still, high values were also obtained in patients with hypertension and those whose causes of chronic kidney disease were other than those mentioned above. The lowest concentrations were obtained in patients with diabetic nephropathy and ADPKD (Fig. 5). The highest norepinephrine concentrations were found in patients whose CKD was caused by ADPKD, or the cause was unknown. The lowest concentration was obtained in patients with arterial hypertension and (taking into account primarily the median NE concentrations) also in patients with diabetic nephropathy (Fig. 6).

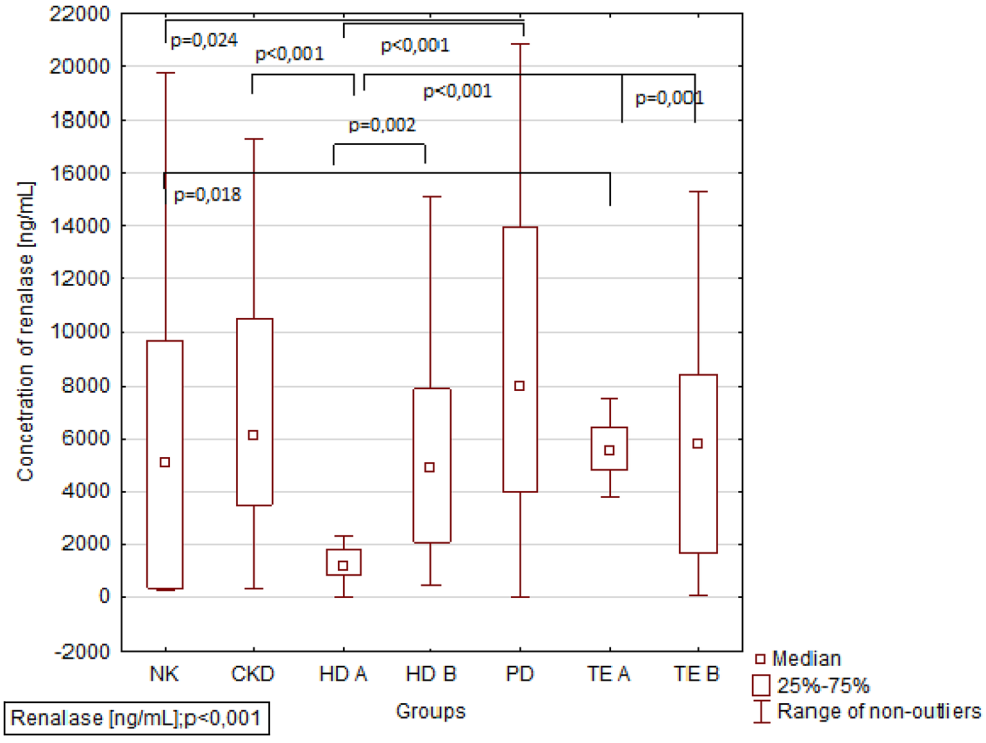

Fig. 1 Kruskal Wallis rank ANOVA analysis and post-hoc analysis renalase concentration - differences between CKD, HD A, HD B, PD, TE A, TE B, and NK groups ($p < 0{,}001$). NK - control group CKD - treated conservatively; HD A - before hemodialysis; HD B - after hemodialysis; PD - peritoneal dialysis; TE A - before kidney transplantation; TE B - after kidney transplantation

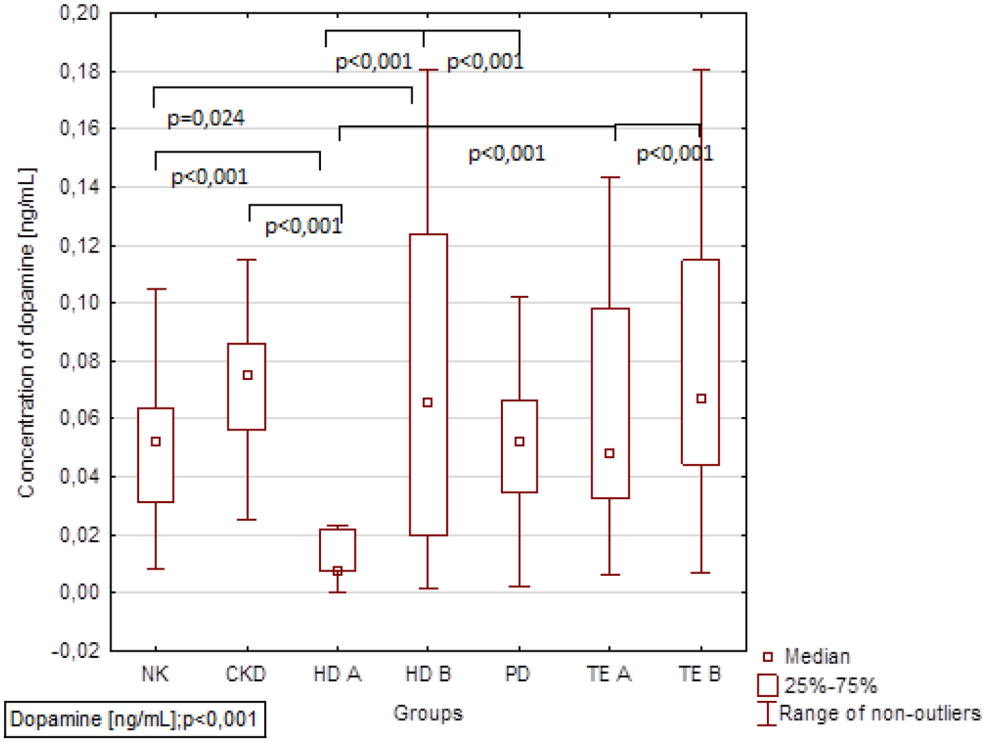

Fig. 2 Kruskal Wallis rank ANOVA analysis and post-hoc analysis of the relationship between the type of renal replacement therapy used and dopamine concentration. Dopamine concentration - differences between CKD, HD A, HD B, PD, TE A, TE B, NK groups ($p < 0{,}001$). NK - control group CKD - treated conservatively; HD A - before hemodialysis; HD B - after hemodialysis; PD - peritoneal dialysis; TE A - before kidney transplantation: TE B - after kidney transplantation

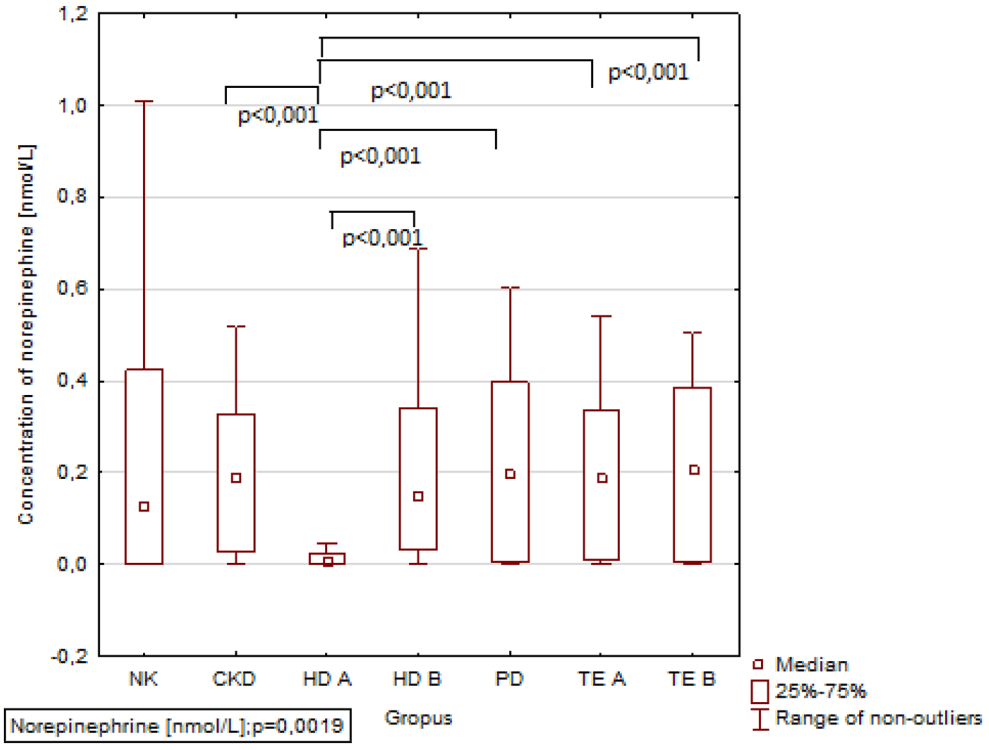

Fig. 3 Kruskal Wallis ranks ANOVA analysis and post-hoc analysis of the relationship between the type of renal replacement therapy used and norepinephrine concentration. Norepinephrine concentration - differences between CKD, HD A, HD B, PD, TE A, TE B, NK groups ($p = 0{,}002$). NK - CKD control group - treated conservatively; HD A – before hemodialysis; HD B – after hemodialysis; PD – peritoneal dialysis patients; TE A - before kidney transplantation; TE B - after kidney transplantation

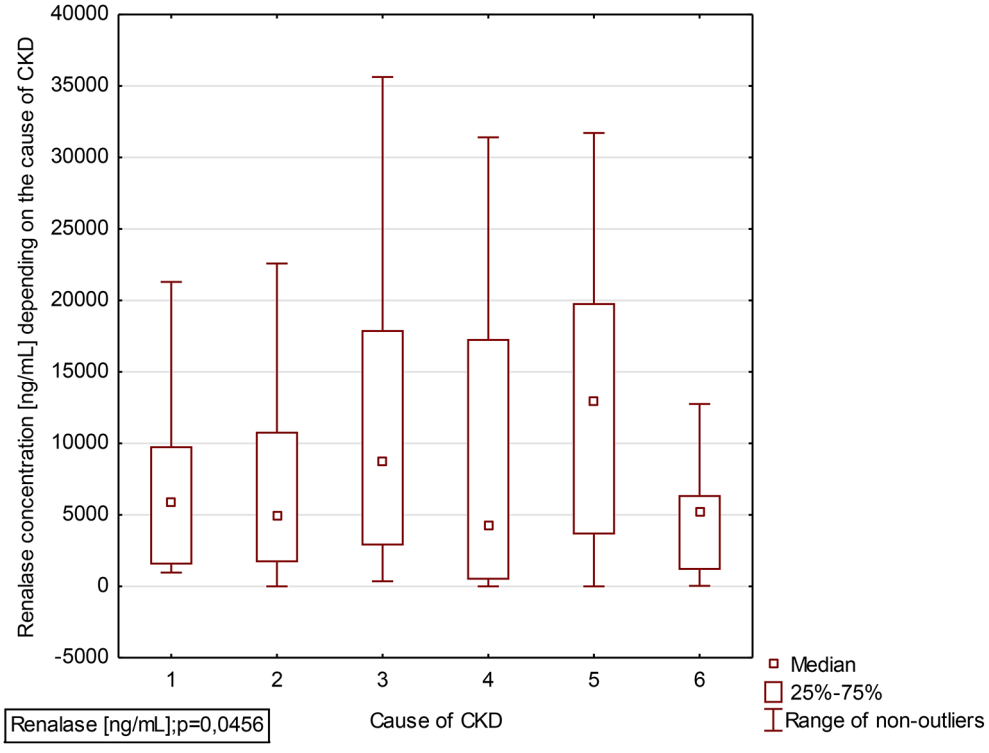

Fig. 4 Kruskal-Wallis rank analysis of the effect of the cause of chronic kidney disease (CKD) on plasma renalase concentration ($p = 0{,}046$). 1-DM - diabetic nephropathy; 2- HA – arterial hypertension; 3- KZN – glomerulonephritis; 4 - APKD – autosomal dominant polycystic kidney disease; 5 – other; 6-unknown

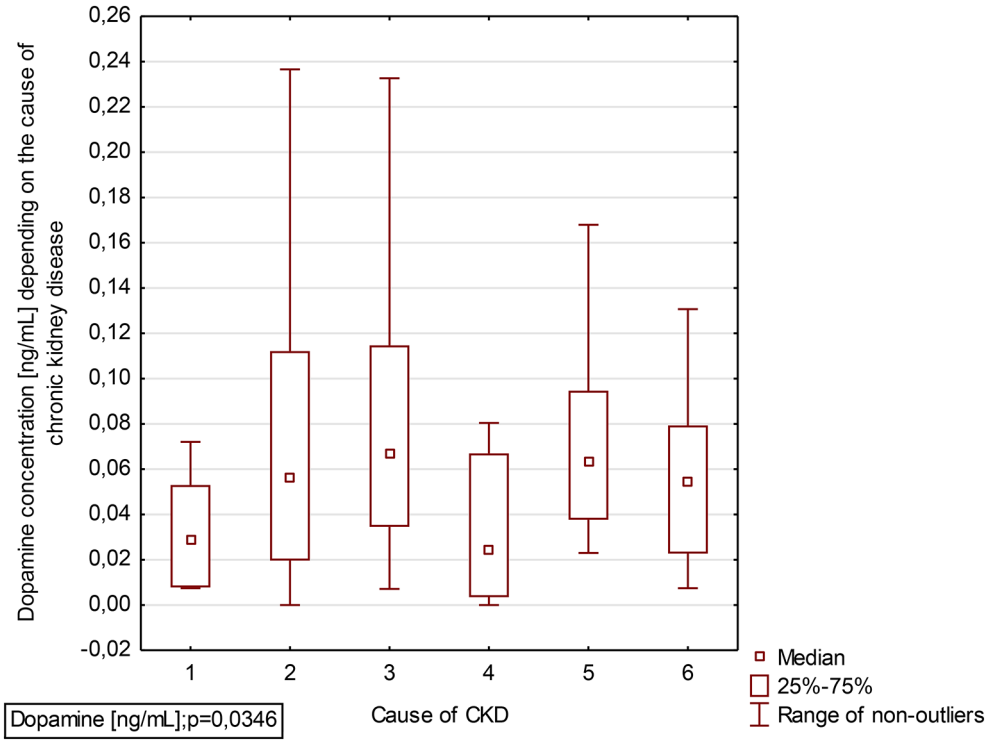

Fig. 5 Kruskal-Wallis rank analysis of the effect of the cause of chronic kidney disease (CKD) on plasma dopamine concentration ($p = 0{,}035$). 1-DM - diabetic nephropathy; 2- HA – arterial hypertension; 3- KZN – glomerulonephritis; 4 - APKD – autosomal dominant polycystic kidney disease; 5 – other; 6-unknown

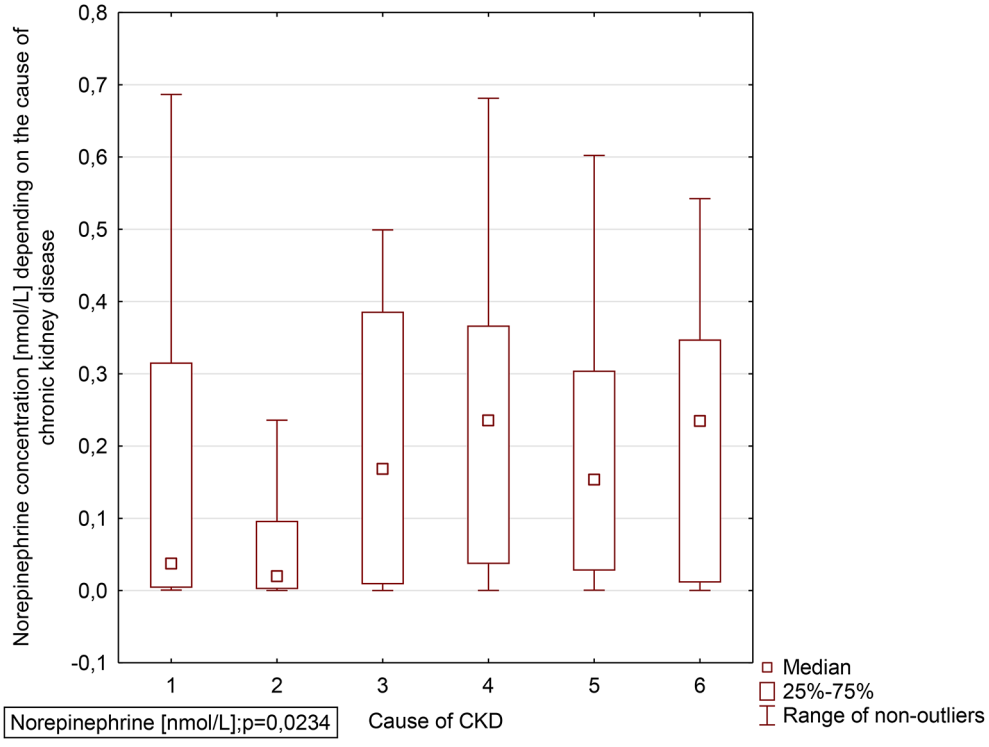

Fig. 6 Kruskal-Wallis rank analysis of the effect of the cause of chronic kidney disease (CKD) on plasma renalase concentration ($p = 0{,}023$)0.1 - DM - diabetic nephropathy; 2- HA – arterial hypertension; 3- KZN – glomerulonephritis; 4 - APKD – autosomal dominant polycystic kidney disease; 5 – other; 6-unknown

The influence of the stage of chronic kidney disease on the concentration of Renalase dopamine and norepinephrine

The influence of the stage of chronic kidney disease on the renalase concentration was demonstrated, both taking into account stages 1–5 (where the first stage is people from the control group) ($p = 0{,}003$) and taking into account stages 3–5 (where the third and fourth stages are people treated conservatively, and fifth were patients qualified for dialysis or kidney transplantation) ($p = 0{,}002$). Low renalase concentration was detected in stages one and five. From the second stage, this concentration increased, reaching the highest values in the fourth stage (Fig. 7a).

The influence of dialysis duration, gender, and age on the concentration of Renalase dopamine and norepinephrine

An influence of dialysis duration on renalase concentration was demonstrated ($p = 0.018$). The lowest concentration was found in patients on dialysis for two to three years, but in the initial dialysis period, renalase concentrations were very similar. The highest renalase concentration was found in patients on dialysis for more than 5 years (Fig. 8). These results are confirmed by a moderately strong positive correlation between renalase concentration and the duration of dialysis therapy in months ($Rs = 0{,}0242$; $p = 0{,}019$). Taking into account only patients whose CKD was caused by hypertension, the influence of the duration of dialysis therapy on renalase concentration was also demonstrated. The lowest renalase concentration was found in patients dialyzed for up to 12 months and the highest for three to four years. No people in this group were on dialysis for over 4 years (Fig. 9). A moderately strong positive correlation was also found between the duration of dialysis therapy and dopamine concentration in the group of patients whose CKD was caused by hypertension. There was no effect of dialysis duration on norepinephrine concentration. Age and gender did not affect the concentration of renalase, dopamine, or norepinephrine.

Spearman rank correlation and multivariate tegression analysis

Spearman's rank correlation analysis was performed between the tested compounds and the concentration of biochemical parameters (creatinine, cholesterol, triglycerides, HDL, LDL, albumin, total protein, glucose), as well as factors such as duration of dialysis, age, gender, GFR, causes and stage of CKD. Statistically significant correlations were found (in the study and control groups) between the renalase concentration and the duration of dialysis (**$Rs = 242; p = 0{,}018$**), as well as the concentration of dopamine (**$Rs = 0{,}311;$ $p < 0{,}001$**), uric acid (**$Rs = 0{,}199; p = 0{,}009$**), and triglycerides (**$Rs = 0{,}234; p = 0{,}001$**). These were moderately

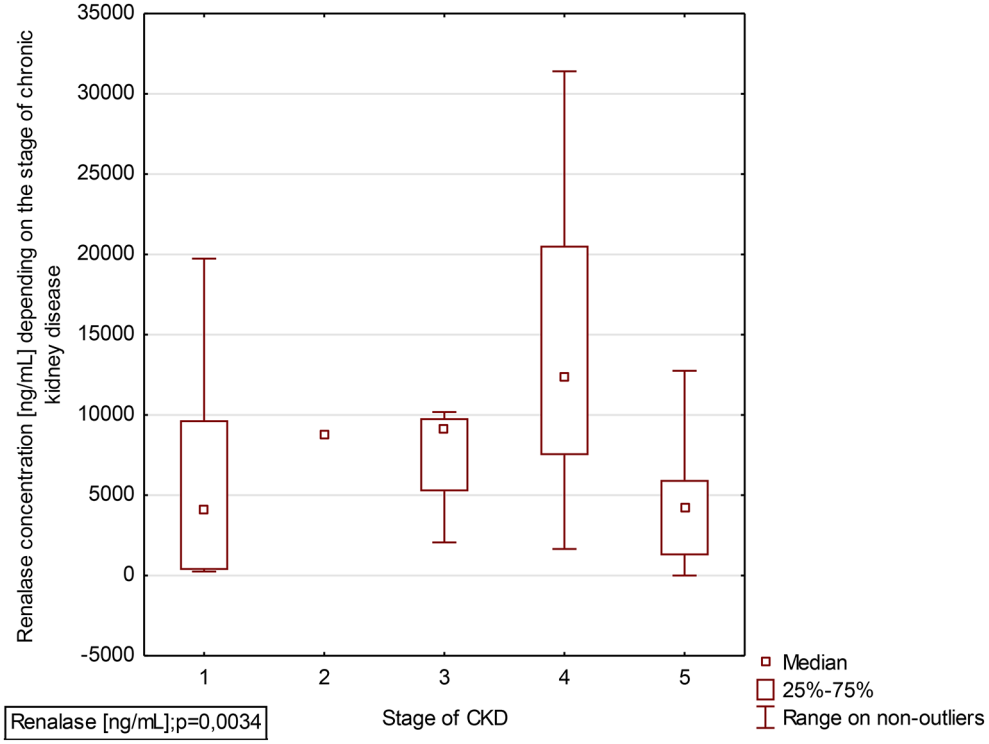

Fig. 7 Kruskal-Wallis rank analysis of the effect of the stage of chronic kidney disease (CKD) on the concentration of renalase in plasma ($p = 0{,}003$). CKD stages 1–5

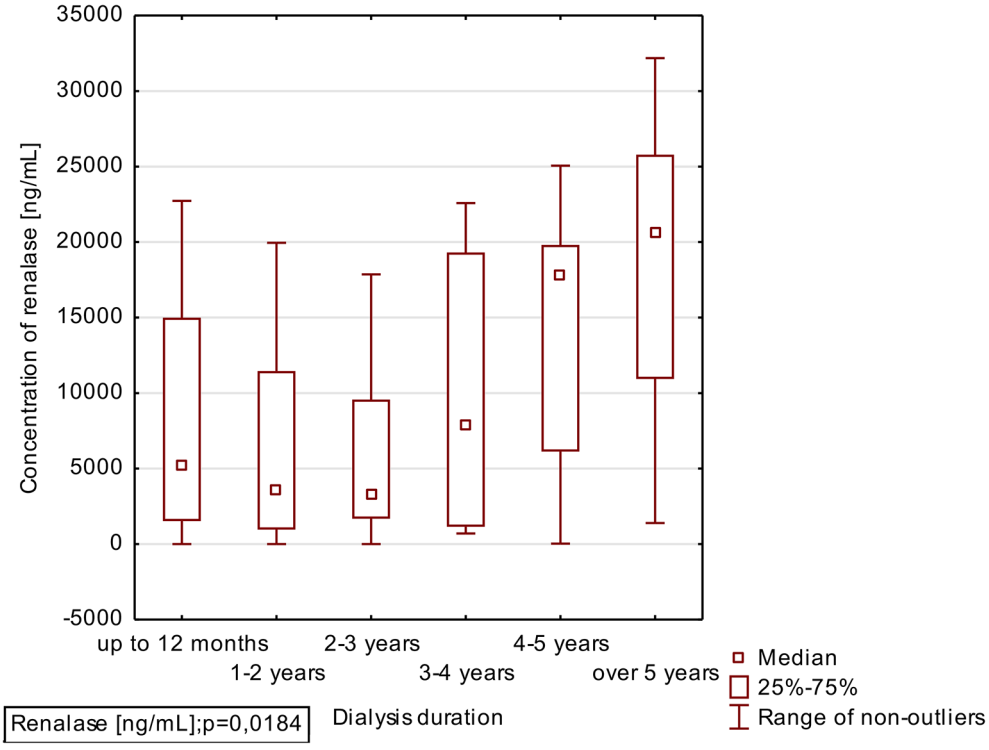

Fig. 8 Kruskal-Wallis rank analysis of the effect of dialysis duration on plasma renalase concentration ($p = 0{,}0184$)

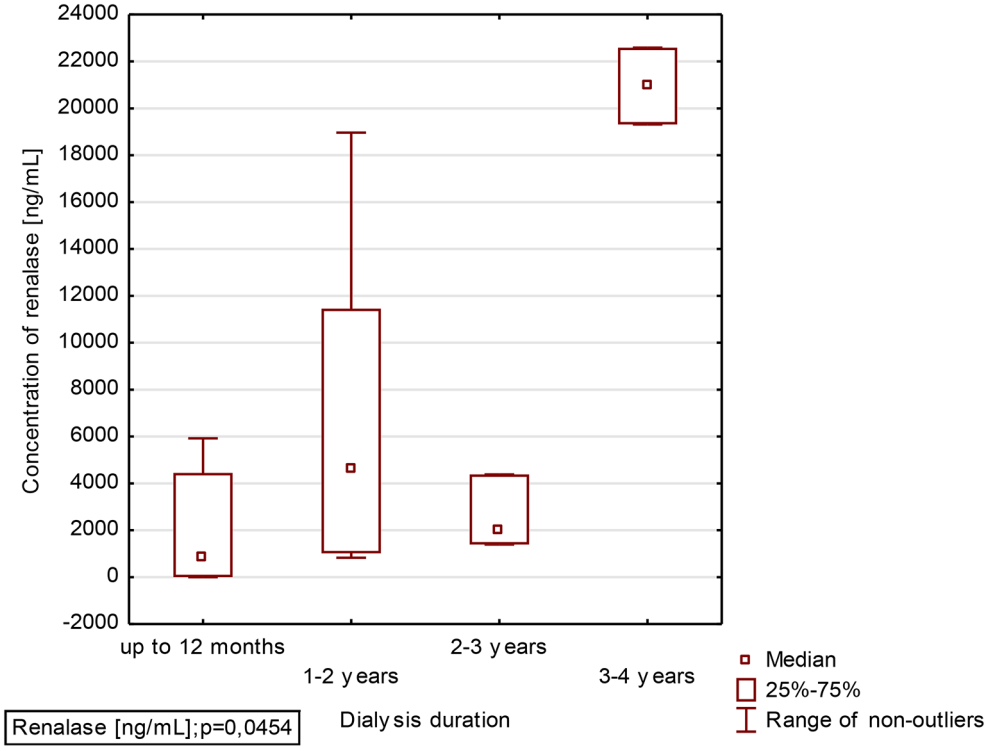

Fig. 9 Kruskal-Wallis rank analysis of the effect of dialysis duration on plasma renalase concentration among patients whose CKD was caused by hypertension ($p = 0{,}045$)

Table 4 Analysis of the tested parameters' influence on the tested parameters' concentration values - multivariate regression analysis

Dependent variable	Independent variables	B	R^2	*P*	*p* for the model	F
Renalase	Age	-0,35	**0,27**	**< 0,001**	**< 0,001**	9,35
	Dialysis duration	0,37		**< 0,001**		
	Causes of CKD	0,01		NS		
	Stage CKD	0,09		NS		
Dopamine	Age	-0,2	0,05	NS	0,07	2,39
	Dialysis duration	-0,15		NS		
	Causes of CKD	0,11		NS		
	Stage CKD	0,28		NS		
Norepinephrine	Age	0,01	**0,11**	NS	**0,024**	3,31
	Dialysis duration	0,34		**0,002**		
	Causes of CKD	-0,13		NS		
	Stage CKD	0,028		NS		

β – standardized coefficient in the regression equation, R2 – coefficient of determination, p-value of the significance coefficient

strong and positive correlations. However, relatively strong negative correlations were found between renalase and norepinephrine concentrations (**Rs= -0,2;*p* = 0,004)** and creatinine **(Rs= -0,162;*p* = 0,03)**. Apart from the renalase mentioned above, the concentration of dopamine correlated negatively with the total protein concentration (weak correlation) (**Rs = 0,-180;*p* = 0,015)**. Taking into account only patients from the study group, statistically significant, positive, moderately strong correlations were found between the renalase concentration and the duration of dialysis (**Rs = 0,268*p* = 0,015)**, the concentration of dopamine **(Rs = 0,308; *p* < 0,001)**, uric acid (**Rs = 0,223;*p* = 0,012**), HDL (**Rs = 0,202;*p* = 0,014**), triglycerides (**Rs = 0,242;*p* = 0,003**), and GFR **(Rs = 0,258;*p* = 0,002**. There was also a negative, moderate correlation between the concentration of renalase with norepinephrine (**Rs= -0,203;*p* = 0,011)**, creatinine (**Rs= -0,273;*p* = 0,001)**, and the age of patients (**Rs= -0,23;*p* = 0,006**), as well as a weak negative correlation between the concentration of dopamine and creatinine **(Rs= -0,4;*p* = 0,032).** Moderately strong positive correlations were also found between dopamine concentration and norepinephrine concentration **(Rs = 0,201;*p* = 0,01)**, GFR **(Rs = 0,201; *p* = 0,01** Taking into account only patients whose CKD was caused by hypertension, moderate positive correlations were found between renalase concentration and GFR **(Rs = 463;*p* = 0,012)**, dopamine **(Rs = 0,474;*p* = 0,008)**, and uric acid **(Rs = 0,461;*p* = 0,02)** concentrations, as well as between dopamine concentration and dialysis duration **(Rs = 0,461;*p* = 0,035)** and GFR **(Rs = 0,385; *p* = 0,038)**. A strong positive correlation was also demonstrated between renalase concentration and TAG (triglycerides) (**Rs = 0,56;*p* = 0,005**). A moderately strong negative correlation was also found between renalase and creatinine concentrations **(Rs=-0,471; *p* = 0,009)**.

Regression analysis

Multivariate regression analysis found that parameters such as the patient's age, duration of dialysis, causes, and CKD stage influenced the concentration of renalase and norepinephrine in approximately 27% and 11%, respectively. With age, the renalase concentration decreases by 0,35 ng/ml per year, and with the duration of dialysis, it increases by 0,37 ng/ml. The concentration of norepinephrine increases by 0,34 nmol with the duration of dialysis.

Discussion

Renalase, dopamine, and norepinephrine concentrations depending on the renal replacement therapy used compared to the control group

Renalase peptide agonists may be therapeutic agents to prevent chronic kidney disease [15]. Our study showed that renalase concentration varies significantly with the type of renal replacement therapy ($p < 0.001$), with the highest levels found in patients undergoing peritoneal dialysis and the lowest in those before hemodialysis. Gog et al. found high renalase concentrations in both peritoneal and hemodialysis patients, linking this to excessive production in end-stage renal disease (ESRD) and suggesting it may help prevent further kidney damage by activating the MAPK kinase pathway [16]. This could also explain the high renalase levels found in patients after hemodialysis. Wiśniewska et al. observed elevated renalase levels in the serum and urine of hemodialysis patients with chronic kidney disease (CKD), attributing this to compensatory production from extrarenal organs due to hypertension and cardiovascular changes [13]. They also reported that the highest renalase levels in dialysis patients stem from extrarenal output, particularly in nephrectomy patients [17]. While our study indicated lower renalase levels in hemodialysis patients compared

to peritoneal dialysis patients and those with CKD, these differences were not statistically significant.

Our study included 37 individuals with chronic kidney disease (CKD) resulting from diabetic and hypertensive nephropathy. This background may explain the elevated levels of renalase observed in patients undergoing peritoneal dialysis, those (TE B), and individuals on hemodialysis (HD B). Yin et al. proposed that renalase may help protect against the progression of diabetic nephropathy and could serve as a novel therapeutic target for treating this condition [18]. Furthermore, Wu et al. suggested that renalase might alleviate diabetic nephropathy by reducing proteinuria, potentially through the protection of podocytes, and by inhibiting oxidative stress and apoptosis [19]. However, Aydin et al. indicated that renalase is associated with dysfunction in the renal glomeruli and tubules and may play distinct roles in the development of hypertension [20]. Zbroch et al. found high renalase concentrations in peritoneal dialysis patients, indicating it circulates as an inactive proenzyme activated by increased plasma catecholamines. In conditions like ESRD, where catecholamine levels are high, renalase is rapidly activated, contributing to the increased levels in our peritoneal dialysis and after hemodialysis [21, 22]. Observing the lowest renalase concentration in patients just before hemodialysis is particularly interesting. Most studies indicate that individuals with CKD, undergoing hemodialysis, kidney transplant recipients, or patients with coronary artery disease (CAD) have higher renalase concentrations in their serum compared to healthy individuals [23–25]. However, these results are different from those obtained by other scientists. Małyszko et al. showed in their study that there was a correlation between urinary renalase concentration and residual diuresis, and the hemodialysis procedure itself did not significantly reduce renalase concentration [26]. Our study revealed that renalase concentration in patients before hemodialysis is very low but increases rapidly after the procedure. This phenomenon may be attributed to the loss of renalase in urine in patients with maintained diuresis and its heightened production after hemodialysis, possibly due to compensation by other organs [16]. Also, the mean values of the ultrafiltration index show that hemodialysis patients are additionally characterized by higher ultrafiltration than peritoneal dialysis patients, even though peritoneal dialysis patients more often maintained residual diuresis. Despite these data, the results obtained in our study are ambiguous and require further analysis.

Patients with chronic kidney disease (CKD) exhibited lower levels of renalase (median 6123 ng/ml) compared to those undergoing peritoneal dialysis (median 6720 ng/ml); however, these levels remained higher than in other groups. Elevated renalase levels may indicate an increased risk of requiring renal replacement therapy, hospitalization, and mortality among CKD patients. In our study, high renalase levels in conservatively treated patients could suggest the progression of kidney disease [27].

Subsequent studies examined dopamine levels in the study and control groups. Our study indicated renal replacement therapy significantly impacts plasma dopamine levels ($p < 0.001$). The highest levels were in patients receiving conservative treatment, while the lowest were seen before hemodialysis. Increased dopamine concentrations were also measured after hemodialysis and kidney transplantation.

Matsuyama et al. found higher dopamine levels in patients receiving conservative treatment, as in our study. However, urine dopamine decreases as CKD progresses while plasma angiotensinogen increases [28]. It's important to note that high urine dopamine is associated with increased urinary excretion [17]. In our cohort, 21 patients developed CKD due to hypertension, with most experiencing hypertension during CKD progression. This explains the higher dopamine levels in those treated conservatively compared to patients before hemodialysis. Notably, dopamine concentrations increase after hemodialysis and kidney transplantation, similar to renalase concentrations in these groups.

Wiśniewska et al. found that hemodialysis patients often have lower plasma catecholamine levels, likely due to increased breakdown by renalase, an enzyme involved in their metabolism [13]. This could explain the reduced dopamine levels in patients awaiting kidney transplantation and those on peritoneal dialysis, as they also show elevated renalase concentrations. In our study, renalase levels in the HD A group were initially low but increased rapidly after hemodialysis, likely due to compensation by other organs. Blood samples were collected immediately after dialysis, so catecholamine breakdown may not have occurred then.

Yao et al. conducted a study on knock-out mice and discovered that increased activity in the dopaminergic system can help prevent hypertension [14, 29]. This suggests that patients receiving conservative treatment with high levels of dopamine may have a lower risk of developing hypertension compared to those on hemodialysis. Additionally, dopamine concentrations differed significantly between healthy controls and those treated conservatively or with hemodialysis. The concentration was lower in the group treated conservatively, confirming the results of Zbroch et al. [21]. However, Wiśniewska et al. [13] obtained different results, suggesting that dopamine was not broken down by renalase in the studied groups [30]. The role of the sympathetic nervous system in chronic kidney disease (CKD) can be understood through its response to uremia, which stimulates chemosensitive afferent fibers in the kidneys and increases

sympathetic activity. This is particularly evident in hemodialysis patients due to the accumulation of uremic toxins. Anemia related to dialysis further reduces the activity of dopaminergic fibers. As dopamine's effects weaken in CKD, sympathetic nervous system activity increases reflexively, releasing norepinephrine and dopamine. This explains the low dopamine levels observed before hemodialysis and the significant rise afterward [31, 32].

Subsequent studies examined norepinephrine levels in the study and control groups. Our study found that renal replacement therapy significantly affects plasma norepinephrine concentration ($p = 0.002$). The highest norepinephrine levels were observed in patients undergoing peritoneal dialysis, those treated conservatively, and after kidney transplantation, while the lowest levels were seen in patients before hemodialysis. The control group also had high norepinephrine levels, comparable to those in the HD B group. The lowest NE concentration before hemodialysis can be explained similarly to dopamine. Uraemia accompanying patients in this group stimulates the sympathetic nervous system, which enables the production of norepinephrine, hence its higher level after hemodialysis [29].

Hering et al. found that norepinephrine (NE) significantly affects tissue homeostasis and CKD progression through adrenergic receptor (AR) signaling. Elevated plasma NE levels are linked to survival and cardiovascular events in ESRD patients and can lead to kidney damage even in those with normal blood pressure. NE from renal nerves promotes inflammation and fibrosis through alpha-2 adrenergic receptors (α2-AR). In conservatively treated and peritoneal dialysis patients, high NE levels may indicate a greater risk of cardiovascular diseases and worsening renal function due to renal fibrosis progression [33].

Zoccali et al. discovered that higher norepinephrine concentration, mediated by renalase, is an independent risk factor for death and cardiovascular diseases in hemodialysis patients [34]. The duration of the uremic state also affects norepinephrine levels, with longer high urea levels leading to higher sympathetic nervous system stimulation and norepinephrine levels after hemodialysis [35, 36]. Elevated norepinephrine levels after kidney transplantation indicate a poor prognosis for the organ. Ischemia-reperfusion injuries often raise NE levels, enhancing signaling of transforming growth factor-β1 (TGF-β1) and promoting α-smooth muscle actin (α-SMA) expression, which leads to excessive collagen deposition. This study suggests that increased NE levels from ischemia-reperfusion may significantly impact long-term outcomes in mice [37, 38].

5.2 The influence of the cause, stage of chronic kidney disease, and duration of dialysis on the concentration of renalase, dopamine, and norepinephrine.

Limited reports exist on how the causes of CKD affect levels of renalase, dopamine, and norepinephrine. Our study indicated that CKD causes significantly influenced the concentrations of these substances ($p = 0.046$, $p = 0.035$, $p = 0.023$). Patients with CKD showed varied renalase levels, with the highest found in those with causes other than diabetic nephropathy, hypertension, and glomerulonephritis. Conversely, the lowest levels were seen in patients with CKD due to autosomal dominant polycystic kidney disease (ADPKD) and hypertension.

Research on renalase levels in less common causes of CKD is limited, particularly in patients with ADPKD. A study by Baek et al. analyzed renalase levels in 384 hypertensive patients and found that for each 10 μg/mL increase in serum renalase, there was a significantly higher risk of all-cause mortality and adverse renal outcomes. However, no association was identified between major adverse cardiovascular and cerebrovascular events (MACCE) and renalase levels [39].

Knop et al. found that elevated renalase concentration correlates with increased mortality in hemodialysis patients and a higher risk of major adverse cardiovascular events (MACE) in CKD patients. Specifically, renalase levels above 25 μg/ml significantly increase the likelihood of MACE [40]. In our study, patients with CKD due to hypertension and ADPKD had low renalase levels, averaging 5 to 7 μg/ml, suggesting a lower cardiovascular risk. In contrast, patients with CKD from other causes had median renalase levels around 13 μg/ml, some near 30 μg/ml, indicating a higher risk. We also found that those with CKD from glomerulonephritis had the highest dopamine concentrations, while patients with hypertension and other CKD causes also showed elevated dopamine levels. Conversely, individuals with diabetic nephropathy and ADPKD had the lowest dopamine concentrations.

The relationship between dopamine levels and hypertension is noteworthy. High dopamine concentrations in hypertensive patients may indicate a better prognosis. A study on mice revealed that blocking kidney dopamine synthesis leads to unregulated responses to Angiotensin II, causing hypertension and reduced life expectancy [41]. Yoshimura et al. found that patients with essential hypertension have lower levels of free and conjugated dopamine despite being hyperadrenergic. In contrast, those with chronic renal failure show elevated conjugated dopamine levels, which decrease significantly after hemodialysis and kidney transplantation. The authors suggest measuring dopamine levels in plasma and urine can help diagnose essential hypertension and renal failure and assess treatment effectiveness [42].

Our study indicates that CKD stages influence renalase concentration. Comparison between stages 1 and 5

showed significant differences ($p = 0.003$), with similar findings between stages 3 and 5 ($p = 0.002$). Low renalase levels were observed in stages 1 and 5, while concentrations increased from stage 2, peaking at stage 4. Wang et al. found that renalase levels are elevated in CKD stages 3 to 5 compared to stages 1 and 2, with no significant difference between stages 1–2 and controls [43]. Quelhas-Santos et al. confirmed a negative correlation between plasma renalase levels and kidney function [44]. Desir et al. reported that blood renalase levels are inversely correlated with GFR, significantly reduced in end-stage CKD but about five times higher in ESRD than controls [45]. Our study's renalase levels are consistent with these findings; they increase from stages 2 to 4 and decrease in end-stage renal disease due to reduced glomerular filtration.

Our study found that norepinephrine concentration is affected by the stage of CKD ($p = 0.027$), with the highest levels in stage 5 and the lowest in stages 3 and 4. Wang et al. also reported that catecholamine levels are significantly higher in CKD stages 3 to 5 compared to stages 1 and 2 [22]. The duration of dialysis significantly affects renalase concentrations. Zbroch et al. found that patients on peritoneal dialysis for over 6 months had higher serum renalase levels than those on it for less than 6 months, with a significant correlation between renalase levels and dialysis duration ($Rs = 0.5464$, $p = 0.003$). This indicates a link to worsening renal function and potential cardiovascular complications [46, 47]. Our study suggests that patients on dialysis for over 5 years have the highest renalase levels, increasing by an average of 0.37 ng/ml annually. In those with CKD from hypertension, renalase levels differ by dialysis duration: the lowest levels are seen in patients on dialysis for up to 12 months, while the highest are in those treated for three to four years. For patients on dialysis for more than five years, the median renalase concentration is about 21,000 ng/ml (21 µg/ml), approaching the critical limit of 25,000 ng/ml (25 µg/ml), where it may indicate poorer survival rates and a heightened risk MACE.

Previous renalase averages in hypertensive patients were considered non-concerning at 5–7 µg/ml, but the impact of dialysis duration was overlooked. Our findings show that dialysis exceeding 3 years raises renalase levels and the risk of death in CKD patients. In those with hypertension-related CKD, more prolonged dialysis correlates positively with dopamine concentration, likely due to disruptions in the dopaminergic system.

Some researchers suggest that high renalase levels are linked to increased dopamine. In contrast, others propose that renalase metabolizes epinephrine, producing antihypertensive effects similar to enalapril at 5 mg/kg, although it metabolizes dopamine more slowly [48].

Conclusions

Based on the findings, the choice of renal replacement therapy may impact renalase, dopamine, and norepinephrine levels. Furthermore, various influencing factors, such as the duration of dialysis therapy, the etiology, and the stage of CKD, are significant considerations. Monitoring the concentration of renalase, dopamine, and norepinephrine can offer valuable insights into the progression of chronic kidney disease, the potential for cardiovascular events, and the prognosis and treatment outcomes for patients with CKD.

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Author contributions
Conceptualization – Rafał Heryć, Magda Wiśniewska Methodology – Elżbieta Cecerska-Heryć; Formal analysis – Elżbieta Cecerska-Heryć Writing – review & editing - Rafał Heryć, Natalia Serwin, Patrycja Stodolak, Elżbieta Cecerska-HerycVisualization- Małgorzata Goszka; Aleksandra Polikowska Supervision – Kazimierz Ciechanowski, Magda Wiśniewska.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate
All patients included in the study gave informed consent to participate. The study was approved by the Bioethics Committee at the Pomeranian Medical University in Szczecin (no KB-0012/36/11).

Consent for publication
Written informed consent was obtained from the patient for the publication of this study.

Competing interests
The authors declare no competing interests.

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