Kardiologia Polska 2016; 74, 9: 937–942; DOI: 10.5603/KP.a2016.0095 ISSN 0022–9032

ARTYKUŁ SPECJALNY / *STATE-OF-THE-ART REVIEW*

Renalase — a new marker or just a bystander in cardiovascular disease: clinical and experimental data

Dominika Musiałowska, Jolanta Małyszko

2nd Department of Nephrology, Medical University of Bialystok, Bialystok, Poland

Dominika Musiałowska was born in 1985 in Bialystok. She graduated the Medical University of Bialystok in 2010 with the average grade of very good. During her studies she was awarded a scholarship from the Minister of Health for her academic results. She successfully completed a short-term fellowship supported by the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) in modulation of sympathetic nerve activity by renal denervation in hypertensive renal transplant patients in the Nephrology Department in Heinrich Heine Universitat Duesseldorf, Germany (October 1, 2012 – March 29, 2013). She became a Doctor of Philosophy in 2014 after a public defence of her manuscript *Renalase concentration in hypertensive patients*. She works in 2nd Department of Nephrology at the Medical University of Bialystok, Poland.

Jolanta Małyszko graduated with merit from the Medical University of Bialystok, Poland. She is a full Professor (2002) and from 2013 a chairman of 2nd Department on Nephrology, Medical University, Bialystok, Poland. Her clinical training was performed in the Intensive Care Unit and Nephrology Department, CHU Rouen, France, Nephrology Department, Heinrich-Heine University, Dusseldorf, Germany (ERA-EDTA clinical scholarship), McKennon Hospital, Sioux Falls, South Dakota, United States (invasive cardiology), Kings' College, London, United Kingdom, and Sourasky Hospital, Israel. During a Japanese Ministry of Education scholarship at Hamamatsu University School of Medicine she defended her PhD thesis on the role of FK 506 in transplantation in 1995. She established a PD program and Hypertension Outpatient Unit at the University and served for many years as a nephrology consultant at the University Teaching Hospital. Her major research includes iron metabolism and anaemia, and cardiovascular complications in kidney diseases. She is a fellow of internal medicine, nephrology, transplantation, hypertension, and diabetology as well as a European Specialist in Clinical Hypertension. She was granted with the title of a fellow of ASN (FASN) and of ERA-EDTA (FERA). She is a member of the Executive Council of ERA-EDTA (the third female in the history of ERA-EDTA) and the Polish Society of Nephrology. She authored and co-authored of over 400 original papers, over 100 review papers, and 30 book chapters, including chapters in French, a chapter in the fourth Oxford textbook of Clinical Nephrology, over 500 IF, over 4000 citations, and h-index-30.

INTRODUCTION

Renalase, a protein with enzymatic activity, was characterised for the first time in 2005 by Xu et al. [1]. It was described as a flavin adenine dinucleotide-dependent amino oxidase, which was thought to be secreted into the blood by the kidneys, and through its participation in catecholamine metabolism should influence blood pressure [1].

Scientists using the human genomic database (Mammalian Gene Collection Project [MGC]) identified a protein that met the three criteria established in the study. Firstly,

Address for correspondence:
Prof. Jolanta Małyszko, 2nd Department of Nephrology, Medical University in Bialystok, ul. M. Skłodowskiej-Curie 24A, 15–276 Białystok, Poland, tel: +48 85 746 80 00, fax: +48 85 746 88 00, e-mail: jolmal@poczta.onet.pl

Received: 19.04.2016 **Accepted:** 28.04.2016 **Available as AoP:** 08.06.2016

they selected a protein, which was characterised by up to 20% amino acid sequence homology to the already known proteins. The second stage of the study was the selection of the proteins containing protein signal peptides, which are the essential elements of all proteins secreted from cells. Proteins containing transmembrane domain were excluded from further study. About 114 genes fulfilling the mentioned criteria were analysed by Northern blot technique.

Further studies concentrated on the isolation of the protein with limited tissue location and high expression in the kidney in the glomerulus and proximal tubule, and lower expression in cardiomyocytes, skeletal muscle, and liver. The isolated protein was named renalase [1]. The human renalase gene is encoded by a 311 Kbp gene with 10 exons located on chromosome 10 at q23.33 [2]. It exists in humans in seven isoforms (h renalase 1-7), which show tissue specificity. The major isoform of renalase (h-renalase-1) contains 342 amino acids. It includes a signal peptide (flavin-adenine dinucleotide [FAD]) binding domain as also monoamine oxidase domain [3, 4]. H-renalase-1 contains seven exons and encodes a protein with calculated molecular mass of 37.85 kDa. This isoform was found primarily in kidney, cardiomyocytes, liver, intestine, and skeletal muscles [1]. In kidney the highest expression of renalase was observed in renal tubule epithelial cells, glomeruli, mesangial cells, and podocytes [5]. The next papers reported h-renalase-1 mRNA to be detected in peripheral nerves, adrenal glands, central nervous system, and in adipose tissue [6, 7]. The other isoforms of renalase probably have different function. Isoforms 3 and 4 have shortened amino acids domain and thereby they do not have amino acid activity [1, 2, 6, 8]. The mouse renalase gene, characterised by Wang et al. [9] is located on chromosome 19 C1. It is related to h-renalase-1, presenting 72% amino acid identity. Xu et al. [1] reported, in the first published paper relating to renalase, that renalase had an FAD-binding domain and that FAD was a cofactor for its stability and monoamine oxidase (MOA) activity. However, the amino acid sequence of renalase differed from MOA, and renalase shared only 13.2% identity with MOA-A [1]. Xu et al. [1] extrapolated MOA activity of renalase measured using the Amplex Red Monoamide Oxidase Assay Kit, based on the detection of H_2O_2 in a horseradish peroxidase-coupled reaction [1].

RENALASE AND HYPERTENSION

Hypertension is an important risk factor for cardiovascular diseases (CVD), and its inappropriate treatment may lead to end-stage renal disease [10]. As reported, 20–50% of the adult population suffer from hypertension [11]. Because of the widespread essential hypertension and its consequences, the search for the best medical treatment is of great importance. Many published experimental data concerned the role of renalase in hypertensive animal models. Xu et al. [1] observed in Sprague-Dawley rats a fall in blood pressure after intravenous administration of renalase. Besides the hypertensive effect, negative chronotropic and inotropic effects were observed [1]. Wu et al. [12] noticed that renalase knock-out mouse was hypertensive and tachycardiac and had higher catecholamine levels compared to wild type mouse. One year later Desir et al. [13] observed a fall in blood pressure after subcutaneous administration of renalase in 5/6 nephrectomised rats. The same effect was observed after administration of 5 mg/kg enalapril. Fedchenko et al. [14] analysed, with the use of real-time polymerase chain reaction, the levels of renalase mRNA expression in brain, heart, and kidneys of spontaneously hypertensive rats. They observed lower mRNA renalase in brain hemisphere and higher kidney and heart renalase mRNA levels in hypertensive rats (RR systolic > 180 mm Hg) in comparison to rats from the control group. The authors concluded that peripheral and brain renalase mRNA levels change in the opposite directions in hypertensive rats [14].

There are some studies analysing renalase gen polymorphism consisting of the substitution of aspartic acid to glutamic acid at codon 37 of renalase gen. It might influence the function of renalase. The the first study in humans showing the correlation between renalase and hypertension, which was a result of single nucleotide polymorphism (SNP) of renalase gene, concerned the Han Chinese population. A total of 2586 subjects were included in the study (1317 with essential hypertension and 1269 healthy volunteers). Zhao et al. [15] described higher incidence of hypertension in subjects with G-allele rs2576178, suspecting this gene to be responsible for essential hypertension. Four years later Stec et al. [16] described association between polymorphism of the renalase gen and hypertension in haemodialysed patients — they observed hypertension more often among patients with a G-allele rs2576178 but also with the G-allele rs10887800. However, in another study in haemodialysis patients, renalase gene rs2576178 polymorphism was not associated with blood pressure [17]. Significant data data was published by Wang et al. [18], describing the association between multiple SNPs in renalase gene (rs919115, rs792205, rs12356177) and blood pressure responses to changes in in dietary salt intake. There is also a study confirming the association of the renalase gen SNP and hypertension in a group of patients with diabetes mellitus type 2 [19]. The presented studies initiated a new direction in the research of the position of renalase in hypertension. Interestingly, a meta-analysis published in 2015, focusing on seven studies exploring SNPs of the renalase gene, indicated no association of renalase gene polymorphism and hypertension [20]. Not many clinical data describing renalase in patients with essential hypertension are available. Wang et al. [21] evaluated blood pressure, serum dopamine levels, and urinary renalase secretion in Chinese adults after salt intake and potassium supplementation. They observed increases in blood pressure, serum dopamine levels, and urinary renalase secretion [21]. The question that Medvedev leaves open is: are

urinary secretion of renalase and increased blood dopamine level, in this situation, the effect of or only merely events resulting in body response to salt overload [22]. Schlaich et al. [23] observed lower renalase levels in 22 patients with resistant hypertension when compared to a normotensive control group. In a recent study renalase concentration in patients with primary hypertension was significantly higher than in a control group. Plasma renalase concentration correlated with norepinephrine level in hypertensive patients, which was not observed in the control group [24]. Schlaich et al. [23] used the Western blot technique to estimate the renalase concentration in the study population compared to the second study group [24], and they estimated renalase concentration with the use of commercially available enzyme-linked immunosorbent assay.

RENALASE AND KIDNEY FUNCTION

Plasma catecholamine levels rise in patients with end-stage renal disease as a result of increased sympathetic activity as well as decreased catecholamine clearance. Increased sympathetic activity in this group of patients worsens their prognosis. Norepinephrine concentration correlates with the survival and the rate of cardiovascular events in patients with end-stage renal disease [25, 26].

Renalase concentration was observed in experimental chronic kidney disease (CKD) model. In the rat model of CKD (5/6 nephrectomised rats) renalase concentration was significantly lower 2–3 weeks after the surgery, and its deficiency was suspected to be the reason for catecholamine levels elevation in 5/6 nephrectomised rats [27]. In another experimental model of CKD on nephrectomised pups, Gosh et al. [7] observed higher norepinephrine levels in the CKD model, suggesting its decreased metabolism. Gu et al. [28] noticed lower renalase expression in the ischaemic kidney model in comparison to healthy one, suggesting that renal blood flow may affect renalase production. There are also some data concerning renalase concentration in patents with end stage renal disease. Xu et al. [1] as well as Wu et al. [12], in small group of patients with end-stage renal disease, measured decreased renalase expression compared to healthy volunteers. Malyszko et al. [29] observed, in a group of 89 kidney transplant recipients, higher renalase concentration than in healthy volunteers. Renalase level was related to kidney function, age, time after transplantation, and blood pressure. This results are in conflict with the data published by Xu et al. [1]. Renalase was measured with the use of different techniques — Xu used Western blot technique with polyclonal antibodies, Malyszko based results on commercially available ELISA assay with monoclonal antibody specific for renalase [12, 29]. Serum renalase was also higher in peritoneal dialysis patients than in healthy control group and its concentration correlated positively with the time of dialysis but there was no correlation between blood pressure control nor residual renal function [30]. A Portuguese group observed also that circulating renalase levels in a group of patients with end stage renal disease, as in transplant recipients, were higher compared to healthy donors. They used, as did Malyszko et al. [29], a commercially available ELISA kit to measure renalase levels [31]. Genetic studies conducted by Stec et al. [16] delivered new information about SNPs in the renalase gene among haemodialysed patients with hypertension. They observed the relationship between hypertension and SNPs in the renalase gene (G allele frequencies of rs2576178 and rs0887800) [16]. An Egyptian study group published data pointing the association of renalase (rs2296545) CC genotype and C allele with CKD. The also observed significantly higher epinephrine levels in CC renalase genotype when compared to GG and CG genotyped in CKD patients [32].

RENALASE AND CVD

Taking into consideration the relationship between renalase and CVD, there are some experimental studies that should be presented. Gu et al. [28], in the study mentioned in the previous paragraph, besides observing renalase in the CKD model, also created a model of heart failure in rats through the ligation of the left anterior descending coronary artery. This group observed increasing renal renalase expression with the highest level one week after myocardial infarction [28]. There are few clinical studies considering renalase concentration in patients with heart failure. Przybylowski et al. [33] observed higher serum renalase concentration in heart transplant recipients compared to healthy volunteers, but the serum creatinine level appeared to a predictor of renalase concentration. There was no correlation between serum renalase and hypertension nor the presence of diabetes [33]. There are also data showing higher renalase levels in heart failure patients (due to coronary artery disease [CAD] or dilatated cardiomyopathy) compared to healthy volunteers. This higher renalase concentration was strongly related to impaired renal function, as observed in heart transplant recipients [34]. He et al. [35] measured renalase concentration in patients with CAD with the use of ELISA kit and interestingly observed statistically significant lower renalase concentrations in patients with multi-branch stenosis as well as in a group with higher Syntax scores compared to those with one-vessel disease and a healthy control group. Renalase level seemed to be a risk factor of CAD, based on logistic regression analysis. There were no differences in kidney function in the study population. The authors concluded than lower renalase concentration may lead to increased sympathetic activity and through this to progression of CAD [35]. Farzaneh-Far et al. [36] found an association between functional missense polymorphism in renalase gene (rs2296545) and cardiac hypertrophy in a Caucasian population. Performing resting and stress echocardiography, they observed that SNP (Glu37Asp) was related to cardiac hypertrophy, ventricular dysfunction, lowered ejection

fraction, and inducible ischaemia in patients with stable CAD. There was no significant association between rs1333049 and blood pressure [36]. Another published prospective cohort observational study based on the Cardiovascular Cohort of "Malmö Diet and Cancer" did not show any effect on blood pressure level and cardiovascular events if two common SNPs of renalase gen (rs2576178 and rs2296545) were taken into account. The hazard ratio for cardiac and cerebrovascular events was not significantly different in carriers of different genotypes. Researchers suggested, that listed polymorphisms are of negligible importance, at least in that population [37]. A recent study by Stec et al. [38] on 309 haemodialysed patients (107 with and 202 without CAD genotyped for two SNPs in the renalase gene [rs10887800 and rs2576178]) rs10887800GG genotype was associated with an increased risk of CAD whereas rs2576178 polymorphism did not influence the risk of CAD. The authors concluded that rs10887800 renalase gene polymorphism could be considered a new genetic risk factor for CAD in this population.

The question about the position of renalase in humans started in 2005 and remains open. Desir et al. [13] suggested that renalase was an amine oxidase that contains a FAD-binding region. Renalase is related to monoamine oxidase A with only 13% of amino acid identity [1]. As mentioned before, renalase is supposed to metabolise circulating in blood catecholamines, but its activity against dopamine, epinephrine, and norepinephrine remains unclear [1, 13]. Moreover, renalase activity measurements need further explanation. Different study groups [1, 31] measured renalase activity with the use of kits designed for measuring MOA activity. The measurement of renalase activity was extrapolated from the reaction based on the detection of H_2O_2 in a horseradish peroxidase-coupled reaction. Boomsma and Tipton [39] deliberated whether or not the method was properly used in those circumstances. Moreover, different scientific groups [40–42] doubt if renalase possesses monoamine oxidase activity. Recombinant human renalase functionally and structurally characterised in vitro contained non-covalently bound FAD with redox features, suggesting dehydrogenase activity. Recombinant renalase was not a catecholamine-degrading enzyme, either through oxidase or NAD(P)H-dependent monooxygenase reactions [40, 43].

Quelhas-Santos et al. [44] designed a study aimed at evaluating the catecholamine-degrading activity of renalase by different technical methods. The rate of resazurin reduction as an indirect measure of renalase oxidase activity measured by Amplex Red Monoamine Oxidase Assay Kit, the consumption of the substrate measured by high-performance liquid chromatography (HPLC) with electrochemical detection, and the formation of the respective catalyse reaction end products as a direct measure of the action of renalase on catecholamines measured by HPLC with photodiode array detection confirmed the position of renalase in the catecholamine degradation process [44]. Published studies suggested also that, independently of renalase enzymatic property, there is also a possibility that renalase acts as a cytokine [3]. In an animal acute kidney injury model renalase decreased kidney damage. Renalase was suggested to interact with a membrane receptor to transmit through the activation of protein kinase [45, 46]. Yin et al. [47] noted that renalase is a cytokine that can mediate cardio-renal protective properties through renalase plasma membrane receptor — a calcium pump participating in Ca^{2+}-dependent signalling. Renalase is supposed to protect against renal injury and cardiac remodelling after subtotal nephrectomy through inhibiting inflammation and oxidative stress [47, 48].

Wang et al. [49] proved that endogenous renalase plays an important role in renal protection of delayed ischaemic preconditioning (IPC). The elevated renalase expression was measured for 24 h after renal IPC, which significantly reduced renal tubular inflammation, necrosis, and oxidative stress following renal ischaemia reperfusion injury. Moreover, the authors concluded that hypoxia-inducible factor (HIF)-1α regulates renalase expression in the kidney and contributes to the renal protection of delayed IPC [49].

But if this thesis may totally explain the study of Wu et al. [12], who reported on hypertense and tachycardiac renalase knockout mice, and the data published by Eikelis et al. [50], who questioned whether renalase can degrade the circulating catecholamines in the mouse model. This group mentioned that the mouse model of renalase did not contain the N-terminal FAD-binding site [50]. The next question, which needs to be answered, is if experimental studies may be extrapolated to the human population. Beside renalase there is also vascular adhesion protein 1 (VAP-1), a copper-containing semicarbazide-sensitive amine oxidase, which may catalyse the breakdown of primary amines to produce aldehyde, hydrogen peroxide, and ammonia. VAP-1 is secreted by vascular smooth muscle cells, adipocytes, and endothelial cells with functional MAO activity [51, 52]. VAP-1 involved in leukocyte extravasation to sites of inflammation may depend on renalase. VAP-1 was related to renalase in kidney allograft recipients. Patients with CKD and essential hypertension had higher VAP-1 and renalase concentration than healthy volunteers. VAP-1 originates also from similar tissues as renalase [24, 53–55]. Elcioglu et al. [56] observed the association between renalase levels and the presence of simple renal cysts in a group of normotensive patients with proper kidney function. They noticed lower renalase levels in patients with simple renal cysts than in control group, and interestingly renalase levels correlated positively with endothelial dysfunction (evaluated by endothelium-dependent vasodilatation) [56].

A uniform view of the results of research on renalase are also unsettled because of different methods used to determine renalase levels. Western blot analysis, used by Xu et al. [1], is a semi-qualitative method. An ELISA kit, using monoclonal

antibody specific to renalase, should measure the level of h-renalase-1, whether it is active or not. There is a possibility that the antibody in that assay may bind other isoforms or fragments of the renalase causing its higher concentration [57].

CONCLUSIONS

Since 2005 the position of renalase has been changing continually. First described as mono amino oxidase degrading circulating catecholamines renalase seemed to be a new important milestone in the diagnosis and treatment of hypertension. The lack of one validated commercially available test measuring the concentration and activity of renalase prevented progress in studies concerning renalase. Different study groups have published contrary results in similar animal models and groups of patients, and the position of renalase still remains unclear. An increasing number of published studies concerning renalase provide new information but do not clearly position it in the pathophysiology process of cardiovascular events or CKD. The new thesis, placing renalase in the huge group of cytokines, need further studies. The question of whether renalase as a new substance may influence hypertension, or kidney or CVD remains open.

Conflict of interest: *none declared*

References

1. Xu J, Li G, Wang P et al. Renalase is a novel, soluble monoamine oxidase that regulates cardiac function and blood pressure. J Clin Invest, 2005; 115: 1275–1280.
2. Xu J, Desir GV. Renalase, a new renal hormon: its role in health and disease. Curr Opin Nephrol Hypertens, 2007; 16: 373–378.
3. Guo X, Wang L, Velazquez H et al. Renalase: its role as a cytokine, and an update on its association with type 1 diabetes and ischemic stroke. Curr Opin Nephrol Hypertens, 2014; 23: 513–518. doi: 10.1097/MNH.0000000000000044.
4. Desir GV. Renalase is a novel renal hormon that regulates cardiovascular function. J Am Soc Hypertens, 2007; 1: 99–103. doi: 10.1016/j.jash.2006.12.001.
5. Wang F, Xing T, Li J et al. Renalase's expression and distribution in renal tissue and cells. PLoS One, 2012; 7: e46442. doi: 10.1371/journal.pone.0046442.
6. Hennebry SC, Eikelis N, Socratous F et al. Renalase, a novel soluble FAD-dependent protein, is synthesized in the brain and peripheral nerves. Mol Psychiatry, 2010; 15: 234–236. doi: 10.1038/mp.2009.74.
7. Gosh SS, Krieg RJ, Sica DA et al. Cardiac hypertrophy in neonatal nephrectomised rats: the role of the sympathetic nervous system. Pediatr Nephrol, 2009; 24: 367–377. doi: 10.1007/s00467-008-0978-8.
8. Desir GV, Peixoto AJ. Renalase in hypertension and kidney disease. Nephrol Dial Transplant, 2014; 29: 22–28. doi: 10.1093/ndt/gft083.
9. Wang J, Qi S, Cheng W et al. Identification, expression and tissue distribution of a renalase homologue from mouse. Mol Biol Rep, 2008; 35: 613–620.
10. Kearney PM, Whelton M, Reynolds K et al. Global burden of hypertension: analysis of worldwide data. Lancet, 2005; 365: 217–223.
11. Redwood H. Hypertension, society and public policy. Eur Heart J Suppl, 2007; 9: B13–B18. doi: 10.1093/eurheartj/sum003.
12. Wu Y, Xu J, Velazquez H et al. Renalase deficiency aggravates ischemic myocardial damage. Kidney Int, 2011; 79: 853–860. doi: 10.1038/ki.2010.488.
13. Desir GV, Tang L, Wang P et al. Renalase lowers ambulatory blood pressure by metabolizing circulating adrenaline. J Am Heart Assoc, 2012; 1: e002634. doi: 10.1161/JAHA.112.002634.
14. Fedchenko V, Globa A, Buneeva O, Medvedev A. Renalase mRNA levels in the brain, heart, and kidneys of spontaneously hypertensive rats with moderate and high hypertension. Med Sci Monit Basic Res, 2013; 19: 267–270. doi: 10.12659/MSMBR.889540.
15. Zhao Q, Fan Z, He J et al. Renalase gene is a novel susceptibility gene for essential hypertension: a two-stage association study in northern Han Chinese population. J Mol Med (Berl), 2007; 85: 877–885.
16. Stec A, Semczuk A, Furmaga J et al. Polymorphism of the renalase gene in end-stage renal disease patients affected by hypertension. Nephrol Dial Transplant, 2012; 27: 4162–4166. doi: 10.1093/ndt/gfr293.
17. Kiseljakovic E, Mackic-Djurovic M, Hasic S et al. Renalase gene rs2576178 polymorphism in hemodialysis patients: study in Bosnia and Herzegovina. Med Arch, 2016; 70: 31–34. doi: 10.5455/medarh.2016.70.31-34.
18. Wang Y, Chu C, Ren J et al. Genetic variants in renalase and blood pressure responses to dietary salt and potassium interventions: a family-based association study. Kidney Blood Press Res, 2014; 39: 497–506. doi: 10.1159/000368460.
19. Buraczynska M, Zukowski P, Buraczynska K et al. Renalase gen polymorphisms in patients with type 2 diabetes, hypertension and stroke. Neuromolecular Med, 2011; 13: 321–327. doi: 10.1007/s12017-011-8158-6.
20. Shi WB, Wang HY. The association study on renalase polymorphism and hypertension: a meta-analysis. Int J Clin Exp Med, 2015; 8: 9505–9511.
21. Wang Y, Wang D, Chu C et al. Effect of salt intake and potassium supplementation on urinary renalase and serum dopamine levels in Chinese adults. Cardiology, 2015; 130: 242–248;
22. Medvedev AE. Does dopamine mediate salt-dependent urinary renalase secretion in man? Cardiology, 2015; 131: 53–54. doi: 10.1159/000376607.
23. Schlaich M, Socratous F, Eikelis N et al. Renalase plasma levels are associated with systolic blood pressure in patients with resistant hypertension. J Hypertens, 2010; 28: e437. doi: 10.1097/01.hjh.0000379519.82971.02.
24. Maciorkowska D, Zbroch E, Malyszko J. Circulating renalase, catecholamines, and vascular adhesion protein 1 in hypertensive patients. J Am Soc Hypertens, 2015; 9: 855–864. doi: 10.1016/j.jash.2015.08.002.
25. Zeigler MG, Morrissey EC, Kennedy B, Elayan H. Sources of urinary catecholamines in renal denervated transplant recipients. J Hypertens, 1990; 8: 927–931.
26. Zoccali C, Mallamaci F, Parlongo S et al. Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. Circulation, 2002; 105: 1354–1359.
27. Li G, Xu J, Wang P et al. Catecholamines regulate the activity, secretion, and synthesis of renalase. Circulation, 2008; 117: 1277–1282. doi: 10.1161/CIRCULATIONAHA.107.732032.
28. Gu R, Lu W, Xie J et al. Renalase deficiency in heart failure model of rats: a potential mechanism underlying circulating norepinephrine accumulation. PLoS One, 2011; 6: e14633. doi: 10.1371/journal.pone.0014633.
29. Malyszko J, Zbroch E, Malyszko JS et al. Renalase, a novel regulator of blood pressure, is predicted by kidney function in renal transplant recipients. Transplant Proc, 2011; 43: 3004–3007. doi: 10.1016/j.transproceed.2011.08.032.
30. Zbroch E, Malyszko J, Malyszko J et al. Renalase in peritoneal dialysis patients is not related to blood pressure, but to dialysis vintage. Perit Dial Int, 2012; 32: 348–351. doi: 10.3747/pdi.2011.00118.
31. Quelhas-Santos J, Soares-Silva I, Fernandes-Cerqueira C et al. Plasma and urine renalase levels and activity dur-

ing the recovery of renal function in kidney transplant recipients. Exp Biol Med (Maywood), 2014; 239: 502–508. doi: 10.1177/1535370214522182.
32. Rezk NA, Zidan HE, Elnaggar YA, Ghorab A. Renalase gene polymorphism and epinephrine level in chronic kidney disease. Appl Biochem Biotechnol, 2015; 175: 2309–2317. doi: 10.1007/s12010-014-1433-x.
33. Przybylowski P, Malyszko J, Kozlowska S et al. Serum renalase depends on kidney function but not on blood pressure in heart transplant recipients. Transplant Proc, 2011; 43: 3888–3891. doi: 10.1016/j.transproceed.2011.08.075.
34. Kochanski K, Przybyłowski P, Bachorzewska-Gajewska H et al. Renalase in patients with heart failure. European Society of Cardiology Congress, Barcelona 30.8–3.09.2014.
35. He B, Hao J, Sheng W et al. Correlation between plasma renalase level and coronary artery disease. Pak J Med Sci, 2014; 30: 863–967. doi: 10.12669/pjms.305.5286.
36. Farzaneh-Far R, Desir GV, Na B et al. A functional polymorphism in renalase (Glu37Asp) is associated with cardiac hypertrophy, dysfunction, and ischemia: data from the heart and soul study. PLoS One, 2010; 5: e13496. doi: 10.1371/journal.pone.0013496.
37. Fava C, Montagnana M, Danese E et al. The Renalase Asp37Glu polymorphism is not associated with hypertension and cardiovascular events in an urban-based prospective cohort: the Malmö Diet and cancer study. BMC Med Genet, 2012; 13: 57.
38. Stec A, Ksiazek A, Buraczynska M. Rs10887800 renalase gene polymorphism is associated with an increased risk of coronary artery disease in hemodialyzed patients. Int Urol Nephrol, 2016; 48: 871–876. doi: 10.1007/s11255-016-1270-7.
39. Boomsma F, Tipton KF. Renalase, a catecholamine-metabolising enzyme? J Neural Transm (Vienna). 2007; 114: 775–776.
40. Baroni S, Milani M, Pandini V et al. Is renalase a novel player in catecholaminergic signaling? The mystery of the catalytic activity of an intriguing new flavoenzyme. Curr Pharm Des, 2013; 19: 2540–2551.
41. Pandini V, Ciriello F, Tedeschi G et al. Synthesis of human renalase1 in Escherichia coli and its purification as a FAD-containing holoprotein. Protein Expr Purif, 2010; 72: 244–253. doi: 10.1016/j.pep.2010.03.008.
42. Medvedev AE, Veselovsky AV, Fedchenko VI. Renalase, a new secretory enzyme responsible for selective degradation of catecholamines: achievements and unsolved problems. Biochemistry (Mosc). 2010; 75: 951–958.
43. Milani M, Ciriello F, Baroni S et al. FAD-binding site and NADP reactivity in human renalase: a new enzyme involved in blood pressure regulation. J Mol Biol, 2011; 411: 463–473. doi: 10.1016/j.jmb.2011.06.010.
44. Quelhas-Santos J, Sampaio-Maia B, Remiao F et al. Assessment of renalase activity on catecholamine degradation. Open Hypertens J, 2015; 7: 14–18. doi: 10.2174/1876526201507010014.
45. Wang L, Velazquez H, Moeckel G et al. Renalase prevents AKI independent of amine oxidase activity. J Am Soc Nephrol, 2014; 25: 1226–1235. doi: 10.1681/ASN.2013060665.
46. Lee HT, Kim JY, Kim M et al. Renalase protects against ischemic AKI. J Am Soc Nephrol, 2013; 24: 445–455. doi: 10.1681/ASN.2012090943.
47. Yin J, Lu Z, Wang F et al. Renalase attenuates hypertension, renal injury and cardiac remodelingu in rats with subtotal nephrectomy. J Cell Moll Med, 2016; 20: 1106–1117. doi: 10.1111/jcmm.12813.
48. Wang L, Velazquez H, Chang J et al. Identification of a receptor for extracellular renalase. PLoS ONE, 2015; 10: e0122932. doi: 10.1371/journal.pone.0122932.
49. Wang F, Zhang G, Xing T et al. Renalase contributes to the renal protection of dalyed ischaemic preconditioning via the regulation of hypoxia-inducible factor-1 . J Cell Mol Med, 2015; 19: 1400–1409. doi: 10.1111/jcmm.12527.
50. Eikelis N, Hennebry SC, Lambert GW, Schlaich MP. Does renalase degrade catecholamines? Kidney Int, 2011; 79: 1380. doi: 10.1038/ki.2011.90.
51. Salmi M, Jankanem S. A 90-kilodaltonendothelial cel molecule mediating lymphocyte binding in humans. Science, 1992; 257: 1407–1409.
52. Mazzone T, Chait A, Plutzky J. Cardiovascular disease risk in type 2 diabetes mellitus: insights from mechanistic studies. Lancet, 2008; 371: 1800–1809. doi: 10.1016/S0140-6736(08)60768-0.
53. Yu PH, Wright S, Fan EH et al. Physiological and pathological implications of semicarbazide-sensitive amine oxidase. Biochim Biophys Acta, 2003; 1647: 193–199.
54. Koc-Zorawska E, Malyszko J, Malyszko JS, Mysliwiec M. VAP-1, a novel molecule linked to endothelial damage and kidney function in kidney allograft recipients. Kidney Blood Press Res, 2012; 36: 242–247. doi: 10.1159/000343413.
55. Lin MS, Li HY, Wei JN et al. Serum vascular adhesion protein-1 is higher in subjects with early stages of chronic kidney disease. Clin Biochem, 2008; 41: 1362–1367. doi: 10.1016/j.clinbiochem.2008.06.019.
56. Elcioglu OC, Afsar B, Takir M et al. Relanase: Another puzzle between hypertension and simple renal cysts? Int Urol Nephrol, 2015; 47: 1181–1186. doi: 10.1007/s11255-015-1008-y.
57. Malyszko J, Malyszko JS, Mikhailidis DP et al. Hypertension and kidney disease: is renalase a new player or an innocent bystandes? J Hypertens, 2012; 30: 457–462. doi: 10.1097/HJH.0b013e32834f0bb7.

Cite this article as: Musiałowska D, Małyszko J. Renalase — a new marker or just a bystander in cardiovascular disease: clinical and experimental data. Kardiol Pol, 2016; 74: 937–942. doi: 10.5603/KP.a2016.0095.