CLINICAL STUDY

Increased serum renalase in hemodialysis patients: is it related to left ventricular hypertrophy?

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ABSTRACT

Introduction: Left ventricular hypertrophy (LVH) is one of the most common cardiac abnormalities in patients with end stage renal disease (ESRD). Hypertension, diabetes, increased body mass index, gender, age, anemia, and hyperparathyroidism have been described as risk factors for LVH in patients on dialysis. However, there may be other risk factors which have not been described yet. Recent studies show that renalase is associated with cardiovascular events. The aim of this study was to reveal the relation between renalase, LVH in patients under hemodialysis (HD) treatment.

Methods: The study included 50 HD patients and 35 healthy controls. Serum renalase levels and left ventricle mass index (LVMI) were measured in all participants and the relation between these variables was examined.

Findings: LVMI was positively correlated with dialysis vintage and C-reactive protein (CRP) \( r = 0.387, p = 0.005 \) and \( r = 0.597, p < 0.001 \), respectively and was negatively correlated with residual diuresis and hemoglobin levels \( r = -0.324, p = 0.022 \) and \( r = -0.499, p < 0.001 \), respectively. There was no significant association of renalase with LVMI in the HD patients \( r = 0.263, p = 0.065 \). Serum renalase levels were significantly higher in HD patients \( 212 \pm 127 \text{ng/mL} \) compared to controls \( 116 \pm 67 \text{ng/mL} \) \( p < 0.001 \). Renalase was positively correlated with serum creatinine and dialysis vintage \( r = 0.677, p < 0.001 \) and \( r = 0.625, p < 0.001 \), respectively.

Discussion: In our study, LVMI was correlated with dialysis vintage, residual diuresis, CRP, and hemoglobin. LVMI tends to correlate with renalase and this correlation may be significant in studies with more patient numbers. The main parameters affecting renalase levels are dialysis vintage and serum creatinine.

Introduction

Left ventricular hypertrophy (LVH) is one of the most common cardiac abnormalities in patients with end stage renal disease (ESRD). LVH increases the risk of cardiovascular and all cause mortality 3.7 times in this population. Hypertension, diabetes, increased body mass index (BMI), gender, age, anemia, and hyperparathyroidism have been described as risk factors for LVH in patients on dialysis. However, there may be other risk factors which have not been described yet. Renalase is a newly discovered hormone that is associated with high cardiovascular risk in patients with chronic renal failure. The primary source of renalase is renal proximal tubules. It was also shown to pass from the heart, the skeletal muscle, the small bowel, and the nervous system into blood. Renalase, a flavoprotein expressed excessively in the kidneys and the heart, effectively metabolizes catecholamines, which regulate heart rate, myocardial contractility, and vessel tone and plays an important role in regulation of blood pressure. Both experimental and clinical studies have shown that renalase deficiency is an important factor in pathogenesis of hypertension. There have been few studies on renalase in patients with renal failure and there are conflicting evidence about the relation between blood renalase levels and hypertension. Failure to treat hypertension adequately is an important risk factor for LVH. Renalase also can play a role in LVH. There has been one study on animals which reveals that treatment with renalase causes regression in LVH. However, there have been no studies associating renalase with LVH in patients on hemodialysis (HD).

We hypothesized that blood renalase levels could be unknown risk factors for LVH. The aim of this study was...
to reveal the relation between LVH, renalase in patients under HD treatment.

Materials and methods

Study population and study design

Eighty patients who were on chronic HD treatment were enrolled in this cross-sectional study. The study included 50 outpatients on HD (study group) and 35 healthy controls (control group). The inclusion criteria were as follows: an age older than 18 years, and at least one year of previous chronic HD treatment, at least three times per week, with each session lasting for at least 4 h. The exclusion criteria were: malignancies and acute infections. As for comorbidities, of 50 patients, 28 had hypertension, 12 had ischemic heart disease, and 10 had diabetes. The control group included healthy individuals aged over 18 years old, not having a known disease and not taking any medications. Medications used by the patients that can affect LVH like erythropoietin, angiotensin-converting enzyme inhibitor (ACEI), and angiotensin II receptor blockers (ARB) were recorded. The Local Ethics Committee of Dışkapi Yıldırım Beyazıt Education and Research Hospital approved the study protocol and all patients signed informed consent in accordance with the principles of the Declaration of Helsinki. Serum renalase levels and left ventricle mass index (LVMI) were measured in all participants and the relation between these variables was examined.

Clinical and biochemical measurements

The mean systolic and diastolic blood pressures measured at home for five days were recorded. The BMI was calculated by dividing the body weight in kilograms by the square of the height in meters (kg/m²). In our study, 10 HD patients had residual renal function (RRF) and this was recorded as mL/day.

Predialysis blood samples were drawn, and routine laboratory assessments were performed by standard laboratory techniques. Serum total cholesterol and triglycerides were quantified by commercial colorimetical assay methods (GPO-PAP and CHOD-PAP; Boehringer-Mannheim, Mannheim, Germany). High-density lipoprotein cholesterol (HDL-C) was quantified by the phosphotungstic acid precipitation method. Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald formula (LDL-C = CHO – TG/5 – HDL-C), where CHO is the serum total cholesterol and TG is the triglycerides. C-reactive protein (CRP) was detected by rate nephelometry (IMAGE). Serum biochemical parameters (creatinine, blood urea nitrogen, glucose, electrolytes, albumin, and complete blood count) and intact parathormone levels were studied by means of a computerized autoanalyzer (Hitachi 717; Boehringer-Mannheim).

Measurement of renalase

For measurements of renalase, 5 mL of predialysis venous blood specimens were obtained, centrifuged at appropriate conditions and kept at −80°C for a maximum of one month. The enzyme-linked immunosorbent assay (ELISA) kit by Uscn Life Science Inc. (Wuhan, China), using a monoclonal antibody specific to renalase, was used. The levels of renalase are presented as ng/mL. The levels of renalase are presented as ng/mL. We used ELISA in renalase measurement because in most of the previous studies ELISA was used and also it was a rapid and practical method.

Echocardiography

All patients underwent two-dimensional M-mode transthoracic color Doppler echocardiographic with a Philips IE-33 system and S5-1 transducer (1e5 mHz, Philips, Bothell, WA). Echocardiography was performed in all the participants by the same cardiologist.

The calculation of LVMI

In left lateral decubitus position from parasternal long-axis views, standard M-mode measurements of interventricular septum thickness (IVST), left ventricular end-diastolic diameter (LVEDD), and left ventricular posterior wall thickness (LVPWT) were measured. Left ventricular mass (LVM) was calculated using the Penn Cube Conversion formula

\[
LVM (g) = 1.04 \times \frac{[(LVEDD + IVST + LVPWT)^3 - (LVEDD)^3]}{13.6}.
\]

LVM was divided by body surface area to find LVMI. LVMI of >131 g/m² for men and >100 g/m² for women was accepted as LVH.

Statistical analysis

For statistical analysis, SPSS (Statistical Package for Social Sciences, Cicago, IL) for Windows 20.0 was used. Data about continuous variables were expressed in mean ± standard deviation if otherwise is not indicated. Intergroup comparisons were made with Student’s t-test (in data with a normal distribution) or with Mann–Whitney U test (in data without a normal distribution). Categorical variables were compared with Chi-square test. Pearson’s correlation coefficient was used for continuous variables with normal distribution and
Spearman’s correlation coefficient was used for continuous variables that are not normally distributed \( p < 0.05 \) was considered significant.

**Results**

**Demographics**

Out of 50 patients included in the study group with a mean age of 55 ± 16 years, 32 (64%) were female and 18 (36%) were male. Out of 35 healthy controls with a mean age of 49 ± 14 years, 22 (62.9%) were female and 13 (37.1%) were male. The two groups did not differ in terms of age and gender. The clinical and biochemical parameters in patient’s HD and patients in control group are presented in **Table 1**.

**Biochemical and echocardiographic findings**

Patients were divided into two groups according to presence of LVH. Thirty (60%) patients had LVH while 20 of them (40%) did not have. Demographical and clinical properties of two groups can be seen in **Table 2**. The two groups did not differ in terms of age and gender.

**Table 1.** Demographic, clinical, and echocardiographic parameters in HD patients and control group.

| Parameter                        | HD patients (n = 50) | Control group (n = 35) | \( p \) |
|---------------------------------|---------------------|------------------------|--------|
| Age (years)                     | 55 ± 16             | 49 ± 14                | 0.075  |
| Gender (male, \( n, \% \))      | 18 (36%)            | 13 (37.1%)             | 0.914  |
| BMI (kg/m\(^2\))                | 23.98 ± 4.41        | 24.03 ± 1.85           | 0.585  |

**Table 2.** Demographic and clinical parameters in LVH and non-LVH in HD patients.

| Parameter                        | LVH (\( n = 20 \)) | LVH (\( n = 30 \)) | \( p \) |
|---------------------------------|---------------------|---------------------|--------|
| Age (years)                     | 55 ± 17             | 55 ± 15              | 0.90   |
| Gender (male, \( n, \% \))      | 9 (18%)             | 9 (18%)              | 0.19   |
| Cause of CKD (\( n, \% \))      | Diabetes (\( n, \% \)) 6 (12%) 4 (8%) 0.10 |
|                                | Hypertension (\( n, \% \)) 12 (24%) 16 (32%) 0.425 |
|                                | Ischemic heart disease (\( n, \% \)) 3 (6%) 10 (20%) 0.198 |
| Cause of CKD (\( n, \% \))      | BMI (kg/m\(^2\))    | 24.40 ± 4.11         | 0.51   |
|                                | Dialysis vintage (years) 6.61 ± 3.02 10.71 ± 5.09 0.005 |
|                                | Residual diuresis 24 h (mL) 47.37 (0–300) 3.23 (0–100) 0.014 |
|                                | Kt/V                 | 1.38 ± 0.21          | 1.43 ± 0.12 0.121 |
|                                | SBP (mmHg)           | 131.6 ± 22.4         | 129.0 ± 14.7 0.58 |
|                                | Hb (g/dL)            | 81 ± 25              | 81 ± 28 0.75 |
|                                | Ferritin (ng/mL)     | 509 ± 269            | 533 ± 207 0.826 |
|                                | PTH (pg/mL)          | 4.55 ± 0.67          | 7.24 ± 1.17 <0.001 |

**Table 3.** The patients having LVH had a LVMI of 157.13 ± 27.84 g/m\(^2\), while the patients without LVH had LVMI of 97 ± 17.02 g/m\(^2\). Dialysis vintage was longer in LVH group compared with non-LVH group (10.71 ± 5.09 versus 6.61 ± 3.02 years; \( p = 0.005 \), respectively). Residual diuresis was 3.23 (0–100) mL/day in LVH group and 47.37 (0–300) mL/day in non-LVH group and this was statistically significant (\( p = 0.014 \)). CRP was statistically significantly higher in LVH group compared with non-LVH group (7.24 ± 1.17 mg/L versus 4.55 ± 0.67 mg/L; \( p < 0.001 \)). Hemoglobin level was found to be statistically significantly lower in LVH group compared with non-LVH group (10.2 ± 0.6 g/dL versus 11.0 ± 0.7 g/dL; \( p = 0.001 \)). The mean renalase levels were 230 ± 136 ng/mL in the patients with LVH on HD and 183 ± 107 ng/mL in the patients without LVH on HD with no significant difference (\( p = 0.153 \)).

In correlation analysis (Table 3), LVMI was positively correlated with dialysis vintage and CRP (\( r = 0.387 \), \( p = 0.005 \) and \( r = 0.597 \), \( p < 0.001 \), respectively, **Figure 1(a,b)**). Besides this LVMI was negatively correlated with residual diuresis and hemoglobin levels (\( r = -0.324 \), \( p = 0.022 \) and \( r = -0.499 \), \( p < 0.001 \), respectively, **Figure 2(a,b)**). There was no significant correlation in correlation analysis for the other parameters.

**LDL-C:** low-density lipoprotein cholesterol; **CRP:** C-reactive protein; **LVMI:** left ventricle mass index; **LVH:** left ventricular hypertrophy; **BMI:** body mass index; **CKD:** chronic kidney disease; **SBP:** systolic blood pressure; **DBP:** diastolic blood pressure; **TC:** total cholesterol; **TG:** triglyceride; **HDL-C:** high-density lipoprotein cholesterol; **LDL-C:** low-density lipoprotein cholesterol; **CRP:** C-reactive protein; **LVMI:** left ventricle mass index; **ACE:** angiotensin-converting enzyme inhibitor; **ARB:** angiotensin II receptor blockers.
between renalase and LVMI in the HD patients \((r = 0.263, p = 0.065, \text{Figure 3})\).

Serum renalase levels were considerably higher in HD patients \((212 \pm 127 \text{ ng/mL})\) compared to controls \((116 \pm 67 \text{ ng/mL}) (p < 0.001, \text{Table 1})\). The correlation between renalase and clinical, biochemical, echocardiographic parameters in HD patients are presented in Table 4. Renalase was positively correlated with serum creatinine and dialysis vintage \((r = 0.677, p < 0.001\) and \(r = 0.625, p < 0.001, \text{respectively})\). There was no significant correlation between renalase levels and neither systolic nor diastolic blood pressures in the HD patients \((r = -0.340, p = 0.815\) and \(r = 0.001, p = 0.994, \text{respectively})\).

**Discussion**

The aim of this study was to investigate whether renalase was one of the unknown factors affecting LVH in HD patients. This is the first study to show the relationships between serum renalase concentrations and LVH in long-term HD patients.

Dialysis vintage was statistically significantly longer in patients with LVH compared with patients without LVH \((p = 0.005)\). In the literature, the results of studies investigating the relationship between dialysis vintage and LVMI are controversial. In a study of Leifheit-Nestler et al., HD vintage was longer in patients having LVH. In a study of Unver et al., there was no correlation between LVMI and HD vintage \((r = 0.159, p = 0.122)\). In our study, residual diuresis was significantly decreased in LVH group compared with non-LVH group \((p = 0.014)\).

RRF is recognized as an important factor influencing morbidity and mortality in chronic dialysis patients. During the conservative management of patients undergoing HD, the decrease of the glomerular filtration rate (GFR) was associated with LVH. Ma et al. studied HD patients in two groups according to the presence of RRF and determined the LVMI of the patients who had RRF to have lower LVMI. Also in the study of Unver et al., the correlation between RRF and left ventricular mass index was observed and LVMI of the patients with daily urine output >250 mL was found to be significantly lower. In our study, LVMI was negatively correlated with RRF \((r = -0.324, p = 0.022)\).

**Table 3.** The correlation between LVMI and clinical, biochemical, echocardiographic parameters in HD patients.

| Variables           | r   | p Values |
|---------------------|-----|----------|
| Age                 | -0.08 | 0.956    |
| BMI                 | -0.176 | 0.220    |
| Dialysis vintage    | 0.387 | 0.005    |
| Residual diuresis 24 h | -0.324 | 0.022    |
| Kt/V                | 0.023 | 0.876    |
| SBP                 | 0.045 | 0.756    |
| DBP                 | 0.243 | 0.088    |
| Glucose             | -0.058 | 0.689    |
| Hemoglobin          | -0.499 | <0.001   |
| Cr                  | 0.042 | 0.771    |
| Albumin             | 0.063 | 0.664    |
| TC                  | 0.009 | 0.948    |
| TG                  | 0.021 | 0.887    |
| HDL-C               | -0.148 | 0.30     |
| LDL-C               | -0.01  | 0.993    |
| CRP                 | 0.597 | <0.001   |
| Calcium             | 0.018 | 0.902    |
| Phosphate           | 0.077 | 0.597    |
| Ferritin            | -0.065 | 0.655    |
| PTH                 | 0.114 | 0.431    |
| Renalase            | 0.263 | 0.065    |

LVMI: left ventricular mass index; HD: hemodialysis; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; Cr: creatinine; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; CRP: C-reactive protein; PTH: parathyroid hormone.

**Figure 1.** LVMI was positively correlated with dialysis vintage (a) and CRP (b) \((r = 0.387, p = 0.005\) and \(r = 0.597, p < 0.001, \text{respectively})\).
In our study, CRP level was significantly higher in patients having LVH ($p < 0.001$). Besides this LVMI was correlated with CRP ($r = 0.597, p < 0.001$). CRP is an acute phase reactant; its level rises dramatically in blood during tissue damage and inflammatory responses. According to the previous reports, CRP as an inflammation marker is able to induce adhesion molecule expression on endothelial cells and is involved in the atherosclerotic process. Persistent elevation of the inflammatory response has recently been recognized as an important risk factor.

**Figure 2.** LVMI was negatively correlated with residual renal function (a) and hemoglobin levels (b) ($r = -0.324, p = 0.022$ and $r = -0.499, p < 0.001$, respectively).

**Figure 3.** There was no significant relation between renalase and LVMI in the HD patients ($r = 0.263, p = 0.065$).

LVMI: left ventricle mass index; CRP: C-reactive protein; HD: hemodialysis.
for the development of cardiovascular complications in HD patients.\textsuperscript{23,24} In HD patients, the data have indicated that CRP levels are frequently elevated due to possible inflammatory conditions such as uremic state, infections, infected vascular access, renal or systemic inflammatory disease, persistent micro-inflammatory state from the extra-corporeal circulation using foreign materials, and contact of blood with toxins from the dialysis water.\textsuperscript{25,26} Like our study, in a study of Monfared et al., hs-CRP was found to have predictive value for the development of LVH in HD patients.\textsuperscript{27} In our study, hemoglobin level was significantly lower in LVH group ($r = -0.001$). In our study, LVMI was found to be negatively correlated with hemoglobin levels ($r = -0.499, p < 0.001$). In a study multiple regression analysis was made and HD vintage, hemoglobin, and CRP were reported to affect LVH in HD patients.\textsuperscript{28} The mean renalase levels were $230 \pm 136$ ng/mL in the patients with LVH on HD and $183 \pm 107$ ng/mL in the patients without LVH on HD with no significant difference ($p = 0.153$).

In our study, renalase levels were higher in the patients on HD than in the healthy controls ($p < 0.001$, Table 1) and creatinine levels and as dialysis vintage increased so did renalase levels ($r = 0.677, p < 0.001$ and $r = 0.625, p < 0.001$, respectively, Table 4). Renalase levels are directly related to GFR.\textsuperscript{29} In one study including 89 renal transplant recipients, another study including 34 HD patients, and another study including 104 HD patients, renalase levels were increased compared to the healthy controls.\textsuperscript{8,10} In the present study, high renalase levels were shown in the patients of HD, which was not affected by age and gender. In another study, blood renalase levels were higher in 130 heart transplant recipients with moderate renal functions (GFR: $55 \pm 28$ mL/min based on CKD-EPI formula) than in healthy controls and had a strong negative correlation with GFR.\textsuperscript{30} Similarly, the present study revealed that renalase levels increased in the patient group as their renal functions worsened. This was caused by the reason that renalase is inversely correlated with GFR. In our study compatible with the literature renalase levels were correlated with dialysis vintage.\textsuperscript{31}

There was no significant relation between renalase levels and neither systolic nor diastolic blood pressures in the HD patients ($r = -0.340, p = 0.065$). In an experimental study on denervated rats, the mean arterial pressure was low while renalase levels were high.\textsuperscript{6} In another study, a single dose of recombinant renalase administered subcutaneously lowered both systolic and diastolic blood pressures. In the rats with a tendency to have hypertension and stroke, both systolic and diastolic blood pressures decreased 12 h after renalase treatment.\textsuperscript{5} There have been few studies on renalase in patients with renal failure and there are conflicting evidence about the relation between blood renalase levels and hypertension.\textsuperscript{8–10} A study on HD patients showed that renalase was related to stroke and organ damage.\textsuperscript{9} However, renalase was not associated with blood pressure in another study on HD patients.\textsuperscript{10} Likewise, in the current study, renalase levels were not correlated with systolic and diastolic blood pressures in the patients on HD.

There was no significant relation between renalase and LVMI in the HD patients ($r = 0.263, p = 0.065$). In experimental studies, administration of recombinant renalase reduced half of the infarct areas in myocardial ischemia.\textsuperscript{32} An experimental study on long-term effects of renalase on blood pressure showed significantly low plasma norepinephrine levels and the mean arterial pressure, LVH and cardiac fibrosis in the rats administered recombinant renalase daily for four weeks compared to the control rats.\textsuperscript{6} Incompatible with results of the experimental studies reported, renalase levels were higher in the patients with LVH. The current study was directed toward determining whether renalase could be a predictor of LVH in its early stage. There was no significant relation between renalase and LVMI in the HD patients.

Our study has several limitations. First of all, the sample size was rather small; it would need to be larger to be of convincing statistical significance. Further studies with a larger number of patients and prospective design are needed to confirm these results. In our study, LVMI tent to correlate with renalase ($p = 0.065$) and this correlation may be significant if patient number involved is increased.

In conclusion, this study indicated that renalase is not related with LVH. The main parameters affecting renalase levels are dialysis vintage band serum creatinine, may be associated with LVH in long-term HD patients, possibly indicating that reduction of serum renalase concentrations is necessary to prevent LVH and to improve the survival of HD patients.

### Table 4. The correlation between renalase and clinical, biochemical, echocardiographic parameters in HD patients.

| Variables       | $r$     | $p$ Values |
|-----------------|---------|------------|
| Age             | $-0.206$| 0.151      |
| Dialysis vintage| 0.625   | $<0.001$   |
| Cr              | 0.677   | $<0.001$   |
| Residual diuresis 24 h | $-0.381$ | 0.006      |
| SBP             | $-0.34$ | 0.815      |
| DBP             | 0.001   | 0.994      |
| LVMi            | 0.263   | 0.065      |
| CRP             | 0.068   | 0.637      |

HD: hemodialysis; Cr: creatinine; SBP: systolic blood pressure; DBP: diastolic blood pressure; LVMi: left ventricular mass index; CRP: C-reactive protein.
Disclosure statement

The authors declare that they have no conflicts of interest.

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