Original Research

The role of urinary renalase on early-stage renal damage in Chinese adults with primary hypertension

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Impact statement

In patients with early-stage kidney damage of primary hypertension, there are no obvious structural or functional changes, which leads to a high level of diagnostic omissions. Therefore, it would be of great clinical value to find an indicator that can accurately evaluate the early-stage renal injury in primary hypertension. Urinary albumin to creatinine ratio (UACR) is a classic indicator used in early-stage renal damage, but it is affected by many factors. Renalase, a protein discovered by Xu in 2005, not only plays an important role in hypertension but also closely correlates with kidney function. In our study, we found that urinary renalase was further decreased in patients with early-stage renal damage in primary hypertension, and it could be used as a predictive index. This finding could help to diagnose the early-stage renal damage in primary hypertension much earlier and improve the prognosis of these patients.

Abstract

It would be of great clinical value to find an indicator that can accurately evaluate the early-stage renal injury in primary hypertension. Previous findings have shown renalase not only plays an important role in hypertension but also closely correlates with kidney function. The purpose of this study is to investigate whether urinary renalase could be used as a predictive index of early-stage renal damage in patients with primary hypertension. Urinary albumin to creatinine ratio (UACR) was used to divide subjects with primary hypertension into two groups: a no renal damage (NRD) group (UACR <30 mg/g) and an early-stage renal damage (RD) group (UACR >30 mg/g). Subjects with normal examination results were randomly included in a healthy control (HC) group. Urinary renalase was determined through an enzyme-linked immunosorbent assay (ELISA). Urinary renalase continued to reduce among the HC ($n = 81$), NRD ($n = 84$) and RD group ($n = 80$), while systolic blood pressure (SBP) increased. Urinary renalase was negatively correlated with SBP in all the groups. Among the subjects with stage 1 primary hypertension, urinary renalase in the RD group was lower than the NRD group, while the UACR was higher, and urinary renalase was negatively correlated with the UACR. A multiple linear stepwise regression analysis showed that there was a linear regression relationship between the increase of the UACR and urinary renalase, heart rate (HR), SBP and serum creatinine. In addition, the standardized partial regression coefficient of urinary renalase was the highest. The performance of urinary renalase as a marker for the diagnosis of early-stage renal damage in patients with primary hypertension was 0.968 with a cut off value of 2.01 µg/ml. Taken together, urinary renalase was further decreased in patients with early-stage renal damage and primary hypertension, and consequently, it could be used as a predictive index.

Keywords: Urinary renalase, primary hypertension, early-stage renal damage, urinary albumin to creatinine ratio, biomarker, predictive index

Introduction

Primary hypertension, a global public health problem and one of the most common clinical cardiovascular diseases, often causes damages to the heart, brain, kidney and other important target organs.[1] In the early-stage kidney injury of primary hypertension, patients often do not have any obvious clinical manifestations. Once they develop symptoms, the kidney injury has usually entered into the middle or late stages. Research has demonstrated that the number of end-stage renal disease (ESRD) patients caused by primary

hypertension has been increasing year by year.[2,3] American data indicates that of all the ESRD causes, primary hypertension accounts for 24%,[4] and dialysis registration data from Beijing suggests that it is the third biggest cause of ESRD. Therefore, early-stage detection and the accurate assessment of kidney injury in patients with primary hypertension are of great significance. Urinary albumin to creatinine ratio (UACR) is an important observation index in early-stage renal damage, but it can be easily affected by many factors, such as position, motion, diet, blood pressure (BP) and so on.[5,6] Therefore, we need to explore a more accurate indicator.

Renalase, a protein discovered by Xu in 2005, is expressed within the kidney, myocardium, skeletal muscle, liver and so on.[7,8] The majority of renalase is synthesized by renal tubular epithelial cells.[9,10] Renalase is considered as an amine oxidase dependent on flavin adenine dinucleotide (FAD), and it can reduce BP through degrading catecholamines.[7,11–14] Our team has proven that renalase gene polymorphism plays an important role in patients with hypertension and concomitant coronary heart diseases,[15] and renalase protects the cardiomyocytes of Sprague-Dawley rats against ischemia and reperfusion injury by reducing myocardial cell necrosis and apoptosis.[16] Other studies have shown that whether in acute kidney injury models (induced by 5/6 kidney resection, cisplatin or contrast agent intervention) or in acute kidney ischemia reperfusion models, plasma renalase levels are markedly lower than the control groups.[17–21] Clinical studies have suggested that plasma renalase levels in end-stage renal disease (ESRD) patients are much lower than those with normal renal function.[22–24]

Therefore, renalase levels are not only related to BP but are also affected by renal function. Plasma renalase levels are lower in patients with hypertension than those who are normotensive, but the levels of urinary renalase in early-stage renal damage of primary hypertension remain unknown. Therefore, the target of this study is to observe the urinary renalase of these patients and to explore whether it could be used as a predictive index for early-stage renal damage in patients with primary hypertension.

Materials and methods

Study cohort

Subjects who were diagnosed as primary hypertension in both the outpatient and inpatient departments of cardiology in the Third Xiangya Hospital of Central South University from September 2017 to January 2018 were included at random. The inclusion criteria were as follows: (1) primary hypertension that met the diagnostic criteria of the 2010 guidelines of *Hypertension Prevention and Treatment in China*; (2) normal plasma creatinine and urea nitrogen and a negative urine protein test in the urine routine. The exclusion criteria were as follows: (1) acute or chronic kidney diseases; (2) acute or chronic infectious diseases; (3) fever; (4) secondary hypertension; (5) connective tissue or other autoimmune diseases; (6) malignant diseases, such as tumors.

There were 164 subjects with primary hypertension who were divided into two groups: a no renal damage (NRD) group (UACR <30 mg/g) and an early-stage renal damage (RD) group (UACR >30 mg/g). There were 84 subjects in the NRD group (44 males and 40 females) and 80 subjects in the RD group (42 males and 38 females). In addition, 81 healthy control (HC) subjects (43 males and 38 females) with normal physical and laboratory examination results were randomly included from the health management center of the Third Xiangya Hospital of Central South University.

Well-trained staff interviewed the participants and collected their data on demographics (age, gender, education, occupation, and physical activity), smoking history (if a patient had a history of smoking but had quit for more than one year this was recorded as a non-smoking history), family history of hypertension, hypertension course and so on. Standard measurement methods were used to measure height, weight and body mass index (BMI = weight (kg)/[height (m)]^2). Physical examinations were also conducted.

This study was approved by the Institutional Review Board of the Third Xiangya Hospital of Central South University (No.: 2019-S544) and all the selected subjects signed the informed consent.

BP measurement

BP was measured by trained staff to obtain three readings using a standard mercury sphygmomanometer and defined as the mean value. The method was as follows: the subjects were instructed to rest for more than 5 min, and their right brachial pressure was measured while they were in a sitting position. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were determined as the first and fifth Korotkoff sounds, respectively. Pulse pressure was considered as the difference between the SBP and DBP. Subjects manifesting a SBP≧140 mmHg and/or DBP≧90 mmHg or using anti-hypertensive medications were defined as hypertensive.[25]

Biochemical analyses

Venous blood samples from all the subjects were collected to detect their biochemical indexes, such as blood glucose, creatinine and urea nitrogen with automatic biochemical analyzers (model 7600 and 7100, Hitachi, Ltd, Tokyo, Japan). At the same time, urine samples (midstream urine) were randomly collected to test urinary microalbumin, urinary creatinine and urinary renalase levels. The UACR was then calculated. Urinary microalbumin was determined by rate scattering turbidimetry using a kit (Yikang Biotechnology Co., Ltd, Hangzhou, China). Urinary creatinine and urinary sugar levels were detected by enzyme endpoint colorimetry with a kit (Yikang Biotechnology Co., Ltd, Hangzhou, China). Urinary renalase was assessed using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (SEC845Hu, USCN Business Co., Ltd, Wuhan, China), and all of the operations were in accordance with the manufacturer's instructions.

Statistical analyses

Data were expressed as means ± standard deviation (SD) for normally distributed values, and as median (25th and 75th percentile) for non-normally distributed values. Student's t tests for unpaired two samples were performed for normally distributed variables, while analysis of variance was conducted for more than two samples of data. Mann–Whitney U tests were conducted for non-normally distributed parameters. Chi-square tests were carried out to compare categorical variables. When residuals were normally distributed, Pearson's correlation coefficients were used to determine correlations between the parameters. Otherwise, Spearman's correlation coefficients were chosen. Multiple linear stepwise regression analysis was also conducted to determine the influence factors for the rise of UACR. A receiver operating characteristic (ROC) curve was performed by plotting the sensitivity and specificity of the urinary renalase values according to Youden's index. Statistical analyses were performed with SPSS version 19.0 for Windows (SPSS Inc., Chicago, IL, USA). A two-tailed $p < 0.05$ was considered significant.

Results

Basic data of the subjects in three groups

Table 1 demonstrated that there were no statistically significant differences in the number of subjects, gender, age, hypertension course, smoking, family history of hypertension, creatinine, urea nitrogen and blood glucose among the three groups ($p > 0.05$). However, the BMIs of the NRD group and the RD group were higher than the HC group ($p < 0.05$).

Comparisons of urinary renalase, SBP and UACR among the three groups

From the HC group to the NRD group to the RD group, urinary renalase continuously decreased (4.22 ± 0.29 vs. 2.32 ± 0.24 vs. 1.74 ± 0.25) μg/ml ($p < 0.05$, Figure 1(a)), and SBP continuously increased (111.90 ± 7.58 vs. 134.83 ± 7.94 vs. 159.03 ± 13.71) mmHg ($p < 0.05$, Figure 1(b)), as did pulse pressure (40.40 ± 8.34 vs. 52.81 ± 9.00 vs. 66.50 ± 12.48) mmHg ($p < 0.05$, Figure 1(c)). The UACR was higher

in the RD group than in the NRD group ($p < 0.05$, Figure 1 (d)). In addition, urinary renalase was negatively correlated with SBP in the HC group ($r = -0.589$, $p < 0.001$), the NRD group ($r = -0.523$, $p < 0.001$) and the RD group ($r = -0.337$, $p = 0.002$), but there was no correlation between urinary renalase and pulse pressure ($p > 0.05$).

The results of the subjects with stage 1 primary hypertension

As shown in Table 2, the differences in gender, age, SBP and pulse pressure among the subjects with stage 1 primary hypertension were not significant ($p > 0.05$). However, urinary renalase in the RD group was still lower than the NRD group (1.79 ± 0.24 vs. 2.17 ± 0.25) μg/ml ($p < 0.05$, Figure 2 (a)), while UACR was higher (64.68 ± 37.48 vs. 8.17 ± 7.14) mg/g ($p < 0.05$, Figure 2(b)). Urinary renalase was negatively associated with the UACR in both the NRD group ($r = -0.365$, $p < 0.001$) and the RD group ($r = -0.778$, $p < 0.001$).

Multiple linear stepwise regression analysis

In the RD group, the UACR was taken as the dependent variable and urinary renalase, age, SBP, DBP, creatinine, BMI, pulse pressure and so on were used as independent variables to conduct a multiple linear stepwise regression analysis (α in $= 0.05$, α out $= 0.10$): $\hat{Y} = 34.715 - 109.794X_1 + 0.466X_2 + 1.251X_3 + 0.794X_4$ [X_1 was urinary renalase, X_2 was SBP, X_3 was heart rate (HR), X_4 was creatinine; $p < 0.001$]. The determination coefficient (R^2) of the regression equation was 0.794 and Table 3 showed that the standardized partial regression coefficient of urinary renalase was the greatest.

ROC curve for urinary renalase to diagnose the early-stage renal damage in primary hypertension

A ROC curve was plotted to determine the diagnostic performance of urinary renalase as a bio-marker for early-stage renal damage in subjects with primary hypertension (Figure 3). The area under the curve (AUC) of urinary renalase was 0.968 (95% CI: 0.940–0.997; $p < 0.001$). When the cut off value was set at 2.01 μg/ml, the sensitivity

Table 1. Demographic and clinical characteristics for all the groups' subjects: the healthy control (HC) group, the primary hypertension without renal damage (NRD) group and the primary hypertension with renal damage (RD) group.

Parameters	HC (n = 81)	NRD (n = 84)	RD (n = 80)
Sex (M/F)	43/38	44/40	42/38
Age (year)	56.29 ± 11.10	57.01 ± 10.85	57.89 ± 13.16
Hypertension course (year)	–	11.38 ± 8.75	12.61 ± 9.55
Smoking (%)	30.9%	32.1%	31.5%
Family history of hypertension (%)	34.6%	35.7%	35.2%
BMI (kg/m^2)	23.35 ± 2.65	24.59 ± 2.94*	25.54 ± 4.45*
Creatinine (μmol/l)	67.85 ± 12.81	67.87 ± 11.81	70.10 ± 13.38
Urea nitrogen (mmol/l)	4.41 ± 1.05	4.38 ± 1.01	4.71 ± 1.14
Blood glucose (mmol/l)	5.07 ± 0.85	4.98 ± 0.87	5.12 ± 0.78

Non-normally distributed variables are expressed as the median (interquartile range). All of the values are expressed as means ± standard deviation (SD) or n, %.
HC: healthy control; NRD: primary hypertension without renal damage; RD: primary hypertension with renal damage; BMI: body mass index, BMI = weight (kg)/[height (m)]^2.
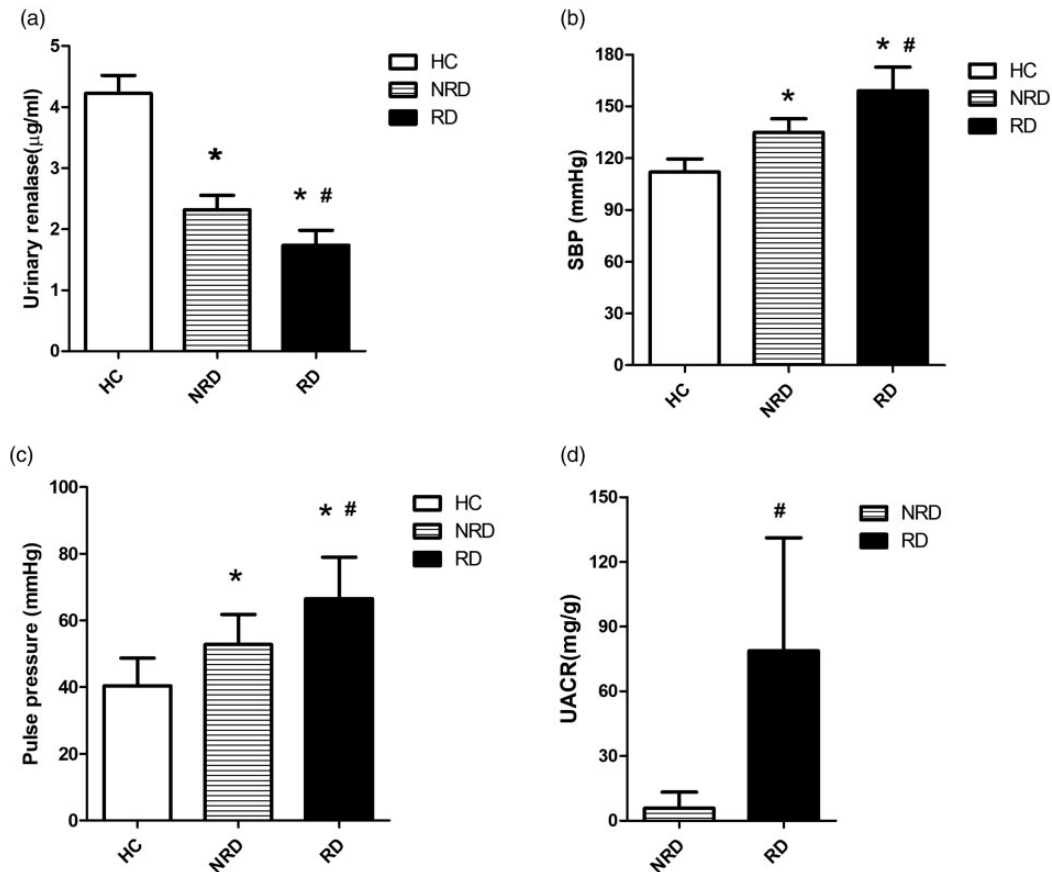*$p < 0.05$, vs. the HC group.

Figure 1. Comparisons of urinary renalase, systolic blood pressure (SBP), pulse pressure and the urinary albumin to creatinine ratio (UACR) among the three groups. From the HC group to the NRD group to the RD group, urinary renalase continuously decreased (a), while SBP and pulse pressure continuously increased (b, c). The UACR also increased from the NRD group to the RD group (d). HC: healthy control; NRD: primary hypertension without renal damage; RD: primary hypertension with renal damage. *p < 0.05, vs. the HC group; #p < 0.05, vs. the NRD group.

Table 2. Clinical characteristics of subjects with stage 1 primary hypertension from the primary hypertension without renal damage (NRD) group and the primary hypertension with renal damage (RD) group.

Parameters	Subjects with stage 1 primary hypertension	
	NRD (n=35)	RD (n=39)
Urinary renalase (μg/ml)	2.17 ± 0.25	1.79 ± 0.24[a]
UACR (mg/g)	8.17 ± 7.14	64.68 ± 37.48[a]
SBP (mmHg)	147.71 ± 4.32	151.54 ± 5.24
Pulse pressure (mmHg)	59.51 ± 9.56	62.56 ± 9.53
Sex (M/F)	19/16	22/17
Age (year)	58.14 ± 11.32	56.67 ± 12.95

Non-normally distributed variables are expressed as the median (interquartile range). All of the values are expressed as mean ± standard deviation (SD) or n, %. NRD: primary hypertension without renal damage; RD: primary hypertension with renal damage; UACR: urinary albumin to creatinine ratio; SBP: systolic blood pressure.
[a]p < 0.05, vs. the NRD group.

for early-stage renal damage in primary hypertension was 90.50% and the specificity was 98.80%.

Discussion

In the early-stage kidney damage of patients with primary hypertension, there are no obvious structural or functional changes, which leads to a high rate of diagnostic omissions. After the occurrence of renal injury in patients with primary hypertension, the BP will further rise. This continual increase in BP aggravates the renal damage and thus forms a vicious cycle.[2] Therefore, it would be of great clinical value to look for an indicator that can accurately evaluate the early-stage renal injury in patients with primary hypertension. The UACR is a classic indicator used for early-stage renal damage, but it is affected by many factors and the result is unreliable.[5,6,26,27] Therefore, researchers have been attempting to seek a more effective indicator. In this cohort of Chinese adults, we found that urinary renalase was further decreased in patients with early-stage renal damage and primary hypertension, and it could be used as a predictive index.

Previous studies have shown that after injecting intravenously recombinant renalase into rats, the rats' BP, HR and myocardial contractility display a dose-dependent decrease.[14] In addition, studies about renalase gene knockout mice and wild mice have revealed that the former would develop hypertension, with tachycardia and high catecholamine levels.[28] This study verifies that urinary renalase is negatively correlated with SBP, which is consistent with the results of previous research.[29,30] Furthermore, there is a lower correlation between urinary renalase and BP in the RD group than the NRD group. We speculate that
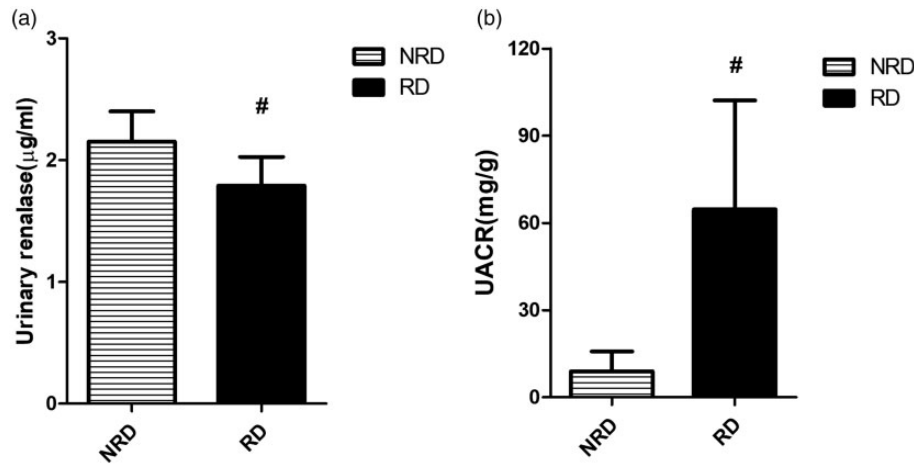
Figure 2. Comparisons of urinary renalase and the urinary albumin to creatinine ratio (UACR) between the NRD group and the RD group. Urinary renalase decreased from the NRD group to the RD group (a), while the UACR increased (b). NRD: primary hypertension without renal damage; RD: primary hypertension with renal damage. [#]p < 0.05, vs. the NRD group.

Table 3. Multiple linear stepwise regression analysis.

Model	Non-standardized coefficients β	Standardized coefficients β	Standard error	T-value	p-value
Constant	34.715	–	63.770	0.544	0.588
Urinary renalase (μg/ml)	−109.794	−0.515	16.537	−6.639	0.000*
SBP (mmHg)	0.466	0.122	0.220	2.113	0.038*
HR (bmp)	1.251	0.236	0.357	3.508	0.001*
Creatinine (μmol/l)	0.794	0.202	0.293	2.705	0.008*

SBP: systolic blood pressure; HR: heart rate.
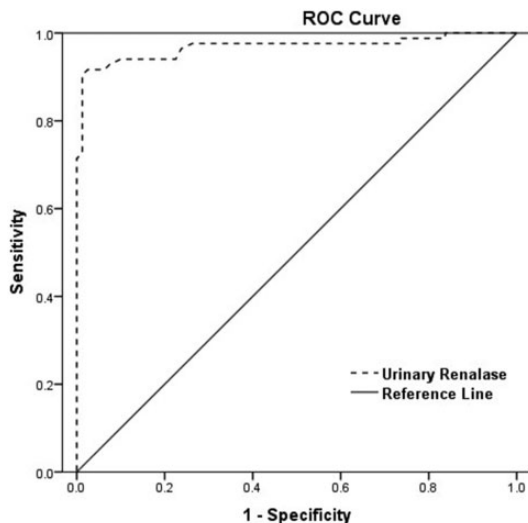*p < 0.05.

Figure 3. A receiver operator characteristic (ROC) curve was performed to assess urinary renalase as a predictive marker for early-stage renal damage in subjects with primary hypertension. The area under the curve (AUC) was 0.968 (95% CI: 0.940–0.997; p < 0.001), while sensitivity and specificity were 90.50% and 98.80%, respectively, using a cut off of 2.01 μg/ml.

when the kidney function is normal, the main effects of renalase are on the metabolism of catecholamine to reduce BP.[7] Once kidney damage occurs, the urinary renalase level is largely affected and its correlation with BP decreases.

Due to the negative correlation between urinary renalase and BP, it is necessary to exclude any interference from BP to investigate whether the early-stage renal injury in primary hypertension is related to urinary renalase. The results from patients with stage 1 primary hypertension demonstrated that urinary renalase in the RD group was still lower than the NRD group, while the UACR was higher. Further analysis revealed that the increase of UACR was negatively correlated with urinary renalase, and their correlation in the RD group was greater than in the NRD group. It is worth noting that the UACR is a classic indicator for early-stage renal damage. Therefore, the result indicates that urinary renalase will further decrease in the early-stage renal damage in patients with primary hypertension. Other researchers have discovered that plasma renalase is closely related to renal function in patients with kidney or heart transplantations: the worse the degree of renal function, the lower the levels of renalase,[17,18] and renalase in patients with ESRD is significantly lower than healthy people.[23,31–33] At the same time, the inflammation, necrosis and apoptosis of the renal tubules in renalase gene knockout mice are more serious than wild mice, and their creatinine and urea nitrogen levels are much higher. After injecting the recombinant renalase protein into these mice, their renal functions are largely improved.[34] All of these imply that renalase is associated with renal function, and renalase has a renal protective function. Our study further confirms the correlation between renalase and renal function.

Among patients with primary hypertension, there are many factors that influence the rise of the UACR. In order to determine which factor was the most important, a multivariate linear stepwise regression analysis was performed. The data from the RD group revealed that the increase of the UACR had a linear regression relationship with urinary renalase, HR, SBP and creatinine, and all of these independent variables explained 79.4% of the variations in the rise of the UACR. Furthermore, the effect of urinary renalase was the greatest. The ROC curve also supports that urinary renalase could be a good predictive indicator for early-stage renal damage in primary hypertension.

In conclusion, there was a linear regression relationship between the increase of the UACR and urinary renalase levels. The performance of urinary renalase as a marker for the diagnosis in early-stage renal damage for subjects with primary hypertension was 0.968. These results indicate that urinary renalase levels fall with hypertension and are further diminished when hypertension is complicated by renal disease. Therefore, we suggest that urinary renalase could be used in the prediction of renal disease in hypertension.

AUTHORS' CONTRIBUTION

DECLARATION OF CONFLICTING INTERESTS

FUNDING

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