REVIEW ARTICLE

Kidney and hypertension: is there a place for renalase?

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KEY WORDS

cardiovascular disease, chronic kidney disease, renalase, sympathetic nervous system

ABSTRACT

Chronic kidney disease (CKD) is associated with a considerably higher risk of cardiovascular disease due to the presence of traditional and nontraditional risk factors. Hypertension occurs in approximately 80% to 85% of the patients with CKD and its etiology is multifactorial. The sympathetic nervous system activity is enhanced in patients witch CKD resulting in increased vascular resistance and systemic blood pressure. This enhanced activity is the result of overspill and reduced catecholamine clearance. Recently, a new protein was discovered, named renalase. Experimental in vitro studies showed that renalase degrades catecholamines and thus may have a significant hemodynamic effect in vivo, for example may decrease cardiac contractility, heart rate, and blood pressure. Studies conducted in CKD and hemodialysis patients demonstrated lower serum renalase levels compared with healthy individuals. Other studies revealed increased serum renalase levels in dialysis population and kidney transplant recipients. There are no data concerning the association between renalase gene expression and activity/concentration and function of renalase; thus, it has to be proved in further studies that renalase is not an innocent bystander but is involved in the pathogenesis of hypertension.

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Introduction Chronic kidney disease (CKD) is associated with a high risk of cardiovascular disease (CVD).[1] There are numerous observational studies that showed an increased chance of cardiovascular events in patients with reduced glomerular filtration rate and proteinuria.[2] It is the result of the presence of traditional and nontraditional risk factors for CVD observed in chronic renal failure. Traditional Framingham risk factors, such as hypertension, diabetes, dyslipidemia, smoking, and older age, are highly prevalent in this population and are associated with a much larger absolute increase in risk.[3] Hypertension is present in approximately 80% to 85% of patients with CKD.[4] The etiology of high blood pressure (BP) is multifactorial in this population and 1 or more risk factors may play a role in an individual patient.

Cardiovascular disorders in chronic kidney disease

Volume expansion is the most important cause of hypertension in end-stage renal disease. It is associated with an inability to excrete sodium and water via the kidneys, which results in an increase in cardiac output and inappropriately high systemic vascular resistance.[5,6] There are a number of differences between peritoneal dialysis (PD) and hemodialysis (HD) patients in BP control during the initial time on renal replacement therapy. In PD patients, control of BP is better even when compared with HD patients. It is called the "honeymoon period" and is associated with better fluid volume control and greater clearance of vasoconstrictor factors with PD.[5] With time, there is a loss of residual function and peritoneal ultrafiltration and subsequent fluid retention leading to a rise in BP.[5] As early as in 1994, Faller and Lameire[7] revealed that patients maintained on PD longer were more overhydrated and had worse BP control. On the other hand, in 1998, Takeda at al.[8] observed that PD patients on longer dialysis had greater left ventricular mass. Later studies confirmed the higher risk of extracellular water excess and the development of left ventricular hyperthrophy in PD patients.[6] Overhydration is also a major problem in HD patients. Tapolyai et al.,[9] using the bioimpedance apparatus to measure the degree of hydration in HD patients, showed a strong association between volume overload and

an elevation of BP, especially systolic BP. Meanwhile, Rahman et al.[10] confirmed (in a multivariate analysis) that a greater interdialytic weight gain is independently associated with high BP. It was also reported in a large observational study that increased interdialytic weight gain was associated with higher mortality.[11]

Activation of the renin–angiotensin–aldosterone system due to primary vascular disease or to regional ischemia induced by fibrosis is often responsible at least in part for hypertension that persists after obtaining normovolemia.[6]

Endothelial cell dysfunction (an increase in endothelium-derived vasoconstrictors, such as endothelin-1, and a reduction in endothelium-derived vasodilators, such as nitric oxide) is observed in uremia.[6] It was found that endothelin-1 levels were elevated in hypertensive HD patients compared with normotensives patients.[12] There is an inhibition of nitric oxide release by the action of endogenous asymmetric dimethylarginine (ADMA).[6] Further research found that ADMA is elevated in HD patients and is associated with increased cardiovascular and all-cause mortality.[13] Oxidative stress, observed in CKD patients, also leads to accumulation of ADMA.[6]

CKD is associated with abnormal calcium-phosphorus metabolism, which results in hyperphosphatemia and secondary hyperparathyroidism. It contributes to alterations in calcium homeostasis and a predisposition to metastatic arterial wall calcification leading to hypertension and CVD.[5,6]

Treatment with erythropoiesis-stimulating agents, particularly intravenous, may cause a rise in BP by hematocrit and blood viscosity elevation and by increased endothelin-1 release, increased sensitivity to angiotensin II, and by adrenergic stimuli.[5,14]

The sympathetic nervous system (SNS) activity is raised in patients with CKD and correlates with increased vascular resistance and systemic BP.[15,16] Recent studies confirmed that the SNS activity substantially contributes to poor prognosis in CKD patients.[17,18] Plasma norepinephrine levels are predictive of both survival and incidents of CVD in end-stage renal disease. The monitoring of sympathetic nerve activity by using microneurography confirmed sympathetic overactivity in patients with renal failure.[18,19] This appears to be driven by diseased kidney while nephrectomy or renal denervation corrected BP and sympathetic nerve activity in human and animal studies.[20] One of important determinants of SNS hyperactivity is abnormal renal sodium excretion and activation of the renin–angiotensin–aldosterone system and then volume overload, which per se may also incorporate here.[21] It has been suggested that the activation of chemoreceptors within the kidney by uremic metabolities plays an important role in SNS overactivity, leading to a neural reflex that traverses afferent pathways to the central nervous system and results in increased efferent sympathetic tone.[22] Recording of postganglionic sympathetic discharge to blood vessels in the skeletal muscle showed increased burst frequency in the sural nerve of HD patients, in predialysis patients and even in hypertensive patients with autosomal polycystic kidney disease.[17,23-25] The elevated level of catecholamines in CKD is the result of the overspill (in the mechanisms that involve inhibition of nitric oxide followed by increased angiotensin II and increased sympathetic afferent outflow from diseased kidneys) and also of reduced catecholamine clearance.[15,26] Norepinephrine clearance is reduced by 20% in mild renal failure and by up to 40% in HD patients. Correction of uremia by successful kidney transplantation does not normalize sympathetic nerve activity.[25] It is known that elevated SNS activity contributes to CVD development in the general population.[27] In renal patients, despite the effect on CVD, it also aggravates renal failure progression, which results in poor prognosis. Norepinephrine affects cardiomyocytes and could be responsible for left ventricular hypertrophy.[26,27] SNS activation and vagal withdrawal may be linked with rhythm disturbances and lead to a sudden cardiac death, a frequent cause of mortality in patients with CKD. Badve et al.,[28] in a meta-analysis of randomized controlled trials, studied the benefits and risk of β-adrenergic antagonists (β-blockers) in patients with CKD stages 3–5 and found that treatment with β-blockers decreased all-cause and cardiovascular mortality in patients with CKD who had heart failure and low left ventricular ejection fraction.

Nontraditional cardiovascular risk factors identified in patients with CKD are as follows: anemia, chronic inflammation, insulin resistance, and vitamin D_3 deficiency.[28-30] The main CVDs observed in CKD are left ventricular hypertrophy (LVH), heart failure (HF), and coronary heart disease. It is known, based on many studies, that anemia is an important, independent risk factor for the development and progression of LVH, HF, and adverse cardiovascular outcomes, including mortality.[31] Tomczak-Watras et al.[32] demonstrated that even short treatment of anemia in patients with CKD stages 3 and 4 caused a decrease in volume and mass of the left ventricle. CKD alone is an independent risk factor for the development of coronary artery disease and for more severe coronary heart disease.[21,33] Renal failure is also associated with increased mortality after an acute coronary syndrome and after percutaneous coronary intervention with or without stenting.[34] In addition, patients with CKD are more likely to present with atypical symptoms, which may delay diagnosis and adversely affect the outcomes.[35]

Renalase – a link between glomeruli and cardiomyocytes **Experimental data** In 2005, Xu et al.[36] discovered and described a new protein released by the kidney – renalase. The calculated molecular mass of renalase is about 38 kDa. The authors observed, according to the information available in the GenBank, that the renalase gene was located

on chromosome 10 at q23.33. It contains 7 exons and has 2 transcription variants (1 and 2). Using in situ hybridization and immunocytochemical tests, the authors detected the specific signal of renalase in renal glomeruli, proximal tubules, and cardiomyocytes. Later studies indicated renalase expression also in the liver, skeletal muscles, peripheral nerves, adrenals, endothelium, central nervous system, 12.5 day-old rat embryo, and human adipose tissues.[37,38] The renalase gene encodes 4 differently spliced isoforms (hRenalase 1–4) which can be tissue specific and reflect a particular function of renalase in these tissues.[37] Xu et al.[36] reported that renalase had a flavin adenine dinucleotide (FAD)-binding region, and that this domain was an essential cofactor for the stability and renalase oxidase activity. They also found weak amino acid similarities of renalase to monoamine oxidase (MAO)-A and MAO-B and distinct substrate specificity and inhibitor profile. Therefore, they postulated that renalase represented a new class of FAD-containing MAO. In an in vitro study, the authors observed that renalase degraded catecholamines and they predicted that it may have a significant hemodynamic effect in vivo. Renalase infusion in rats caused a dose-dependent decrease in cardiac contractility, heart rate, and BP and prevented a compensatory increase in peripheral vascular tone. Experimental data showed that renalase KO mice were hypertensive, had tachycardia, and higher catecholamines levels than wild-type animals[39] and were prone to myocardial damage during acute ischemia. A model of heart failure in rats (ligation of the left anterior descending coronary artery) showed increased renal renalase expression together with a rise in norepinephrine levels.[40] However, the authors did not study serum creatinine to better understand the observations. What is interesting, Pandini et al.,[41] using 2 different methods, were unable to prove that renalase had MAO activity. Nevertheless, when administered to rats, it demonstrated hypotensive properties but did not influence the heart rate. Therefore, the question whether renalase is really MAO is still unresolved. Moreover, Milani et al.[42] suggested that renalase was not a monoamine oxidase and most probably not an oxidase at all. One explanation of the discrepancies may result from the fact that Xu et al.[36] conducted their experiments in HEK293 cell line and claimed that renalase was synthesized by the kidney. This cell line was generated in the early 1970s by transformation of normal human embryonic kidney cells, obtained from a healthy aborted fetus with shared adenovirus 5 DNA.[43] For years, it has been assumed that HEK293 cells are generated by transformation of either a fibroblastic, endothelial or epithelial cell, which are abundant in the kidney. A few years before the discovery of renalase, Shaw et al.[44] demonstrated that the widely used HEK293 cells had an unexpected association with neurons, a finding that might require reinterpretation of numerous previous studies which assumed that HEK293 cells resembled more typical kidney epithelial cells. They also concluded that HEK293 cells were not typical kidney cells and thus could not be used as kidney controls or to study any normal-related kidney function. Therefore, the issue whether renalase is synthesized or just excreted by the kidney remains to be elucidated and so does the origin of renalase.

Clinical data In their landmark study, Xu et al.[36] showed, using the Western blot test, qualitatively lower serum renalase levels in 8 HD patients with end-stage renal disease compared with 4 healthy individuals. However, a study by Wang et al.[45] also showed a diminished renalase expression in 1 patient with CKD, 1 patient with HD, and 2 healthy controls. It would be interesting to examine renalase expression, levels, and activity in patients after bilateral nephrectomy and show no renalase expression, levels, and activity in this patient group. Moreover, in a prospective study, it would be useful to assess renalase before and after unilateral and bilateral nephrectomy as a proof-of-concept study.

Other studies using a commercially available assay reported increased serum renalase levels.[46-49] In addition, serum renalase was predicted predominantly by kidney function in kidney transplant recipients or heart transplant recipients. In patients on renal replacement therapy renalase was also dependent on residual renal function.[46,48,50] Renalase was significantly higher in hypertensive kidney allograft recipients than in normotensives.[49] The problem of the assessment of renalase levels was discussed in detail elsewhere.[51]

The association between renalase and hypertension was first reported by genetic studies.[52,53] Zhao et al.,[52] as pioneers, found in the Han Chinese population, that the renalase gene was a novel susceptibility gene for essential hypertension and its genetic variations may affect BP. Two single nucleotide polymorphisms (SNPs), namely rs2 576 178 GG genotype and rs2 296 545 CC, with the former located in the noncoding region and the latter within the FAD-binding domain. In this Asian population of subjects with essential hypertension and healthy controls, they found that 3 SNPs, rs2 576 178, rs2 296 545, and rs2 114 406, showed significant associations with essential hypertension ($P < 0.05$). It was probably connected with sex differences in the autonomic nervous system activity, which is higher in men.[54] Zhao et al.[52] suggested replications in other populations and further functional studies to confirm and interpret the association of renalase gene with essential hypertension. In Caucasians from the Heart and Soul Study, Farzaneh-Far et al.[53] reported that a functional missense polymorphism (C allele) in renalase (Glu37Asp) was associated with LVH, both systolic and diastolic dysfunction, poor exercise capacity, and inducible ischemia. However, there was no association between this CC genotype and BP in the population of patients

with stable coronary artery disease. On the other hand, CC genotype was also associated with a decrease in affinity for NADH and reduction in maximal renalase activity.

In their recent paper, Stec et al.[55] described polymorphisms of the renalase gene in HD patients and their associations with hypertension. They defined hypertension as systolic BP 140 mmHg or higher, diastolic BP 90 mmHg or higher, or use of hypotensive medications. The rs2 576 178 polymorphism was genotyped in 369 HD patients, including 200 hypertensives and 169 normotensives, but the rs10 887 800 polymorphism was genotyped in 421 HD patients, including 278 hypertensives and 143 controls. They found that not only the G allele frequencies of rs2 576 178 showed a significantly higher incidence, but also G allele frequencies of rs10 887 800 showed a significantly higher incidence in hypertensive HD patients. The carrier state of the G allele of the rs2 576 178 polymorphism was associated with a 1.55-fold higher risk of hypertension, while the carrier state of the G allele of the rs10 887 800 polymorphism was associated with 1.76-fold higher risk. It would be rather more interesting to show the prevalence of both polymorphisms in the same population, because the prevalence of hypertension was 54% and 66% in these 2 HD populations, respectively.

Buraczyńska et al.[56] investigated the involvement of renalase gene polymorphism in hypertension also in type 2 diabetes patients. The study involved 892 diabetic patients (130 patients with stroke) and 400 healthy individuals. The authors analyzed 2 SNPs in the renalase gene that were found to be associated with hypertension in the Asian study by Zhao et al.[52] and 1 of those that were not associated – C allele. They reported that the C allele of rs2 296 545 SNP was associated with hypertension ($P < 0.01$).[55] For rs10 887 800 SNP, the differences in the G allele frequencies were observed in hypertensive patients with stroke, with 66% of patients being GG homozygotes. To confirm the observed association, they later genotyped 130 stroke patients without diabetes. The odds ratio for risk allele was 1.79 (95% confidence interval, 1.33–2.41). The most interesting result was a strong association of the rs10 887 800 polymorphism with stroke in patients with and without diabetes. Therefore, the investigators postulated that the G allele of renalase gene polymorphism might be a risk factor for stroke in hypertension. Particularly, they did not indicate an association between the studied SNPs and BP rate in stroke patients so there was no question of the severity of hypertension. Thus, the authors concluded that the G allele of renalase gene polymorphism might be useful in identifying diabetic patients and others at risk of stroke. In our preliminary study, we observed that serum renalase was significantly lower in HD patients with a history of stroke (21%) compared with other patients.[57] Unfortunately, none of the genetic studies provided data on serum renalase; therefore, we do not know about any associations of these alleles with either lower or higher renalase levels.

Practical implications Renalase, a novel hormone probably associated with hypertension and cardiovascular complications, might be an attractive therapeutic target in the most vulnerable population such as dialyzed patients. However, it has to be proved that renalase is not an innocent bystander, but is involved in the pathogenesis of hypertension. In addition, a validated assay is urgently needed to establish renalase levels and activity and their correlation with renalase expression using Western blotting. As suggested recently by Unger et al.,[58] renalase substitution is an intriguing novel therapeutic option, provided that renalase deficiency is present in CKD.

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ARTYKUŁ POGLĄDOWY

Nerki i nadciśnienie tętnicze: czy renalaza ma tu swoje miejsce?

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SŁOWA KLUCZOWE

choroby sercowo-naczyniowe, przewlekła choroba nerek, renalaza, współczulny układ nerwowy

STRESZCZENIE

Przewlekła choroba nerek (PChN) charakteryzuje się znacznie zwiększonym ryzykiem rozwoju chorób sercowo-naczyniowych wskutek występowania tradycyjnych i nietradycyjnych czynników ryzyka. Nadciśnienie tętnicze dotyczy ok. 80–85% chorych na PChN, a jego patogeneza ma wieloczynnikowy charakter. W tej grupie chorych aktywność współczulnego układu nerwowego wzrasta, powodując zwiększenie oporu obwodowego oraz ciśnienia tętniczego. Ta wzmożona aktywność układu sympatycznego jest wynikiem nadmiernego wytwarzania oraz zmniejszonej redukcji katecholamin. W ostatnich latach zidentyfikowano nowe białko – renalazę. Badania eksperymentalne *in vitro* wykazały, że poprzez degradację katecholamin renalaza może wywierać istotny efekt hemodynamiczny *in vivo*, polegający np. na zmniejszeniu kurczliwości mięśnia sercowego, zwolnieniu czynności serca oraz obniżeniu ciśnienia tętniczego. W badaniach przeprowadzonych u chorych na PChN oraz hemodializowanych stwierdzono zmniejszone stężenie renalazy w porównaniu z osobami zdrowymi. Z kolei inne badania wykazały zwiększone stężenie renalazy w surowicy pacjentów dializowanych i po przeszczepieniu nerki. Nie ma danych dotyczących powiązania ekspresji genu renalazy z jej aktywnością/stężeniem oraz funkcją, dlatego rola renalazy jako czynnika patogenetycznego nadciśnienia tętniczego, a nie jedynie biernego obserwatora wymaga potwierdzenia w dalszych badaniach.

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