Renalase in Haemodialysis Patients with Chronic Kidney Disease

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Abstract: Chronic kidney disease (CKD) is an inflammatory disease leading to kidney insufficiency and uremia. Renalase is a novel flavoprotein with enzymatic activities. Previous studies have shown that chronic kidney disease may influence renalase serum levels. Renalase metabolises catecholamines and therefore may be involved in the pathogenesis of hypertension and other diseases of the circulatory system. In this study, we examined renalase levels in serum, erythrocytes and urine from haemodialysis CKD patients. The study enrolled 77 haemodialysis CKD patients and 30 healthy subjects with normal kidney function as the control group. Renalase serum and urine concentrations in CKD patients were significantly increased when compared with control subjects (185.5 ± 64.3 vs. 19.6 ± 5.0 ng/mL; p < 0.00001 and 207.1 ± 60.5 vs. 141.6 ± 41.3 ng/mL; p = 0.00040, respectively). In contrast, renalase levels in erythrocytes were significantly lower in CKD patients when compared with control subjects (176.5 ± 60.9 vs. 233.2 ± 83.1 ng/mL; p = 0.00096). Plasma levels of dopamine, adrenaline and noradrenaline were also significantly lower in CKD patients when compared with controls. Conclusions: Increased serum and urine concentrations of renalase in haemodialysis CKD patients are likely related to compensatory production in extrarenal organs as a result of changes in the cardiovascular system and hypertension. The decreased plasma concentrations of catecholamines may be due to their increased degradation by plasma renalase. Decreased renalase levels in erythrocytes may be probably due to lower renalase synthesis by the kidneys in CKD. The results indicate the presence of renalase in erythrocytes.

Keywords: renalase; chronic kidney disease; haemodialysis

1. Introduction

Chronic kidney disease (CKD) is an inflammatory disease leading to kidney insufficiency and uremia [1]. Many metabolic changes have been found in this disease that increase the risk of developing cardiovascular complications. Numerous enzymes, cytokines and other mediators are involved in the development of circulatory system diseases in patients with CKD [2,3].

Renalase is a flavoprotein with enzymatic activities of amine oxidase detected in 2005 by Xu et al. [4]. This enzyme is mainly released in proximal tubules of the kidney but also by hepatocytes, cardiomyocytes and myocytes in skeletal muscles. Renalase is also produced in adrenal cells, adipose tissue and the central and peripheral nervous system [5]. Renalase metabolises catecholamines and therefore may be involved in the pathogenesis of...
hypertension and other diseases of the circulatory system [6–8]. Therefore, some authors suggest that this enzyme may be the risk factor for developing circulatory system diseases. Previous studies showed that chronic kidney disease (CKD) may influence renalse serum levels [6]; however, the results are inconsistent. The results of some studies suggest that patients with CKD have lower levels of renalse in serum, while others suggest that CKD patients have increased levels of renalse [1,8–10]. In the previous work, we studied renalse concentrations in CKD patients with preserved renal function and correlated with parameters of kidney function [11]. Patients with end-stage kidney disease most often suffer from anuria and require hemodialysis, which changes many biochemical parameters. The aim of this study was to examine renalse levels in serum, erythrocytes and urine from haemodialysis CKD patients.

2. Materials and Methods

2.1. Patients

This study included 77 patients with CKD. The causes of CKD were hypertension (33.8%), diabetes mellitus (22.1%), glomerular kidney disease (15.6%), polycystic kidney disease (6.5%), birth defects (3.9%) and unknown (18.1%).

The control group included 30 healthy subjects, with normal kidney function (normal GFR values and normal creatinine serum levels) [11]. The GFR was estimated using the CKD-EPI equation (eGFR). All participants from the study group were patients in the Clinic of Nephrology, Transplantology and Internal Diseases, Pomeranian Medical University in Szczecin, Poland. The study was approved by the ethics committee in Pomeranian Medical University, Szczecin, Poland (KB-0012/122/14), and written informed consent was obtained from all subjects.

2.2. Methods

Venous blood sampling was prepared in the morning with the use of Sarstedt Monovette tubes (Nümbrecht, Germany) containing a clotting activator. Serum samples were prepared by centrifugation (10 min, 1000 × g) and stored frozen until use.

Additionally, whole blood samples were drawn into K3 EDTA Monovette tubes (Sarstedt, Nümbrecht, Germany) to obtain erythrocyte lysates. Erythrocytes were separated from plasma by centrifugation (10 min, 1000 × g) and washed three times saline (0.9%). Each wash was followed by centrifugation as described above and removal of the supernatant fraction. Erythrocytes samples were stored frozen at −80 °C until use. Before use, to obtain erythrocytes lysis, samples were diluted 1.3 (v/v) in distilled water. The dilution coefficient was included in the determination of haemoglobin concentration measured with the use of Drabkin’s reagent (Sigma-Aldrich, St Louis, MO, USA). Renalse in erythrocytes was measured using a serum renalse kit (WuHan ELAab, Wuhan, China).

Serum, erythrocytes and urine concentration of the renalse were assessed with the use of the human renalse specific ELISA kit (WuHan ELAab, Wuhan, China). Additionally, adrenaline, noradrenaline and dopamine concentrations were evaluated in blood plasma with the use of the ELISA kit (LDN Labour Diagnostika Nord GmbH & Co. KG, Nordhorn, Germany). The total concentration of renalse in the erythrocytes (expressed in ng/mL), as well as the concentration of renalse expressed per 1 g of Hb (ng/1 g Hb), are presented. Renalse concentration is expressed per 1 g of Hb to account for variability in the erythrocyte and haemoglobin values of the patients.

Standard laboratory serum parameters were determined using the Architect c8000 analyser (ABBOTT, Austin, TX, USA).

2.3. Statistical Analysis

Data were analysed with STASTISTICA 12.5 program (StatSoft, Tulsa, OK, USA). Shapiro–Wilk test was used to verify normality of distributions. It showed that most quantitative variables have distributions significantly different from normal distribution. Therefore, non-parametric Mann–Whitney test was used to compare values between groups.
The strength of correlations between selected quantitative parameters was measured using non-parametric Spearman’s rank correlation coefficient ($R_s$). Associations with $p < 0.05$ were considered statistically significant for all analyses.

3. Results

In this study, we measured renalse levels in serum, erythrocytes and urine, as well as plasma concentrations of dopamine, noradrenaline and adrenaline, in healthy subjects and haemodialysis CKD patients. Serum and urine renalse levels in CKD patients were significantly increased when compared with control subjects (185.5 ± 64.3 vs. 19.6 ± 5.0 ng/mL; $p < 0.00001$ and 207.1 ± 41.3 ng/mL; $p = 0.0004$, respectively). However, renalse levels in erythrocytes were significantly lower in CKD patients when compared with control subjects (176.5 ± 60.9 vs. 233.2 ± 83.1 ng/mL; $p = 0.00096$) (Table 1). Plasma levels of adrenaline, noradrenaline and dopamine were also significantly lower in CKD patients when compared with controls (Table 1).

Table 1. Comparison of studied parameters between hemodialysis patients and control subjects.

| Parameters                        | Control               | HD Patients           | HD vs. Control |
|-----------------------------------|-----------------------|-----------------------|----------------|
|                                   | Mean ± SD             | Median (Q1–Q3)        | Mean ± SD      | Median (Q1–Q3) | $p$       |
| Age (years)                       | 57.37 ± 18.46         | 54.5 (45.0–72.0)      | 65.44 ± 15.55  | 68.0 (57.0–77.0) | 0.027     |
| HGB (mmol/L)                      | 7.89 ± 0.63           | 7.95 (7.30–8.40)      | 6.77 ± 1.00    | 6.90 (6.10–7.40) | <0.0001   |
| RBC (T/L)                         | 4.85 ± 0.41           | 4.84 (4.50–5.21)      | 3.54 ± 0.53    | 3.50 (3.19–3.90) | <0.0001   |
| MCHC (mmol/L)                     | 19.48 ± 0.65          | 19.5 (18.9–19.9)      | 20.54 ± 0.61   | 20.6 (20.2–21.0) | <0.0001   |
| Uric acid in serum (mg/dL)        | 5.51 ± 0.61           | 5.55 (5.00–6.00)      | 7.42 ± 1.83    | 7.21 (6.40–8.20) | <0.0001   |
| Total protein in serum (g/dL)     | 7.44 ± 0.43           | 7.45 (7.30–7.80)      | 5.85 ± 0.82    | 5.80 (5.31–6.28) | <0.0001   |
| Albumin in serum (g/dL)           | 3.70 ± 0.16           | 3.75 (3.60–3.80)      | 3.18 ± 0.51    | 3.25 (2.89–3.55) | <0.0001   |
| Glucose in serum (mg/dL)          | 86.67 ± 7.19          | 87.0 (81.0–92.0)      | 108.55 ± 36.14 | 98.0 (86.0–125) | 0.00096   |
| Creatinine in serum (mg/dL)       | 0.83 ± 0.12           | 0.82 (0.74–0.94)      | 8.42 ± 3.58    | 8.40 (5.75–10.3) | <0.0001   |
| Creatinine in urine (mg/dL)       | 90.03 ± 54.06         | 78.4 (42.5–125)       | 90.76 ± 77.55  | 65.0 (40.0–124) | 0.64      |
| Adrenaline in plasma (pg/mL)      | 30.45 ± 33.88         | 17.7 (10.5–39.3)      | 14.64 ± 11.81  | 12.2 (7.32–18.3) | 0.016     |
| Noradrenaline in plasma (pg/mL)   | 399.10 ± 318.99       | 275 (197–604)         | 345.74 ± 999.82| 118 (51.1–228)  | 0.00019   |
| Dopamine in plasma (pg/mL)        | 440.95 ± 343.22       | 313 (215–638)         | 177.26 ± 124.40| 135 (83.3–252)  | <0.0001   |
| Renalse in serum (ng/mL)          | 19.63 ± 4.99          | 17.7 (16.3–21.8)      | 185.55 ± 64.31 | 187 (154–215) | <0.0001   |
| Renalse in erythrocytes (ng/mL)   | 233.23 ± 83.11        | 254 (166–293)         | 176.51 ± 60.93 | 178 (135–206) | 0.00096   |
| Renalse in erythrocytes (ng/mL)   | 697.65 ± 273.43       | 707 (485–857)         | 579.11 ± 214.26| 575 (387–772) | 0.04      |
| Renalse in urine (ng/mL)          | 141.57 ± 41.31        | 144 (116–170)         | 207.14 ± 60.53 | 205 (150–260) | 0.0004    |
| Renalse/creatinine (ng/1 mg        | 252.38 ± 210.81       | 201 (96.7–285)        | 431.01 ± 333.13| 354 (179–480) | 0.031     |
| creatinine in urine)              |                       |                       |                |                |           |

$^6$ Mann–Whitney U test. HD patients—hemodialysis patients; HGB—haemoglobin; MCHC—mean corpuscular haemoglobin concentration; Q1—lower quartile; Q3—upper quartile; Renalse HB—renalase concentrations calculated as hemoglobin (ng of renalse/1 g haemoglobin in lysates); RBC—red blood cells; SD—standard deviation.

We also analysed correlations between renalse levels in serum and in erythrocytes and renalse levels, calculated per gram of haemoglobin, with plasma levels of adrenaline, noradrenaline, dopamine, serum total protein, serum albumin and haemodialysis diuration. Renalse levels in erythrocytes, and renalse levels calculated per gram of haemoglobin correlated negatively with plasma dopamine concentrations. Renalse serum levels positively but weakly correlated with serum total protein (Table 2, Figures 1–3). There were no significant correlations between serum and erythrocyte renalse concentrations, in both hemodialysis patients and controls (Figure 4).
Table 2. Correlations between studied parameters in hemodialysis patients.

| Parameters              | Renalase in Serum | Renalase in Erythrocytes | Renalase Hb |
|-------------------------|-------------------|--------------------------|-------------|
|                         | Rs                | p            | Rs          | p            | Rs          | p            |
| Adrenaline in plasma    | 0.07              | 0.56         | 0.06        | 0.62         | −0.04       | 0.73         |
| Noradrenaline in plasma | 0.20              | 0.085        | 0.06        | 0.61         | 0.11        | 0.35         |
| Dopamine in plasma      | −0.08             | 0.51         | −0.42       | 0.00013      | −0.55       | <0.00001     |
| Serum total protein     | 0.24              | 0.034        | −0.05       | 0.67         | −0.05       | 0.68         |
| Serum albumin           | −0.10             | 0.39         | 0.00        | 0.97         | −0.08       | 0.48         |
| Duration of hemodialysis| 0.08              | 0.50         | 0.02        | 0.83         | −0.02       | 0.84         |

Rs—Spearman rank correlation coefficient. Hb renalase concentrations calculated as haemoglobin (ng of renalase/1 g haemoglobin in lysates).

Figure 1. Correlation between concentrations of renalase in erythrocytes and dopamine in plasma of haemodialysis patients.

Figure 2. Correlation between concentrations of renalase per Hb (ng of renalase/1 g haemoglobin in lysates) and dopamine in plasma of hemodialysis patients.
4. Discussion

The aim of this study was to examine renalase levels in serum, erythrocytes and urine in haemodialysis CKD patients. To our knowledge, this is the first study examining the concentrations of renalase in hemodialysis CKD patient erythrocytes. Our results showed that serum and urine renalase levels in CKD patients were significantly increased, whereas erythrocyte levels were lower when compared to healthy patients. Erythrocytes,
being nuclear-free cells without mitochondria, do not carry out classical metabolism and, therefore, are a very good “transporter” of many substances. Previous studies have shown that the concentration of renalse is significantly increased in patients with chronic kidney disease (CKD), and additional studies have demonstrated that this change is correlated with disease severity [8–11]. Patients with CKD characteristically display a high level of anaemia that is mainly associated with impaired erythropoietin production, although haemolysis and a significantly shortened erythrocyte survival time have also been implicated [12,13]. This phenomenon is even more common in hemodialysis (HD) patients. Additionally, erythrocytes are involved in the storage of many cytokines involved in cell signalling [14]. Renalase, as a potential cytokine, could also be subject to such transport and storage. Moreover, the receptor for renalse has been shown to be PMCA4b, one of the four isoforms of the PMCA calcium pump. PMCA4 is the main isoform of this pump in erythrocytes [15]. Therefore, it cannot be ruled out that renalse without the involvement in catecholamine metabolism is responsible for autocrine functions. Renalase also exhibits enzymatic activity, although only at the intracellular level, stabilizing the active NAD(P)H isoform. Erythrocytes are a reservoir of a very large number of enzymes, primarily antioxidants, which provide erythrocytes with access to ATP and NAD(P)H [16]. Many of these enzymes require NADPH, which is derived from the pentose phosphate pathway. Our results indicate that renalse is present in erythrocytes; however, the function of renalse in erythrocytes is not yet known.

Previous studies have shown that renalse levels in CKD patients were decreased, suggesting correlations between lower serum renalse levels and increased catecholamine levels. Xu et al. indicated that patients with end-stage renal disease had decreased plasma levels of renalse when compared with healthy subjects [4]. In another study, Desir et al. indicated that increased catecholamine levels in CKD cause renalse deficiency and contribute to hypertension and cardiovascular disease [5,6].

In contrast, studies by Małyszko et al. suggested that CKD patients and kidney allograft recipients had increased plasma renalse levels [8–10]. Zbroch et al. examined serum renalse levels in haemodialysis patients [9]. Mean serum renalse levels in patients were significantly higher than in the control group. Moreover, serum renalse levels were significantly lower in patients with residual renal functions when compared to anuric patients. There was a significant inverse correlation between serum renalse levels and residual renal function. In another study, renalse levels were higher in dialysis groups when compared to healthy subjects [10]. Renalse levels correlated with dialysis vintage, and inversely correlated with residual diuresis. Elevated circulating renalse levels in dialysis patients may be related to kidney function and activation of the sympathetic nervous system detected in these patients.

Furthermore, other studies have suggested that renalse levels were positively correlated with impaired kidney function [17,18]. Stojanovic et al. indicated that renalse levels were negatively correlated with estimated glomerular filtration rates and positively correlated with creatinine levels [19]. Baek et al. suggest that increased levels of renalse in CKD patients may be the risk factor of several cardiovascular complications [20].

Previous studies have indicated that renalse not only has enzymatic properties, but also should be considered as a cytokine [21]. Additionally, renalse may exert anti-apoptotic action and may protect against ischemia reperfusion injury and toxicity induced by cisplatin [22]. It has been shown that renalse may activate several signalling pathways associated with of extra-cellular signal-regulated kinase, protein kinase B and p38 mitogen-activated kinase [23]. Additionally, renalse protects against ischemic acute kidney injury and renal fibrosis via inhibiting oxidative [24–26].

Li et al. have indicated increased renalse serum levels in CKD patients, which correlated with increased levels of endotelin, a hormone involved in pathogenesis of cardiovascular diseases [27].
The expression of renalase is regulated by dopamine receptors, especially receptor D5. It is likely that dysfunction of this receptor and aberrant regulation of renalase function may be associated with development of hypertension [28].

In our previous study, we examined renalase concentrations in CKD patients with preserved renal function [11]. Renalase serum concentrations correlated negatively with parameters of kidney function. These results suggest that renalase concentrations increase with the development of the disease and the deterioration of renal function.

In this study, we examined renalase levels in haemodialysis patients with CKD. These patients had increased levels of renalase in the serum and urine and lower levels in erythrocytes. The studies indicate that renalase production is primarily impaired in CKD patients and increases with disease development. Increased serum and urine concentrations of renalase in haemodialysis CKD patients are likely related to compensatory production in extrarenal organs as a result of changes in the cardiovascular system and hypertension. The decreased plasma concentrations of catecholamines may be due to their increased degradation by serum renalase. This may confirm the role of renalase in catecholamine metabolism. We hypothesise that decreased renalase levels in CKD patient erythrocytes may be due to primarily lower renalase synthesis by the kidneys in CKD. Nevertheless, renalase’s function and properties remain poorly understood and require further investigation.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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Conflicts of Interest: The authors declare no conflict of interest.

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