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Review

Roles and mechanisms of renalase in cardiovascular disease: A promising therapeutic target

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ABSTRACT

Cardiovascular disease (CVD) is prevalent worldwide and remains a leading cause of death. Although substantial progress has been made in the diagnosis and treatment of CVD, the prognosis remains unsatisfactory. Renalase is a newly discovered cytokine that is synthesized by the kidney and then secreted into blood. Numerous studies have suggested the efficacy of renalase in treating CVD by metabolizing catecholamines in the circulatory system. As a new biomarker of heart disease, renalase is normally recognized as a signalling molecule that activates cytoprotective intracellular signals to lower blood pressure, protect ischaemic heart muscle and promote atherosclerotic plaque stability in CVD, which subsequently improves cardiac function. Due to its important regulatory role in the circulatory system, renalase has gradually become a potential target in the treatment of CVD. This review summarizes the structure, mechanism and function of renalase in CVD, thereby providing preclinical evidence for alternative approaches and new prospects in the development of renalase-related drugs against CVD.

1. Introduction

Cardiovascular disease (CVD) is a general term for conditions affecting the heart or blood vessels and includes hypertension, atherosclerosis (AS), coronary artery disease (CAD), coronary microvascular dysfunction (CMD), valvular disease, heart failure (HF) and sudden cardiac death [1]. Despite improvements in the outcomes of CVD, it is one of the main causes of morbidity and mortality [2–5]. Specifically, CVD has led to the deaths of more than 18 million people worldwide, accounting for approximately 30 % of the global death toll. In particular, the CVD-related death rate is approximately 45 % in Europe [6], approximately 40 % in China [7], and 23.4 % in the United States [8]. In other countries and regions, such as Canada [9] and sub-Saharan Africa [10], the total number of deaths is even higher (Fig. 1), and more than 80 % of deaths in relatively low-income countries are attributable to CVD. If the current trend continues, 23.6 million people will have died of CVD by 2030.

Crosstalk occurs between CVD and chronic kidney disease (CKD). The pathophysiological relationship between the heart and kidneys is complex and bidirectional. Under physiological conditions, the heart acts as a pump in the circulatory system to provide continuous blood flow and remove carbon dioxide as well as other waste products

Abbreviations: ABPM, ambulatory blood pressure monitoring; AS, atherosclerosis; BP, blood pressure; BUN, blood urea nitrogen; BW, body weight; CAD, coronary artery disease; CA/PCI, coronary angiography/percutaneous coronary intervention; CI-AKI, contrast-induced acute kidney injury; CKD, chronic kidney disease; CMD, coronary microvascular dysfunction; CVD, cardiovascular disease; DBP, diastolic blood pressure; DA, dopamine; ESRD, end-stage renal disease; EF, ejection fraction; ET-1, endothelin-1; ERK, extracellular signal-regulated kinase; FAD, flavin adenine dinucleotide; GRK2, G protein-coupled receptor kinase-2; HF, heart failure; HD, aemodialysis; HW, heart weight; I/R, ischaemia/reperfusion; LV, left ventricular; LVEF, left ventricular ejection fraction; LVAWd, LV end-diastolic anterior wall thickness; LVAWs, LV end-systole anterior wall thickness; LVPWd, LV end-diastolic posterior wall thickness; LVPWs, LV end-systole posterior wall thickness; LVIDd, LV internal diastolic diameter; LVIDs, LV internal systolic diameter; MAP, mean arterial pressure; MMP-1, matrix metalloproteinase-1; NAD, nicotinamide adenine dinucleotide; SIRT1, sirtuin1; NADH, reduced form of nicotinamide adenine dinucleotide; NE, norepinephrine; PD, peritoneal dialysis; PKC, protein kinase C; SBP, systolic blood pressure; SNP, single nucleotide polymorphism; TC, total cholesterol; TG, triglyceride; TGF-β, transforming growth factor-β; TIMP-1, tissue inhibitor of metalloproteinase-1.

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throughout the body. The kidneys not only remove metabolic waste and water from the body and control the balance of specific compounds such as sodium, phosphorus and potassium in the blood but also secrete hormones, such as renin, erythropoietin and prostaglandin, into the blood to regulate blood pressure (BP); moreover, they also promote the production of red blood cells. In addition, the heart and kidneys cooperate synergistically to regulate the blood supply to human tissues and organs. When cardiac or renal dysfunction occurs, the heart and kidneys interact with each other through neurohormonal regulatory mechanisms, worsening the condition [11]. A large number of studies have indicated that CKD is associated with an increased and more severe risk of suffering from cardiac events [12,13], while the mortality rate of individuals with CKD is twice that of the general population. Over 50 % of deaths in patients with CKD are related to CVD; moreover, CKD patients are more likely to die from CVD than they are to develop end-stage renal disease (ESRD) [14,15]. Furthermore, patients with CKD are particularly prone to miss or underappreciate early HF symptoms [16]. At present, many biomarkers have been proposed for timely diagnosis and prognosis; however, other than natriuretic peptides, none have achieved sufficient clinical significance. Therefore, new targets and biomarkers must be identified to better determine and further understand CVD and the interaction between CVD and CKD.

As a new target in CVD and CKD, renalase has shown great potential in terms of cardioprotective effects [17]. It is a flavin/adenine/dinucleotide-dependent amine oxidase secreted into the blood by the kidneys and expressed in the heart, liver, pancreas, skeletal muscle and reproductive system [18–21]. Renalase expression is mainly related to renal function, renal perfusion and catecholamine expression [22]. Previous evidence initially suggested that renalase was involved in catecholamine metabolism due to its oxidase activity [17], while specific single nucleotide polymorphisms (SNPs) in renalase were closely associated with an increased risk of developing essential hypertension, CKD and CVD [23,24]. However, our understanding of the cellular role of renalase is undergoing a paradigm shift due to the available data indicating that renalase may function as a cytokine in the human body, especially in physiological and pathological cardiac states. In this review, a general overview of these new findings will be provided, with a primary focus on the advances and progress in the fields of CVD and CKD concurrent with CVD. This work also provides a valuable reference for improving the diagnosis, treatment and prognosis of CVD in clinical practice.

2. Structure of renalase

The renalase gene, located on chromosome 10 of q23.33, contains 9 exons and spans 309,462 bp (NC_000010.11). Its encoded protein exhibits three major characteristics: less than 20 % similarity to known proteins, presence of a signal peptide structure, and absence of a transmembrane structure. The structure of renalase includes two mRNA variants: transcript variant 1 and transcript variant 2. These variants encode putative protein products known as the renalase isoform 1 precursor (NP_001026879.2) and the renalase isoform 2 precursor (NP_060833.1) (sometimes described as hRenalase1 and hRenalase2, respectively). At least four alternative splicing isoforms have been identified in humans (from hRenalase1 to hRenalase4) [25]. At present, seven subtypes of renalase have been identified, with each playing different roles in tissues [26]. Of these, hRenalase1 is the most abundant subtype in the human body. The dominant mRNA is 1477 nucleotides in length and encodes a protein with 342 amino acids and a predicted mass of 37.58 kDa. As the subtype with the longest sequence and the main form of renalase, hRenalase1 has a conserved structure with homology to the amino acid sequence of renalase in chimpanzees (95 % identical) and cyanobacteria (20 % identical) [27]. hRenalase2 contains 315 amino acids with a calculated molecular mass of 34.95 kDa and differs from hRenalase1 by one SNP in the first exon, which results in a substitution of Glu37 → Asp37. Both subtypes include an N-terminal signal peptide (amino acids 1–17), a flavin adenine dinucleotide (FAD) binding site (amino acids 3–42) and an amino oxidase domain (amino acids 75–335). Due to the relatively short aminoxin domains, hRenalase1 and hRenalase2 are less likely to have monoamine oxidase functions. To date, hRenalase3 and hRenalase4 have not yet been adequately studied. β-NADH and β-NADPH are considered cosubstrates of renalase [28]; both can be oxidized by renalase to produce β-NAD(P)$^+$ by transferring two electrons to the flavin cofactor and converting the configuration of ribose C1 from α to β. The chemistry catalysed by renalase is shown in Fig. 2 [29,30]. This catalytic activity provides detoxification as well as metabolite repair function, and it is also partially inhibited by non-catalytic isomers or products.

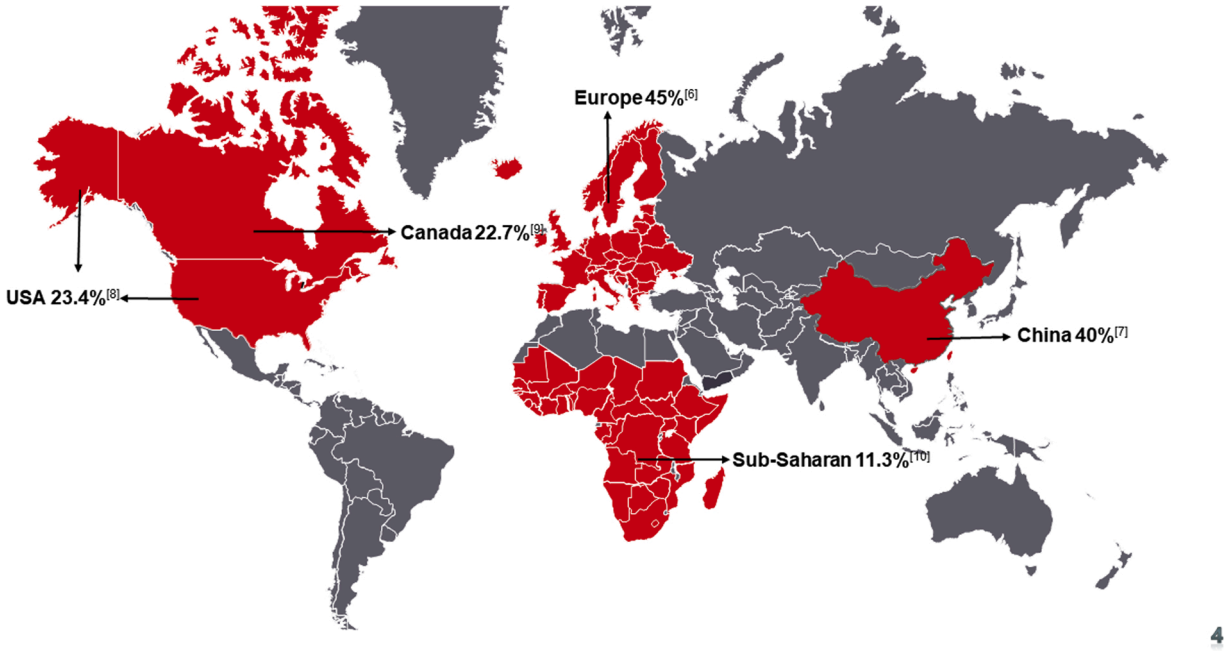

Fig. 1. Proportion of CVD-related deaths in countries around the world.

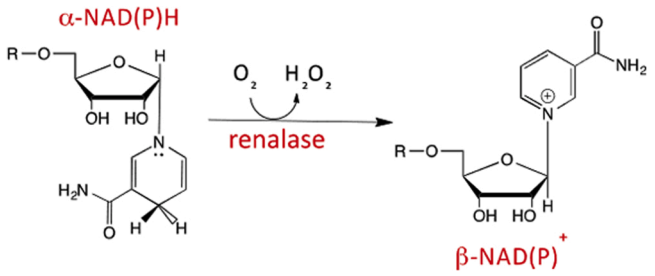

Fig. 2. The chemistry catalysed by renalase [30].

The tertiary structure of renalase is known and consists of approximately equal proportions of α and β secondary structures. Nineteen residues directly participate in FAD binding, and 6 of these have electrostatic or polar interactions with FAD. The enzyme contains FAD cofactors, which are mostly buried in extended conformations among the proteins, indicating that renalase is a member of the flavin protein superfamily [31]. The three-dimensional structure of renalase is shown in Fig. 3. The renalase substrate-binding domain revealed a mode of association that was consistent with substrate reactivity. As a secreted protein, renalase is different from the monoamine oxidases MAO-A and MAO-B in metabolizing catecholamine in cells. It is mainly synthesized by renal tubular epithelial cells and secreted in the blood to directly metabolize catecholamines. However, Brett et al. claimed that the putative catecholamine oxidase activity of renalase was determined based on flawed methods [32].

Understanding and analysing the molecular structure of renalase can allow further exploration of its function and mechanism of action. Furthermore, it also lays a solid foundation for the development of synthetic analogues with potential therapeutic significance in CVD.

3. Role of renalase in CVD

Renalase is intensely expressed in the heart as well as the kidneys and effectively metabolizes catecholamines using nicotinamide adenine dinucleotide as a cofactor [27]. In addition, renalase may also play a certain cardioprotective role as a cytokine. Multiple recent observational studies have shown that renalase was closely associated with hypertension, CAD, CMD, HF and AS. All of these effects are described and discussed in detail in the following sections. Tables 1 and 2 summarize all of the basic studies and research, while the related effects or mechanisms are shown in Fig. 4.

3.1. Renalase and hypertension

Hypertension refers to a continuous increase in BP and represents a long-term medical disease. Chronic hypertension is a major risk factor for CAD, stroke, HF, atrial fibrillation, peripheral arterial disease, and CKD [33,34]. Experimental and clinical studies have proven and confirmed the relationship between renalase and BP. However, the results remain ambiguous and require further comprehensive and in-depth scientific exploration.

Renalase plays an important role in the regulation of BP. The relationship between renalase and BP was confirmed in knockout mice. Compared with wild-type mice, renalase knockout mice not only showed increased blood catecholamine levels and developed hypertension symptoms but also exhibited an increased heart rate pressure after norepinephrine (NE) perfusion [24]. Xu et al. found that after intravenous injection of recombinant renalase to SD rats, systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were significantly reduced, heart rate slowed down, and myocardial contractility decreased [17]. Generally, the mechanism by which renalase lowers BP can be divided into three aspects. First, it can indirectly lower BP by metabolizing catecholamine. Li et al. found that lower baseline renalase levels can be intensely activated within a few minutes after catecholamine infusion, and then the body degraded catecholamines to inhibit the rapid increase in BP [22]. In addition, data collected by Ghosh et al. showed that the decreased expression of renalase in rats undergoing subtotal nephrectomy (5/6 Nx) was related to the increase in the plasma NE concentration and SBP, suggesting that renalase was related to catecholamine metabolism and involved in the occurrence of hypertension [35]. Second, BP is regulated by inhibiting the activation of the renal dopamine (DA) system [36]. Sizova's study showed a two-fold increase in DA in the urine of renalase knockout mice, indicating that renal DA system activity increased after renalase knockout and that renalase may be involved in the regulation of renal DA system activity [37]. Another study found that the DA D1-like receptor agonist fenoldopam increased renalase mRNA and protein expression in Wistar Kyoto (WKY) rat renal proximal tubule cells. The same study further found that renalase was regulated by the D1-like receptor mainly via the D5 receptor because silencing of D5 by antisense oligonucleotides blocked the stimulatory effect of the D1-like receptor on renalase expression in WKY cells. Moreover, inhibition of protein kinase C (PKC) blocked the stimulatory effect of fenoldopam on renalase expression, while stimulation of PKC increased renalase expression, indicating that the stimulatory effect of D1-like receptors on renalase expression was mainly mediated by the D5 receptor through the PKC pathway in WKY cells and further affected BP [38]. Third, BP can be regulated by inhibiting renal sympathetic nerve activity. As Jiang

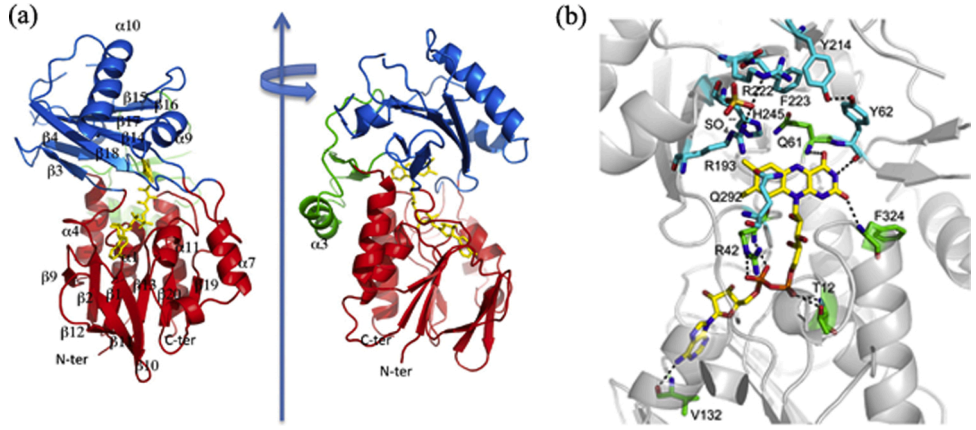

Fig. 3. Three-dimensional structure of renalase [29,31]. (a) Red indicates the FAD binding domain, blue indicates the substrate-binding domain, and green indicates the 62–108 subdomain. (b) View of the renalase active-site region (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Table 1
Effects of renalase in patients with CVD.

No.	Disease type	Treatment groups	Location of expression	Sample group comparison	Medical effects	Reference
1	Hypertension	52 hypertensive patients (HT) 51 normotensive controls (Con)	Plasma	HT VS Con	↑24-h ABPM mean SBP ↑24-h ABPM mean DBP ↑miRNA 4516 expression ↓miRNA 145 expression No significant difference in renalase expression	[41]
2	Primary hypertension	38 adolescents with primary hypertension (aged 11−18 years, HT) 50 subjects with normal BP (aged 11−18 years, Con)	Serum	HT VS Con	↑Renalase Positive relationship between serum renalase and uric acid and BMI Z-score	[42]
3	Hypertension	Hypertensive patients over 65 years (range 65−86, HT) Hypertensive patients below 65 years (range 19−64, Con)	Plasma	HT VS Con	↑Renalase concentration ↑DA concentration ↓DBP Advanced abnormalities on echocardiography More often suffered from diabetes and coronary artery disease	[43]
4	Hypertension	60 hypertensive patients with no CAD (H-Tens, corresponding dose of losartan, captopril, atorvastatin, aspirin, clopidogrel, nitrocantin, metoprolol and carvedilol) 61 CAD patients with no hypertension (CAD, corresponding dose of losartan, captopril, atorvastatin, aspirin, clopidogrel, nitrocantin, metoprolol and carvedilol) 69 nonhypertensive with no CAD (Con, lower dose of losartan, captopril, atorvastatin, aspirin and metoprolol)	Serum	H-Tens VS Con CAD VS Con	↑Renalase activity ↓Renalase activity	[44]
5	Hypertension	1317 hypertensive people (HT) 1269 normotensive people (Con)		HT VS Con	↑The frequencies of rs2576178 G allele and rs2296545 C allele (0.55 vs 0.49, $P<0.0001$; 0.61 vs 0.55, $P<0.0001$) ↓Serum uric acid	[49]
6	Preeclampsia (PE)	40 women aged between 20–39 years with normotensive pregnancy (Normal pregnant) 40 women aged between 20–39 years with newly diagnosed preeclampsia (Pregnant with PE) 40 nonpregnant control female subjects aged between 20–39 years (Con)	Serum	Normal pregnant VS Con Pregnant with PE VS Con Pregnant with PE VS Normal pregnant	[21] ↓Serum creatinine ↓BP ↑Renalase ↑BP ↑Serum uric acid ↑Proteinuria/24 h ↓Renalase ↑BP ↑Serum uric acid ↑Proteinuria/24 h ↑SGA incidence ↓Renalase ↓Gestational age ↓Birth weight ↓Birth weight	
7	PE	179 women with PE (PE) 202 normotensive pregnant women (Con)	Genomic DNA from peripheral venous blood	PE VS Con	↑BP ↑RNLS rs10887800 GG and rs2576178 GG	[53]
8	CAD	499 Patients with a comorbidity of coronary artery disease (CAD) and impaired kidney function	Genomic DNA from patients' peripheral blood		Genome-wide association study: Rs139401390 was significantly associated with eGFR ($p = 0.033$)	[56]
9	CHD, HF	802 patients with HF alone (HF) 791 patients with both HF and CHD (HF/CHD)	Renalase gene data of Han Chinese individuals in Beijing were screened on NCBI and HapMap	HF/CHD VS HF	Allele A of rs2576178 was significantly associated with CAD ($p = 0.001$, OR = 1.625, 95% CI: 1.221−2.160)	[57]
10	CAD	449 CAD patients (CAD) 507 healthy controls (Con)	Matrix-assisted laser-desorption ionization (MALDI)/time of flight (TOF)-mass spectrometry (MS) from venous blood samples	CAD VS Con	Renalase rs2576178 polymorphism was significantly associated with increased risk of CAD (GG compared with AA, OR: 1.60, 95 % CI: 1.07–2.39, $P = 0.022$)	[58]
11	CAD	CAD patients with end-stage renal disease (ESRD) undergoing HD 107 patients with CAD (CAD+)	Genomic DNA from peripheral blood	CAD+ VS CAD−	↓Haemoglobin and albumin level ↑Frequency of the G allele of rs10887800 polymorphism (0.54 vs 0.47) or 1.34 (95 % CI: 0.96–1.86), $p = 0.088$	[59]

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Table 1 (*continued*)

No.	Disease type	Treatment groups	Location of expression	Sample group comparison	Medical effects	Reference
		202 patients without CAD (CAD−)			↓Frequency of the GG genotype [GG vs AG + AA], or 1.78 (95 % CI: 1.04–3.03), p=0.035	
12	CAD	406 Caucasian individuals with a history of CAD or myocardial infarction or myocardial ischaemia participants who had the GG or CG genotype of rs2296545 (GG/CG) 184 Caucasian individuals with a history of CAD or myocardial infarction or myocardial ischaemia participants with the CC genotype of rs2296545 (CC)	Genomic DNA from peripheral blood	GG/CG VS CC	↑Odds of left ventricular hypertrophy (OR = 1.43; 95 % CI: 0.99–2.06), systolic dysfunction (OR = 1.72; 95 % CI: 1.01–2.94), diastolic dysfunction (OR = 1.75; 95 % CI: 1.05–2.93), poor exercise capacity (OR = 1.61; 95 % CI: 1.05–2.47), and inducible ischaemia (OR = 1.49, 95 % CI: 0.99–2.24).	[60]
		140 healthy subjects (Con)		CAD VS Con	↓Renalase ↑Carotid atherosclerotic plaque and changes in the ST segment	
13	CAD	CAD patients according to the coronary angiography (CAG) method: normal subgroup without CAG abnormality (NS); subgroup with one branch with stenosis (1S); subgroup with two branches with stenosis, and a subgroup with multiple branches with stenosis (≥2S)	Plasma	≥2S VS NS	↓Renalase	[61]
		CAD patients according to the Syntax scores: low-risk subgroup (LRS, 1∼22); medium-risk subgroup (MRS, 23∼32); high-risk subgroup (HRS, ≥33)		LRS VS MRS/ HRS MRS VS HRS	↑Renalase ↑Renalase	
		14 normal patients (Con)		CMD VS Con	↑Median renalase (median: 4266 ng/mL; IQR 1503; p = 0.02) ↑CRP and VEGF	
		22 CAD or coronary calcification (CALC) patients (CAD/CALC)		CMD VS CAD/ CALC	Patients with CMD were younger ↓Mean CFR (mean CFR = 1.61 vs. 1.98). ↑Median renalase (median 4069 ng/mL IQR 1850; p = 0.004)	
14	CMD	44 CMD patients (CMD)	Serum	CAD VS CMD	↑VEGF, TNF-a and MMP-9 Each 1000 ng/mL increase in renalase increased the odds of CMD by 34 % (adjusted OR: 1.34, 95 % CI: 1.1, 1.7; p = 0.02) The addition of renalase improved the C-statistic to 0.70 to allow better detection of ischaemia (95 % CI: 0.59−0.82)	[70]
		75 H F patients: 27 reduced HF (HFrEF); 23 mid-range HF (HFmrEF); 25 HFpEF		HFrEF VS HFmrEF/ HFpEF	Aetiology: ↑Incidence of CAD HFrEF (80.8 %), HFmrEF (69.6 %) and HFpEF (48 %) ↑BNP concentration ↑Renalase	
15	HF		Plasma		↑BNP concentration ↑Renalase	[74]
		35 healthy volunteers (Con)		HF VS Con	Biomarkers: The renalase concentration was positively associated with the left ventricular mass index in HFrEF (p = 0.029), as well as an increased concentration of BNP (p = 0.006)	
		212 ischaemic stroke patients from the northern Chinese Han population (IS)			↑BP ↑BMI ↑Glucose ↑TC ↑TG ↑LDL ↓HDL	[79]
16	Ischaemic stroke	244 healthy controls from the northern Chinese Han population (Con)	Genomic DNA Con from peripheral blood	IS VS Con	The genotypic distribution (p = 0.049) and allele frequency (OR = 1.55; 95% CI: 1.095–2.199; p = 0.013) of rs10887800 polymorphism were significantly different	

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Table 1 (*continued*)

No.	Disease type	Treatment groups	Location of expression	Sample group comparison	Medical effects	Reference
17	AF	62 patients with paroxysmal AF 7 patients with persistent AF 15 patients without AF (Con)	Plasma	AF VS Con paroxysmal AF VS persistent AF	↑Renalase (mean 27.99 vs. 21.48 μg/mL, $p = 0.004$) ↑Renalase (mean 28.77 vs. 19.05 μg/mL, $p = 0.048$) Logistic regression: Global four-chamber LA strain was the only independent predictor of renalase variability; Renalase concentration did not predict AF recurrence at six-month follow-up (area under curve [AUC] = 0.614, $p = 0.216$)	[80]
18	Aortic stenosis	657 patients with aortic stenosis (387 men and 270 women) referred for aortic valve replacement	Genomic DNA from peripheral blood		In females: Asp37 variant of the Glu37Asp polymorphism was associated with a higher left ventricular mass, intraventricular septal thickness and posterior wall thickness	[82]
19	CAD	85 CAD patients with an eGFR <60 mL/min/1.73 m^2 were allocated to the CKD (+) group 257 CAD patients with an eGFR ≥60 mL/min/1.73 m^2 were allocated to the CKD (−) group	Serum	CKD (+) VS CKD (−)	↑ET-1 ↑Renalase Patients with both CKD and a high renalase level (>the median of 36.2 ng/mL) exhibited the highest serum ET-1 level According to multivariate linear regression analysis: The combination of a high serum renalase level with CKD was a significant risk factor for an increased serum ET-1 level	[96]
20	CAD	95 consecutive patients with CAD subjected to elective or urgent CA/PCI 9 patients who developed CI-AKI	Urine	CI-AKI VS non-CI-AKI	↓Urinary renalase-to-creatinine ratio ↓Urinary renalase Absolute decrease in renalase below 25 % was a predictor of CI-AKI (OR = 5.4, 95 % CI: 1.3–21.9, P=0.027)	[97]
21	ESRD	4 healthy individuals (Con) 8 patients with ESRD (ESRD)	Plasma	ESRD VS Con	↓Renalase	[17]
22	HD	50 haemodialyzed patients (HD) 35 healthy controls (Con)	Serum	HD VS Con	↑Renalase Renalase was positively correlated with serum creatinine and dialysis vintage LVMI was positively correlated with dialysis vintage and C-reactive protein LVMI was negatively correlated with residual diuresis and haemoglobin	[98]
23	HD + Heart disease Haemodialyzed patients	High renalase level (HR) Low renalase level (LR)	Plasma	HR VS LR	↑miRNA-146a expression In LR: ↓miRNA-146a expression ↑Survival time Patients with low miRNA-146a expression: Survival time in contrast to that of patients with high miRNA-146a expression level (median: 69 vs. 56 months; $P = 0.430$, HR = 1.728; 95% CI: 0.995–3.002)	[99]
24	PD	40 PD patients 40 healthy controls	Serum	PD VS Con	↑Median serum renalase Renalase was positively correlated with C-reactive protein Renalase was negatively correlated with RRF	[100]

reported, renal denervation can reduce BP, as it may contribute to the suppression of sympathetic nerves and increase the plasma renalase content as well as renalase expression in the kidneys [39]. However, studies by Wang et al. have shown that phentolamine may inhibit the expression of renalase and subsequently lead to increased BP, which was in contrast to previously reported findings [40]. The different conclusions may be attributed to the activity of renalase, which might not have been detected in the experiments by Wang et al. Additionally, phentolamine truly inhibited the increase in adrenaline-induced renalase expression, although whether it also inhibits the expression of renalase under alkaline conditions was not determined. Furthermore, the modulations of biological molecules were much more intricate in vivo than in vitro. Previous research was conducted in a proximal renal tubular epithelial cell line only, which limited the accuracy of the experimental results.

Most researchers have concluded that renalase expression is decreased in hypertensive patients. However, a recent study reported no significant difference in renalase between hypertensive patients and normotensive control subjects. Notably, miRNA 4516 and miRNA 145 were found to be independent determinants of essential hypertension, with renalase exhibiting a negative correlation with miRNA 4516 and a positive correlation with miRNA 145 in hypertensive patients and controls [41]. Another study demonstrated that serum renalase was significantly higher in hypertensive adolescents than in healthy people and correlated with serum uric acid; indeed, patients with elevated serum uric acid exhibited significantly higher renalase levels, which remained independent of BP [42]. Zbroch et al. assessed the effects of age on renalase and catecholamine concentrations in hypertensive patients and

Table 2
Effects of renalase on CVD in vivo and in vitro.

No.	Disease type	Treatment groups	Renalase expression location	Sample group comparison	Medical effects	Reference
1	Cardiac hypertrophy	SD rats with 5/6 Nx (5/6 Nx) Pair-fed controls (PF) SD rats in Sham-operated (SH) group	Heart	5/6 Nx VS PF/SH	↑Plasma urea nitrogen ↑Serum creatinine ↑Mean arterial BP ↑Heart-weight/body-weight ratio ↑Plasma NE ↑Alpha-1A receptor protein expression ↓Cardiac beta-1 and beta-2 receptor protein expression ↑GRK2 expression ↓NE transporter protein ↓Renalase protein expression	[35]
2	CKD/ hypertension	H9c2 cells incubated with 20 μmol/ L DA for up to 12 h CKD model (5/6 Nx) rats after surgery CKD model (5/6 Nx) rats received a 2-minute infusion of epinephrine, NE, or DA at a concentration (Model) Normotensive rats infusing epinephrine over a 2-minute period at doses ranging from 0.1–100 μg/ kg (Con)	Cells Kidneys; heart; blood Plasma	Model VS Con	↑Renalase mRNA (10-fold) ↓Blood renalase ↓Renalase in kidney and heart tissues ↑Blood prorenalase ↓Magnitude and duration of activation	[22]
3	Hypertension	Renalase KO mice (KO) WT mice (WT)	Kidneys	KO VS WT	KO fed with regular diet, containing 0.9 % Pi: ↓Serum PO_4^- ↑Urinary PO_4^- excretion KO mice fed a low-PO_4^- diet: ↓Serum PO_4^- ↓DA excretion ↓Urinary excretion in both WT and KO KO mice on a regular Pi diet: ↑Daily urinary excretion of DA KO mice maintained on a regular diet: ↑Daily urinary excretion of DA	[37]
4	Hypertension	Renal proximal tubules cells from Wistar Kyoto rats (WKY) WKY treated with D1-like receptor agonist fenoldopam (Fen-W) Fen-W treated with PKC inhibitor (Fen-W-I) WKY treated with PKC activator (WKY-A) Renal proximal tubule cells from spontaneously hypertensive rats (SHR) SHR treated with D1-like receptor agonist fenoldopam (Fen-S)	Kidneys	SHR VS WKY Fen-W VS WKY Fen-W-I VS Fen-W WKY-A VS Con Fen-S VS SHR	↓Renalase expression ↑Renalase protein and mRNA expression ↑NADH oxidation ↓Renalase expression (Blocked the stimulatory effect of fenoldopam on renalase expression) ↑Renalase expression ↓Renalase protein and mRNA expression ↓NADH oxidation	[38]
5	Spontaneous hypertension	Spontaneous hypertension rats with renal denervation	Plasma, kidneys		Before renal denervation surgery in spontaneous hypertension rats: ↓Plasma renalase content ↑SBP, DBP and MAP Before renal denervation surgery in spontaneous hypertension rats: ↑Plasma renalase content ↑Kidney renalase expression ↓MAP and tyrosine hydroxylase expression in the kidneys	[39]
6	Myocardial hypertrophy	HK2 cell: preconditioned for 30 min with phentolamine or tosyl phenylalanyl chloromethyl ketone (TPCK) before incubation with epinephrine	Cell culture supernatant; HK2 cells	After epinephrine treatment After phentolamine or TPCK treatment	↑Renalase protein ↑Renalase mRNA ↓Renalase protein ↓Renalase Mrna	[40]
7	Hypertension	Dahl SS rats and SS–13BN male rats: Normal salt (0.3 % NaCl) BN (13BN normal-salt group); SN (SS normal-salt group); Dahl SS rats and SS–13BN male rats: High salt (8% NaCl) BH (13BN high-salt group); SH (SS high-salt group); Dahl SS rats and SS–13BN male rats: High salt/potassium (8% NaCl and	Kidneys	SN VS BN SH VS SN SH VS BH	↑BP ↑Plasma DA ↑Plasma DA ↑BP ↓Renalase gene expression ↓Renalase protein ↑Plasma DA	[48]

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Table 2 (*continued*)

No.	Disease type	Treatment groups	Renalase expression location	Sample group comparison	Medical effects	Reference
		8% KCl) BHP (13BN high-salt with potassium group) SHP (salt-sensitive high-salt with potassium group)		SHP VS SH	↑BP ↓Renalase gene expression ↓Renalase protein ↓BP ↑Renalase gene expression ↑Renalase protein	
		Renalase$^{(-/-)}$ mice (Model)			↓Plasma DA ↑Heart rate ↑BP ↑Plasma DA, epinephrine, and NE	
8	Ischaemic cardiomyopathy	WT mice		Model VS Con	↑SBP and DBP ↑LV posterior wall thickness ↓The ratio of NAD/NADH ↓Plasma and tissue NADH oxidase activities ↑Myocardial injury degree	[24]
		Model group with myocardial I/R (MIR)		MIR VS Con	After assessing recombinant renalase: ↓Ischaemic myocardial injury area	
		C57BL/6 mice (Con)			↑Renalase protein and mRNA expression	
		C57BL/6 mice received myocardial I/R surgery (Model)	Cardiac muscle	Model VS Con	C57BL/6 mice were injected with renalase siRNAs and received myocardial I/R surgery: ↑Ratio of myocardial infarct size/area at risk (MI/AAR) ↓EF and fraction shortening (FS) Administration of renalase recombinant protein: ↑MI/AAR ↑FS	
		HCM cells (Con-c)			↑HIF-1α and ↑Renalase ↑Vascular endothelial growth factor α ↑ Glucose transporter 1	
9	I/R				HCM cells were incubated with HIF-1α agonist CoCl2: ↑Renalase mRNA and protein levels	[63]
		HCM cells were subjected to hypoxia (Model-c)	Cells	Model-c VS Con-c	HCM cells were transfected with HIF-1α-expressing plasmid: ↑Renalase mRNA and protein levels HCM cells were transfected with HIF-1α siRNA: ↓Renalase mRNA and protein levels Model-c group reoxygenation :	
		C57BL/6 mice were injected with HIF-α-siRNAs and received myocardial I/R surgery (HIF-α-siRNA)	Cardiac muscle	HIF-α- siRNA VS Con	↑Renalase expression ↑MI/AAR Administration of renalase recombinant protein: ↑MI/AAR ↑SBP ↑HW/bw and LV weight/bw ↑LVPWd and LVPWs ↑LVAWd and LPAWs ↓LVIDd and LVIDs ↑Cross-sectional area of cardiomyocytes ↑Deposition of extracellular matrix ↓MMP-1 ↑TGF-β and TIMP-1 ↑ERK-1/2 expression in heart and kidneys	
		SD rats: Sham-operated group treated with tail vein injection of 1.2 mL Hanks' balanced salt solution (Sham)		STNx + Ad-β-ga VS Sham		
10	CKD	SD rats: Subtotal nephrectomy group treated with tail vein injection of 1.2 × 10^10 PFU control adenovirus (STNx + Ad-β-gal)	Kidneys	STNx + Ad-renalase VS Sham	↑SBP ↑HW/bw and LV weight/bw ↑LPAWs	[93]
		SD rats: Subtotal nephrectomy group treated with tail vein injection of 1.2 × 10^10 PFU adenovirus-renalase (STNx + Ad-renalase)		STNx + Ad-renalase VS STNx + Ad-β-ga	↓SBP ↓HW/bw and LV weight/bw ↓LVPWd and LVPWs ↓LVAWd and LPAWs ↑LVIDd and LVIDs ↓Cross-sectional area of cardiomyocytes ↓Deposition of extracellular matrix ↑MMP-1 ↓TGF-β and TIMP-1 ↓ERK1/2 expression in heart and kidneys	
		Normal rats (Con)			↓Expression of renalase	
11	HF	Unilateral renal artery stenosis rats (Model)	Kidney	Model VS Con	Utilized an isolated perfused rat kidney model:	[75]

(*continued on next page*)

Table 2 (*continued*)

No.	Disease type	Treatment groups	Renalase expression location	Sample group comparison	Medical effects	Reference
		Infarction-induced heart failure rats (Model-I)		Model-I VS Con	Clearance rate of NE decreased with reduction in perfusion flow ↓Flow velocity of renal artery ↓Renalase expression Renalase expression associated with an increase in circulating NE	
		ApoE$^{-/-}$mice fed a high-fat diet (HF group)		HF group VS NC group	↑TC, TG, and LDL-C Observed atherosclerotic plaque ↑ Renalase mRNA expression in abdominal fat and brain	
		C57 mice fed a standard chow diet (NC group)		26-week High-Fat Diet group VS NC group	↑Renalase mRNA expression in kidneys, testes, and brain ↓Renalase mRNA expression in liver ↓Renalase expression in the cortex and medulla of the adrenal glands and liver	
12	AS	13-week high-fat diet ApoE$^{-/-}$mice treated with valsartan for an additional 13 weeks (Valsartan)	Abdominal fat; brain; kidneys; testes; aorta, heart; liver; serum	26-week high-fat diet ApoE$^{-/-}$mice VS 13-week high-fat diet ApoE$^{-/-}$mice	Immunohistochemistry: Predominant renalase expression in the fibrous cap of atherosclerotic plaque in the aortae ↓Renalase expression in the fibrous cap of atherosclerotic plaque ↑Thickness of the fibrous cap of the atherosclerotic plaque ↓Ratio of extracellular lipid to atherosclerotic plaque	[18]
		13-week high-fat diet ApoE$^{-/-}$mice treated with simvastatin (positive control drug) for an additional 13 weeks (Simvastatin)		Valsartan VS Control group	↑Expression of Arg-1 and a-actin in the fibrous cap of the atherosclerotic plaque ↑Renalase expression in the serum ↑Renalase expression in the fibrous cap of atherosclerotic plaque ↓Serum level of TG ↑ mRNA expression of renalase in liver tissue	
		13-week high-fat diet ApoE$^{-/-}$mice treated with distilled water (control group) for an additional 13 weeks (Control group)			Renalase mRNA and protein expression	
		Genetically hypertensive BP high mice (Hypertensive)			↑miR-29b	
13	Hypertensive	Genetically hypotensive BP low mice (Hypotensive)	Kidneys	Hypertensive VS Hypotensive	Common single nucleotide polymorphism in human renalase 3′-UTR (C/T; rs10749571) creates a binding site for miR-146a; miR-146a downregulated human renalase 3′-UTR/luciferase activity in that case of the T allele, suggesting its potential role in the regulation of renalase in humans	[83]
		Sham-operated rats that received phosphate-buffered saline (PBS) subcutaneously (Group I)			↑ MAP ↑LV/BW ratio ↑LV hydroxyproline concentration	
				Group II VS Group I	↑Plasma creatinine ↑BUN ↑NE levels ↓LV papillary muscle developed tension. ↓MAP	
14	Chronic renal disease	Rats that underwent 5/6 Nx and then received PBS daily (Group II)				[92]
		Rats that underwent 5/6 Nx and then received recombinant renalase daily (Group III)		Group III VS Group II	↓LV/BW ratio ↓LV hydroxyproline concentration ↓NE levels ↑LV papillary muscle developed tension	

the possible relationship between these factors and BP or CVD. The results showed that the elevated levels of renalase in elderly hypertensive patients were more closely related to kidney function and CVD than to age itself. Therefore, they suggested that renalase appeared to be a possible new marker of these indications in this specific population [43]. According to Akbari et al., atorvastatin and losartan therapy were assumed to be of considerable significance in alleviating hypertension by increasing renalase activity [44]. In addition, high salt intake was associated with high BP [45], whereas potassium could reverse high salt-mediated BP elevation [46,47]. Zheng et al. demonstrated that renalase could mediate a salt-induced increase and a potassium-induced decrease in BP [48]. Moreover, genetic polymorphisms in renalase were also related to hypertension, and by detecting SNPs at specific sites in the renalase gene, the risk of hypertension could be predicted. All eight selected SNPs in the renalase gene were genotyped and tested in Zhao's study of 2586 Chinese participants, including 1317 hypertensive patients and 1269 controls. They found that the genotypes rs2576178 GG and rs2296545 CC were associated with essential hypertension [49], suggesting that patients with these variants were more likely to suffer from hypertension. Polymorphisms in the renalase gene appear to confer an increased risk of hypertension.

Additionally, pregnancy-induced hypertension is a unique yet common complication in pregnant women that affects approximately 5–10% of all pregnant women [50]; moreover, preeclampsia (PE) is the leading contributor to maternal and neonatal morbidity and mortality worldwide [51,52]. Yılmaz et al. discovered that the development of PE in pregnant women was accompanied by changes in the serum renalase level. In this way, low renalase levels partly mediated hypertension and kidney damage in PE. Moreover, they found that the renalase level was inversely associated with 24-h urinary protein excretion, uric acid and haemoglobin levels, which were positively correlated with the glomerular filtration rate (GFR) and birth weight [21]. Through this mechanism, the relationship between renalase and PE provided new possibilities for the treatment of PE. The GG genotype and G allele of the

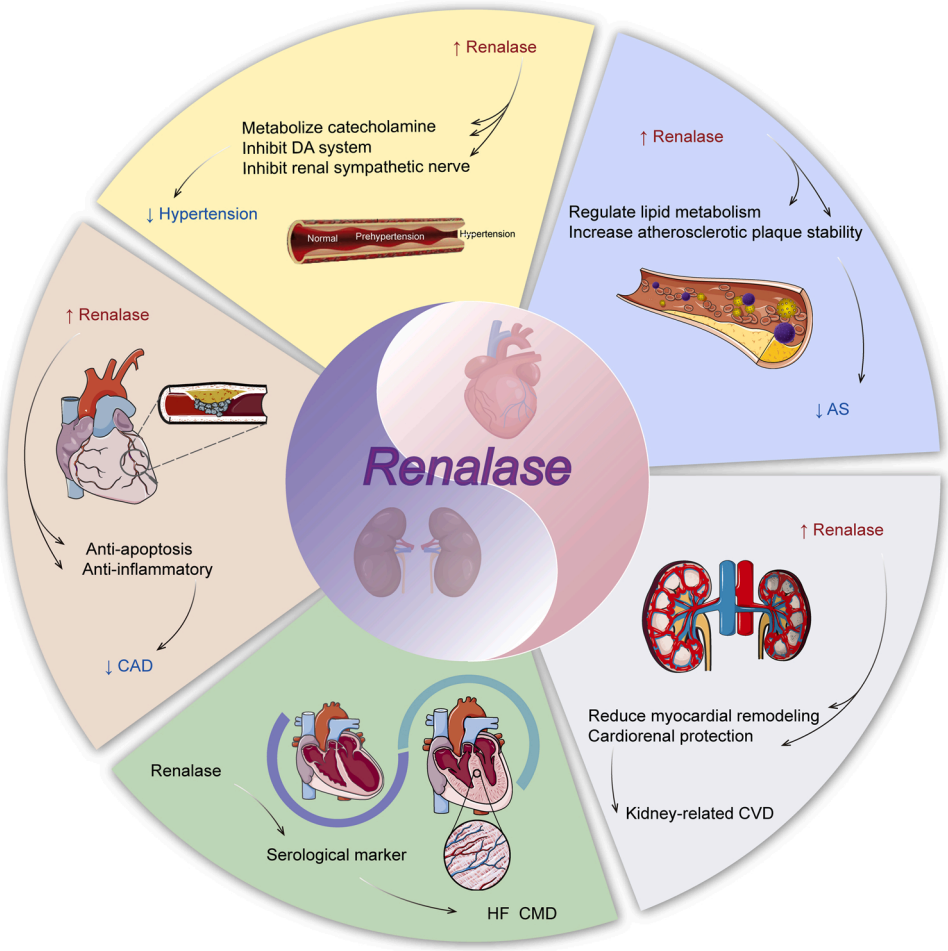

Fig. 4. Mechanisms of renalase in CVD.

rs10887800 polymorphism might increase BP, and the polymorphism might increase susceptibility to PE; however, specific associations have not been observed between the RNLS rs10887800 and rs2576178 polymorphisms and PE. Teimoori et al. suggested that in women from Southeast Iran, the combined effect of the rs10887800 GG and rs2576178 GG genotypes was associated with an 8.4-fold increase in the risk of PE [53]. Of course, those research results were influenced by sample size and environmental and ethnic differences. Although a meta-analysis showed that the renalase gene rs2296545 polymorphism was significantly associated with an increased risk of hypertension, the rs2576178 polymorphism may not be correlated with hypertension susceptibility [54]. Therefore, whether the genetic polymorphisms in renalase are associated with hypertension still needs further investigation.

Thus, current research suggests that increasing the expression of renalase can effectively reduce BP. Research on the mechanism of renalase has primarily focused on animal experiments; however, most of these studies may not be sufficiently in depth, and clinical research generally concentrates on the exploration of phenotypes and phenomena. Nevertheless, renalase has great potential as a powerful hypotensive drug, and recombinant or synthetic renalase may represent a new method for the treatment of hypertension in the future.

3.2. Renalase and CAD

CAD is one of the most common types of heart disease worldwide as well as one of the leading causes of death annually. Therefore, the specific pathogenesis of CAD continues to be explored. Candidate gene approaches and genome-wide association studies have successfully identified CAD susceptibility-related genes in the general population [55]. To date, several studies have already evaluated the correlation between SNPs in the renalase gene and CAD in patients with normal renal function.

Boris et al. collected CAD patients with ≥50 % stenosis (≥1 coronary artery), and the creatinine-based estimated GFR (eGFR) was estimated to be 30−75 ml/min/1.73 m^2. In these samples, rs139401390, which is located 58.8 kb upstream of renalase, was significantly associated with the eGFR at the genome-wide level in patients with CAD presenting mildly decreased renal function [56]. The rs2576178 polymorphism was found to be involved in CAD risk in Chinese patients by Li et al. [57], and allele A of rs2576178 showed potential as a predisposing factor for CAD in hypertensive patients. Hu et al. suggested that the GG genotype or G allele of the rs2576178 polymorphism contributed to an increased risk of CAD [58]. In a case-control study using the PCR-RFLP method to genotype 309 haemodialyzed patients (107 with and 202 without CAD), two SNPs in the renalase gene (rs10887800 and rs2576178) were genotyped; the most interesting finding was that the rs2576178 polymorphism did not influence the risk of CAD, while the rs10887800 renalase gene polymorphism showed potential involvement in the pathogenesis of CAD in haemodialyzed patients [59]. These discrepancies among studies might also be attributed to different geographical settings, sample sizes and study designs. Moreover, the variability in clinical heterogeneity and polymorphisms among races may also be a contributing factor. In a study of 590 Caucasians with stable CAD, the CC genotype of the rs2296545 polymorphism was found to be associated with left ventricular (LV) hypertrophy, cardiac systolic and diastolic

dysfunction, poor exercise capacity and inducible ischaemia [60]. He et al. held the opinion that the plasma renalase level could be used to indicate the progression of CAD, and changes in renalase might reflect the degree of coronary artery stenosis [61].

In addition, ischaemic cardiomyopathy is a special type of CAD. Wu et al. found that renalase knockout mice showed decreased tolerance to cardiac ischaemia, and when exposed to an ischaemic insult, these mice developed more severe myocardial necrosis than wild-type mice. These authors also found that renalase deficiency was associated with a significant decrease in the cellular nicotinamide adenine dinucleotide (NAD)/reduced form of nicotinamide adenine dinucleotide (NADH) ratio. NAD is important in energy metabolism and electron transfer reactions, and it regulates the activity of the NAD-dependent type III deacetylase sirtuin1 (SIRT1), which participates in metabolic homeostasis and cell survival pathways [62]. Thus, elevated NAD levels would enhance SIRT1 activity, leading to downstream targets such as transcription factors (FOXO1 and FOXO3a) and peroxisome proliferator-activated receptor-c coactivator 1a. The decrease in the NAD/NADH ratio caused by a lack of renalase would be expected to aggravate myocardial damage during ischaemia and impair cardiac contractility during reperfusion [24].

It has also been reported that renalase could reduce myocardial ischaemia/reperfusion (I/R) injury. Du et al. administered a cardiac injection of renalase siRNA to specifically downregulate renalase expression in the hearts of C57BL/6 mice. The increase in the area of myocardial infarction in these mice was accompanied by a decrease in the ejection fraction (EF), while the administration of recombinant renalase reduced the infarct area and prevented a decrease in EF. Furthermore, they identified renalase as a novel target gene of hypoxia-inducible factor-1α (HIF-1α), which participates in a new mechanism of I/R injury by inducing renalase gene expression. Hence, administration of renalase reduced the infarct area and rescued the deterioration of cardiac function in myocardial HIF-1α knockdown mice subjected to I/R injury. In addition, after recombinant renalase treatment, the level of NE decreased in serum, while the levels of NAD + and ATP in the myocardium increased, which implied that the cardioprotective effect of renalase against I/R might be partly related to its metabolism of catecholamines and regulation of energy [63]. Li et al. also confirmed the protective and survival effects of renalase, and they demonstrated that renalase protected cardiomyocytes from I/R damage through anti-apoptotic and anti-inflammatory mechanisms [64]. According to the results of the above study, renalase undoubtedly has a valuable function in preventing ischaemic injury of the heart and CAD, providing a therapeutic strategy for improving myocardial viability.

All of these observations prove to some extent the interconnection between renalase and CAD. However, based on the relevant current literature, the tested polymorphisms may not provide a comprehensive view of the genetic variation in renalase. Therefore, further fine-mapping studies on renalase and CAD should be performed in the future.

3.3. Renalase and CMD

CMD, also known as nonobstructive CAD, presents as a narrowing of small blood vessels that branch from the coronary arteries and deliver oxygen-rich blood to the myocardium, decreasing the amount of blood entering the cardiac muscle and leading to chest pain. In addition, CMD is also the most common cause of angina pectoris in non-CAD and accounts for 21–63 % of cases of chest pain in patients with obstructive CAD without angiography [65]. Furthermore, CMD mediates ischaemia and may cause an increased risk of CVD [66–69]. Therefore, accurate and reliable identification of blood biomarkers in CMD patients is necessary for clinical diagnosis.

Safdar et al. analysed blood samples from 14 patients with normal haemodynamic parameters as well as 44 patients with CMD and found that the renalase level was significantly higher in CMD patients than in normal people, supporting the physiological role of renalase in response to ischaemia in CMD patients [70]. However, Medvedev et al. performed similar research including mass spectrometry (MS) analyses, which did not detect the specific prototypic peptide (residues 100–116) of renalase in healthy volunteers, although the renalase values determined using commercial ELISA kits (45.6 ± 5.4 μg/mL) were even higher than those reported in Ref [70]. Moreover, they reported that CMD might differ from other pathological conditions depending on the serum renalase isoform and suggested that its individual identification as well as quantitative analysis might help determine the role of renalase as biomarkers [71].

3.4. Renalase and HF

HF occurs when an abnormal cardiac structure or function results in increased intracardiac pressure or decreased cardiac output, thereby leading to the inability of the heart to pump a sufficient volume of blood to meet the body's needs [72]. With increasing morbidity and mortality globally, HF also represents a growing health problem [73].

Stojanovic et al. collected data from 75 H F participants and 35 community-based healthy volunteers. A comparison among patients with HF, including HF with a mid-range LV ejection fraction (LVEF, HFmrEF, 40–49 %) and HF with a preserved LVEF (HFpEF, LVEF ≥ 50 %), showed that the HF patients presented a higher plasma renalase concentration than patients in the control group and that this concentration was the highest in patients with a reduced LVEF (LVEF < 40 %). These findings suggested that the plasma renalase level could be measured to differentiate patients with an LVEF below 40 % and may serve as a potent biomarker for identifying HF patients with a reduced LVEF. Moreover, they also demonstrated that in patients with a reduced LVEF, high plasma renalase concentrations were positively correlated with LV hypertrophy and closely related to an increased LV mass index [74]. However, the shortcoming of this study was that the plasma renalase level was a relatively poor marker for the stratification of patients with HF compared with the plasma brain natriuretic peptide (BNP) level, and the link between renalase and BNP was not explored. In the future, multi-marker approaches for HF management should be promoted.

In addition, sympathetic overactivity and catecholamine accumulation are important characteristics in HF. HF can cause kidney ischaemia, whereas ischaemic kidneys can decrease the expression of renalase in renal tubules. In HF model rats generated via acute myocardial infarction, renalase expression in renal tissue reached a peak within 1 week and then gradually decreased, showing a significant decline in the 4th week, which was accompanied by a decrease in renal artery blood flow velocity. Moreover, the concentration of renalase in the blood was also markedly reduced, while the concentration of catecholamines was significantly increased. This suggested that the expression and secretion of renalase were reduced, leading to inhibition of sympathetic nerves, weakening of the degradation of catecholamines, and subsequent participation in the pathological process of HF [75].

3.5. Renalase and AS

AS is the root cause of the majority of CVD cases [76,77]. It is a chronic inflammatory disease of the arterial wall arising from an imbalance in lipid metabolism and the inflammatory response [78].

Our team used apolipoprotein E (ApoE) (-/-) mice fed a high-fat diet to examine the tissue distribution of renalase and the effect of valsartan on renalase expression. The results showed that ApoE knockout caused a dramatic increase in renalase expression in adipose tissue. In lipid metabolism disorders caused by a high-fat diet, the expression of renalase is decreased in the liver. Renalase was also expressed in smooth muscle cells and M2 macrophages in atherosclerotic plaques, and its expression gradually decreased during the transition from stable to fragile atherosclerotic plaques. To address this issue, valsartan was used as an AT1 receptor antagonist that stabilized atherosclerotic plaques by

increasing the serum level of renalase and the expression of renalase in the fibrous cap of atherosclerotic plaques. Moreover, valsartan reduced serum triglyceride (TG) levels and increased renalase expression in the liver. All of these results demonstrated that renalase may be related to lipid metabolism and AS and that it may be a possible molecular target of valsartan to help stabilize atherosclerotic plaques [18]. In future work, our research group will further explore the molecular mechanism of renalase in AS to provide a specific theoretical basis for the clinical treatment of AS. Additionally, Li et al. have shown that the rs10887800 SNP in the renalase gene was closely related to severe intracranial cerebral atherosclerotic vascular stenosis in ischaemic stroke patients of northern Chinese Han origin [79].

Other studies showed that although the expression of renalase could not predict sinus rhythm maintenance and did not appear to be useful in predicting the recurrence of atrial fibrillation (AF) over a six-month observation period, low renalase levels might be related to impaired rate control, increased AF burden, and left atrial remodelling progression in AF patients with pulmonary vein isolation [80]. Therefore, some academics believed that renalase has utility as a biomarker of the risk of AF and potentially as a marker of disease progression [80,81]. The renalase Glu37Asp polymorphism has been reported to be associated with LV hypertrophy in females with aortic stenosis. The Glu37Asp polymorphism not only leads to amino acid substitutions in the FAD binding domain but also may alter the binding affinity of hypoxia- and hypertrophy-related transcription factors, thereby ultimately affecting renalase expression [82]. Interestingly, regulation of the renalase gene, especially at the posttranscriptional level, is emerging as a novel regulator of CVD. Kalyani et al. found that miR-29 and miR-146 participated in posttranscriptional regulation of the renalase gene and had implications in interindividual variations in cardiometabolic traits [83].

A large number of studies have concluded that a close relationship occurs between renalase and CVD. Therefore, further work is necessary to better define the role of renalase in CVD.

4. Role of renalase in kidney-related CVD

CKD is defined as a reduced GFR, increased urinary albumin excretion or both, and it is a growing public health issue. Complications include increased all-cause and cardiovascular-related mortality, renal disease progression and acute kidney injury (AKI) [84]. A close relationship is observed between renal disease and CVD, and both can aggravate each other. People with CKD are known to be at an increased risk of CVD due to circulatory alterations caused by renal disease [85–88]. Moreover, CVD is the leading cause of death in patients with CKD. Future renal function indices should reflect not only the extent of kidney injury but also the magnitude of the combined cardiorenal pathology. Circulating renalase could be used as a predictor of mortality and adverse renal prognosis in patients with CKD [89] and as a possible predictor of kidney-related CVD [90,91].

Renalase protects against the development of cardiac hypertrophy associated with CKD. Baraka et al. observed a significant increase in MAP, LV/body-weight (BW) ratio, LV hydroxyproline concentration, and NE levels as well as LV papillary muscle dysfunction in rats undergoing 5/6 nephrectomy (5/6 Nx). Notably, recombinant renalase treatment was shown to significantly ameliorate all of the studied parameters [92]. Additionally, using similar animal models, Yin et al. confirmed that renalase could reduce proteinuria, glomerular hypertrophy and interstitial fibrosis and significantly reduce fibrosis markers, pro-inflammatory cytokines and NADPH oxidase components. Systemic delivery of recombinant renalase reduced the development of hypertension, myocardial hypertrophy and myocardial interstitial fibrosis and prevented cardiac remodelling by inhibiting the expression of fibrotic genes and phosphorylation of ERK-1/2 [93]. Together, these data indicated that renalase shows potential as a therapeutic target for the prevention and treatment of CVD in patients with chronic kidney disease.

Moreover, an increase in circulating renalase levels has been associated with CAD in patients with CKD [94]. Endothelin-1 (ET-1) was correlated with endothelial dysfunction as well as vasoconstriction, while elevated circulating ET-1 levels were associated with long-term CVD-related mortality [95]. A cross-sectional study showed a synergistic effect of serum renalase and CKD on increased serum ET-1 levels in 342 nondiabetic patients with confirmed CAD. The combination of high serum renalase levels and CKD was a significant risk factor for elevated serum ET-1 levels, which subsequently increased the danger of coronary heart disease [96]. Wybraniec et al. found that the development of contrast-induced AKI (CI-AKI) might be related to the urinary renalase concentration, which was reduced in the aftermath of coronary angiography/percutaneous coronary intervention (CA/PCI) [97].

CVD is often complicated by advanced renal disease, and haemodialysis (HD) is one of the most important treatments for renal replacement in patients with acute and chronic renal failure. A study that included 50 HD patients with heart disease or diabetes and 35 healthy controls suggested that in patients undergoing HD treatment, the LV mass index tended to correlate with the renalase level, which was also positively correlated with the serum creatinine level and dialysis vintage [98]. Furthermore, it was confirmed that high renalase activity yielded a significantly longer survival time in HD patients with heart disease [99]. In addition, renalase was associated with C-reactive protein, and residual renal function acted as a CVD risk factor in peritoneal dialysis (PD) patients [100]. Together, these findings strongly suggested that renalase prevents acute cardiac injury and mitigates the development of cardiac diseases associated with CKD. Renalase may constitute a biochemical link in the mutual interplay between renal and cardiac pathology. In the future, the potential of renalase as a pathological or serological marker of CVD and CKD in patients should be further investigated.

5. Conclusions and future perspectives

In recent decades, with the continuous changes in social, environmental, medical technology and other factors, the spectrum of CVD and the incidence, prognosis and outcome of CVD have changed accordingly. At present, the pathogenesis of CVD is constantly under investigation, and new diagnostic techniques and biomarkers are continuously being applied. CVD prevention and control methods have achieved gratifying results, although gaps and shortcomings remain in the process of the prevention, diagnosis and treatment of CVD. For example, the number of biomarkers for the diagnosis and exclusion of CVD remains small, which may lead to some missed diagnoses and delays in treatment opportunities. Therefore, the need to continuously improve the diagnosis and treatment of CVD is urgent.

Experimental results obtained from animal and human studies strongly support the notion that renalase, a newly discovered protein derived from the kidneys and highly expressed in the kidneys and heart, plays a key role in the metabolism of catecholamine and in the protection of cardiovascular cells. The development of an understanding of the structure and function of renalase as well as early clinical studies exploring its relationship with different human diseases have identified renalase as a substance with potential pathophysiological relevance and diagnostic/therapeutic utility.

Similarly, studies have shown that the injection of recombinant renalase could reduce arterial pressure in 5/6 Nx rats and that renalase knockout increased susceptibility to cardiac ischaemic damage [35]. Moreover, CKD was associated with decreased cardiac renalase expression, and the lack of renalase may lead to an increased risk of CVD in patients with CKD [94,97]. Thus, we speculate that renalase replacement therapy will improve cardiovascular outcomes in CKD.

However, certain problems remain in the research on renalase. For example, some of the contradictions between the ELISA and Western blot results might be caused by the low specificity of antibodies in the ELISA kit, which represents an important factor that may explain why studies exploring the molecular mechanism underlying renalase were

limited. Therefore, the development of more standardized and validated methods or kits to evaluate the activity and level of renalase in tissue and various fluids, including blood and urine, is particularly important. Developing a unified standard will lead to more precise, in-depth and diverse explorations of renalase. The molecular mechanism of renalase in cells must be further explored to identify whether it acts as an enzyme, signalling molecule or transcription factor. Moreover, the specific regulatory mechanism of the corresponding function needs to be identified. At the American Society of Nephrology (ASN) annual meeting in 2014, Desir reported that the possible receptor for renalase should be PMCA4b, which laid a good foundation for the study of the role of renalase-related cytokines [27]. Although current relevant research has partially answered this question, the results are not sufficiently in-depth. For example, the key cytokines specifically targeted by renalase to exert its cardioprotective function during the development of diseases such as hypertension, myocardial infarction, coronary heart disease, and HF remain unknown. In addition, the drugs, molecules, or targets that can regulate the expression of renalase have not been clarified. Although Sonawane et al. found that the transcriptional regulators Sp1, STAT3 and ZBP89 participate in renalase expression and could regulate the activity of the renalase promoter [101], these factors have not yet been thoroughly explored in CVD.

All phenotypic studies suggested that renalase is a promising and potential drug target. Given the link between CVD and renal disease in the endocrine nutriregulation mechanism, renalase has become a drug target for CVD. Thus, further work is needed to clarify these observations and the potential of renalase for development into a new drug to effectively treat CVD, and its clinical application merits further attention. More discoveries and applications are expected in the near future.

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Declaration of Competing Interest

There are no conflicts of interest.

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