Renalase: Gene polymorphism and its association with hypertension in some diseases

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Abstract. Hypertension is a significant public health problem due to its high prevalence and association with increased risk of cardiovascular disease (CVD), and thus the major cause of death in developed countries. Most of diabetes mellitus and hemodialysis patients are expected to have hypertension and of around 10% of pregnant women have hypertension, which increases preeclampsia; the most important medical problem that threatened the life of maternal and neonatal. Previous studies showed that genetic factors could play an important role in predicting hypertension. Recently, a novel soluble flavin adenine dinucleotide (FAD)-dependent amine oxidase, called renalase, found to decrease blood pressure by degrading catecholamines. It is secreted by the kidney and is found in the heart, small intestine, skeletal muscle, endothelium, and nervous system. Renalase polymorphism of the renalase gene may affect the renalase activity and increase susceptibility to some diseases. This review highlights the structure, function, polymorphisms of renalase, and its association with hypertension in hemodialysis, cardiovascular, preeclampsia, and diabetes mellitus patients. As a conclusion, the rs10887800, rs2576178, and rs2296545 renalase gene polymorphism could thus be a risk factor for hypertension.

Keywords: RNLS, Hypertension, Diabetes, Hemodialysis, CVD, Polymorphism.

1. Introduction
Hypertension is a significant public health associate with the risk of cardiovascular diseases (CVD) including atherosclerosis and coronary heart diseases [1–3] On the other hand, there is a close association between blood pressure and kidney diseases including chronic kidney disease (CKD) which is usually accompanied by CVD [4]. High blood pressure associates with a complication in the brain and eyes [5]. Recently, it has been reported that hypertension associated with developing preeclampsia disease; the main cause of death in the fetus and mother during pregnancy [6–8] High blood pressure is also causes complications of type 2 diabetes, such as coronary artery disease, peripheral arterial disease, stroke, diabetic nephropathy, neuropathy, and retinopathy [9–13] Thereby, hypertension is a multifactorial disorder caused by many genes and environmental factors. Several studies demonstrated the association between polymorphism in some genes and the higher risk of hypertension[14]. In 2005, Xu and Desir discovered a novel soluble flavin adenine dinucleotide (FAD)-dependent amine oxidase enzyme, called Renalase, that acted as blood pressure and cardiac function regulator [15,16] Renalase often referred to as monoamine Oxidase-C (MAO-C) that involves in catecholamine metabolism but its
activity does not affect by inhibitors of MAO (i.e., pargyline and clorgyline). [15,17] High renalase activity has been observed in catecholamines, such as epinephrine, dopamine, and norepinephrine, while its low activity determined in some amines namely; serotonin, benzyl amine, tyramine, and methylamine [18]. In this review, we highlight the association between polymorphism of renalase gene and some diseases such as hypertension.

2. Human Renalase

2.1. Structure of Renalase
Renalase mainly distributes in kidney tissues and has been detected in the heart, small intestine, skeletal muscle [16], endothelium and nervous system [19]. Renalase, the active form of Prorenalase, decreases the blood pressure by degrading the catecholamines (i.e., dopamine, epinephrine, and norepinephrine) [14,18,20,21] Recent data have shown that renalase deficiency is associated with an increase of blood pressure as well as catecholamine level [22]. Renalase has seven isoforms [23] arises from some transcript variants of the renalase gene (RNLS). These isoforms have various roles in the body and they are important to detect the amount of their corresponding proteins [14][24]. Among these, human renalase1 (h Renalase 1) is the most abundant form in the body [15] and well maintained with sequence homology in chimpanzee and cyanobacteria at which 95% and 23%, respectively, of amino acids were identified. Its structure contains a fragment of 1–17 amino acids on putative signal peptide. The sequence 75–335 includes flavine adenine dinucleotide (FAD)-binding domain (amino acids 3–42) and an amine oxidase domain, as shown in Figure 1 [25]. Although renalase belongs to the super-family of flavoprotein that implicates oxidase and monoxidase enzymes. The catalytic residues in renalase structure differ from MAO-A and MAO-B because there is no need for critical residues for their amino-oxidation, unlike MAO-A and MAO-B. This suggest that hRenalase1 metabolizes catecholamines differ from traditional monoamine oxidases [26]. Knowing the structure of renalase has significantly offered the chance to better characterize the molecular mechanisms of its function and to create synthetic analogs with potential therapeutic relevance [27].

Figure 1. Three-dimensional structure of renalase. (A) Represent overall structure: the blue color region is putative substrate-binding domain (PDB accession number: 3QJ4); (B) higher resolution crystal structure of active binding domain: FAD is seen along with residues sharing hydrogen bonds with FAD and the main residues above FAD lining the cavity [25].

2.2. Function of Renalase
Renalase secreted into the blood stream by the kidney which acts as blood pressure regulator through mechanisms depending on nicotinamide adenine dinucleotide (NADH), sodium and phosphate excretion regulators [15]. Previous study reported natural compounds as substrates of renalase namely; o-methylidopa, dobutamine, and isoproterenol[28]. The secreted renalase can be evaluated in plasma and circulating, where it degrades catecholamine. In this regards, low renalase and high catecholamine levels have been observed in chronic renal failure and nephrectomy patients. When animals treated with
renalase, the blood pressure and catecholamine dropped down which could explain the action of renalase as energy metabolism regulator inside the cell [29]. Recently, renalase acts as a cytokine or pro-survival signal that supplies protection to cells, tissues, and organs through binding to the receptor of the cell membrane. The plasma membrane calcium adenosine triphosphates isoform PMCA4, stimulates some intracellular signaling pathways such as the protein kinase B (AKT), extracellular- signal-regulated kinase (ERK), and signal transducer and activator of transcription 3 (STAT3) pathways[23]. On the other hand, the fast growth of malignant cells in several tumors may be due to dysregulated in renalase signaling pathway that stimulates the growth-related gene expression. For instance, the mortality increased in pancreatic cancer and melanoma patients when renalase gene expression increased [29],[30]. Treatment with renalase decreased the damage in several cases such as myocardial infarction [31], ischemic tubular necrosis[32], and acute pancreatitis [15]. However, deficiency of renalase in acute and chronic renal injury was treated by cisplatin, which is substituted by renalase administration [15],[32].

2.3. Renalase gene polymorphism
Renalase known as (RNLS) comprises of 311,000 base pairs (bp) and has 13 exons situated in chromosome 10 (q23.33) [33,34]th 342 amino acids at molecular weight of 37.8 kDa [35]. RNLS gene is highly polymorphic, where several single nucleotide polymorphisms (SNPs) characterized [33]. The latest results showed the association between polymorphisms of the RNLS gene (i.e., rs2296545, rs2576178, and rs10887800) and many diseases. The rs2296545 (C/G) locates in the second exon of RNLS which affects on the Asp37Glu amino-acid substitution and thus on the gene function [36]. The polymorphism rs2576178 (G/A) locates at the 5-flanking region while rs10887800 polymorphism situate at the intron 6, these polymorphisms might affect regulation and gene expression of RNLS [37].

2.4. Impact of Renalase gene polymorphism on some diseases

2.4.1. Hemodialysis disease
Several factors increase the risk of hypertension, including high sympathetic activity, erythropoietin, hypervolemia, and recently genetic factor. In the last decade, renalase and its role in the regulation of blood pressure have been extensively studied, of which patients with hemodialysis showed a higher risk of hypertension [38]. Previous studies revealed an association between increased blood pressure in hemodialysis patients and renalase gene polymorphisms. Stec et al., studied the genotyping of rs10887800 and rs2576178 by restriction fragment length polymorphism-polymerase chain reaction (RFLP-PCR). In a study for Hemodialysis patients with hypertension (n=369), patients with G allele of SNPs have showed higher risk of hypertension [39]. In another study by Kiseljakovic et al., 137 individuals from Bosnia and Herzegovina were examined and showed that (rs2576178) polymorphism of RNLS has no effect on increasing the risk of hypertension in hemodialysis patients.[38]. Furthermore, a study by Stec et al that found no significant differences in the genotype distribution of rs10887800 and rs2576178 between hemodialysis patients and control groups and yet rs10887800 affect the level of renalase. Patients with AA genotypes of rs10887800 had low renalase activity compared to AG, GG genotypes [34]. An Egyptian study on hypertension patients with end-stage renal disease, under hemodialysis, revealed that patients with (rs10887800) AA genotype and (rs2576178) GG genotype had a higher risk of end-stage renal disease complication [17]. Generally, the rs10887800 and rs2576178 polymorphism increase the risk of hypertension in hemodialysis patients, however, this result needs further investigation.

2.4.2. Cardiovascular disease
In 2016, Stec et al. showed that the rs10887800 plays a significant role in the pathogenesis of chronic artery disease (CAD) in hemodialysis patients. Patients with GG genotypes had a higher risk of CAD (OR 2.66, 95 % CI, 1.10–4.02), therefore, it can be considered a good predictive factor of CVD, while
rs2576178 polymorphism had no impact on the risk of CVD in the same hemodialysis patients[18]. A recent study in 449 CVD patients and 507 healthy subjects revealed that the patients with G allele or with GG genotypes had higher CVD risk [40]. Farzaneh-Far et al. found that the rs2296545 polymorphism (Glu37Asp) links to ischemia, cardiac hypertrophy, cardiac dysfunction in coronary artery patients [29], this association was confirmed in 657 of females with aortic stenosis. It was observed that Aortic Stenosis female patients with Asp37 variant of the rs2296545 had higher risk of left ventricle hypertrophy [41]. Thus, the renalase gene polymorphism is associated with an increased risk of CVD.

2.4.3. Preeclampsia

Ten percent of pregnancies suffer a hypertensive disorder that implicates on many cases such as chronic hypertension, hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, gestational hypertension, eclampsia and preeclampsia (PE)[42,43] Moreover, 2-8% of pregnancies suffer preeclampsia, which characterized by hypertension and proteinuria in the second half of pregnancy [19,44–47] Despite the developments in antenatal and neonatal care, PE continues to be one of the major causes of maternal and neonatal morbidity and mortality worldwide [48]. PE patients showed high catecholamine levels, high blood pressure and low serum renalase levels [22] [49]. Renalase reduces blood pressure by inhibiting the contraction of the cardiac muscle and negatively affecting the defense mechanism which allows the peripheral levels of vascular tone to rise[50]. A previous study mentioned that the risk of PE is increased in pregnancy with GG of rs10887800 polymorphism [27].

Binnur et al. studied two polymorphisms of RNLS (rs10887800 and rs2576178) on 110 women with PE and 102 normal pregnant. The results revealed that G allele and GG genotype of rs10887800 increases PE risk; with increasing systolic and diastolic blood pressure. As for rs2576178 polymorphism, the study revealed that this SNP has no effect on PE risk and the GG genotype of rs2576178 increases systolic blood pressure only [22]. Another study by Niadany showed the relation between RNLS rs10887800 polymorphism and its serum level with susceptibility to PE which were examined on 150 women using real-time PCR to detect rs10887800 and enzyme-linked immunosorbent assay (ELISA) technique to evaluated serum Renalase. This study revealed that the rs10887800 polymorphism was associated with low serum renalase level and increased PE risk [51]. As a conclusion, the RNLS polymorphism increases the risk of PE.

2.4.4. Diabetes Mellitus

Most of diabetic patients suffer high blood pressure [8]. However, the association between hypertension and diabetes mellitus remains unrevealed, but identification of genetic factors of hypertension is important for the prediction of CVD risk. A study by Zhao et al. showed that polymorphism of RNLS (rs2576178 and rs2296545) are linked with hypertension [52,53] Monika et al, investigated three SNPs of RNLS (rs2576178, rs10887800, and rs2296545) in 892 type 2 diabetes patients (with and without hypertension) and 400 normal subjects. The results revealed that the C allele of rs2296545 was associated with increased susceptibility of hypertension in type 2 diabetic patients. They also observed significant differences in genotype distribution of rs2576178 between diabetic and healthy subject, but no significant difference between hypertensive type 2 diabetic and normotensive type 2 diabetic patients. Moreover, the percentage of GG genotype of diabetic with hypertension who had a history of stork was 66%. These results were confirmed in stroke patients without diabetes. Therefore diabetic patients with G allele have a higher risk of stork [37]. However, another study revealed that the frequency of GG genotype for rs2576178 and rs10887800 was higher in diabetic patients with hypertension compared to those without hypertension. They also found that the GG genotype was higher in both diabetic groups compared to normal subjects [54]. A recent study investigated the association between rs2576178, rs10887800, and renalase level with gestational diabetes. The results exhibited no significant difference in the serum levels of renalase between gestational diabetes and the control group (p>0.05). They also showed that the G allele of rs10887800 associated with an increased risk of gestational diabetes mellitus (OR=2.79), while weak association with polymorphism of rs2576178 [55]. The baseline characteristics
of all these studies are shown in Table 1. As a summary, there is a possible relationship between the polymorphism of the renalase gene and diabetes.

**Table 1.** Characteristic of case-control studies on renalase rs2296545, rs2576178, rs10887800 polymorphism and the risk of hypertension in diabetes mellitus patients.

| SNP        | Country       | Genotypes distribution for cases | Genotypes distribution for normal | Genotyping method | References                      |
|------------|---------------|---------------------------------|-----------------------------------|-------------------|---------------------------------|
| rs10887800 | Poland        | 223/411/258 n=892               | 100/185/115 n=400                 | PCR–RFLP method*  | (Buraczynska et al., 2011)[37] |
|            | Egypt         | 44/118/18 n=180                 | 6/15/29 n=50                      | PCR method**      | (Refaie and Elewa, 2013)[54]   |
|            | Pakistan      | 27/44/28 n=99                   | 10/32/57 n=99                     | PCR-RFLP method*  | (Fatima et al., 2017)[55]      |
| rs2576178  | Poland        | 129/415/348 n=892               | 31/181/188 n=400                  | PCR–RFLP method*  | (Buraczynska et al., 2011)[37] |
|            | Egypt         | 103/42/35 n=180                 | 8/12/30 n=50                      | PCR method**      | (Refaie and Elewa, 2013)[54]   |
|            | Pakistan      | 12/38/49 n=99                   | 7/29/63 n=99                      | PCR-RFLP method*  | (Fatima et al., 2017)[55]      |
| rs2296545  | Poland        | 182/386/324 n=892               | 88/204/108 n=400                  | PCR–RFLP method*  | (Buraczynska et al., 2011)[37] |

* RFLP: Restriction fragment length polymorphism, **PCR: Polymerase chain reaction

3. Conclusion
Renalase is an amine oxidase enzyme that acts as a regulator of blood pressure. Polymorphism of Renalase gene is a predictive factor of some diseases, such as preeclampsia and cardiovascular diseases especially in patients with hypertensive diabetes and chronic kidney disease. Renalase can be used as a novel medicine to treat and prevent hypertensive.

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