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Polymorphisms of renalase gene in Egyptian prevalent hemodialysis patients with and without hypertension

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Abstract

Introduction: Chronic kidney disease (CKD) is considered a very serious worldwide health problem. Renalase is flavin adenine dinucleotide-dependent amine oxidase. It is secreted from the kidney. Renalase release in blood to regulate cardiac function as systemic blood pressure. Relative decrease in renalase enzyme in patients with CKD can be a cause of occurrence of hypertension in CKD patients and an increased risk of cardiovascular complications in end stage renal disease (ESRD) patients.

Objectives: In this study, we tried to study the association of the two renalase gene polymorphisms rs2296545 and rs10887800 in ESRD patients and occurrence of hypertension in Egyptian prevalent hemodialysis (HD) patients.

Patients and Method: Rs2296545 polymorphism and rs10887800 polymorphism were genotyped in 337 subjects that divided into 2 groups: group I; 252 prevalent HD patients that subdivided into two subgroups: Subgroup Ia included 187 subjects with hypertension and subgroup Ib included 65 subjects without hypertension. Group II included 85 healthy control subjects. We used the technique of polymerase chain reaction (PCR), followed by cleavage with Eco81 I restriction endonuclease for rs2296545 polymorphism and Pst I restriction endonuclease for rs10887800 polymorphism.

Results: Comparison showed that rs2296545 CC genotype showed significant increase in HD patients when compared to healthy control and that rs2296545 CC genotype showed significant increase in HD patients with hypertension than those without hypertension. In addition, rs10887800 AA genotype showed significant increase in HD patients when compared to healthy control.

Conclusion: Renalase gene polymorphisms might have role in pathophysiology of ESRD especially in hypertensive patients.

Keywords: Gene polymorphism, Single nucleotide polymorphisms, Renalase enzyme, Chronic kidney disease, End stage renal disease, Hypertension

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Introduction

Chronic Kidney Disease (CKD) is considered as a multifactorial disease resulting from complex interaction of many genetic and environmental factors. Familial clustering of CKD, ESRD has been identified (1,2). Hypertension has long been an established risk factor for both CKD and ESRD (3), also hypertension can be a consequence of CKD; with advancing CKD, hypertension can be caused by various mechanisms as increased the sympathetic activity, expansion of the extracellular volume and activation of renin angiotensin system (4).

Renalase was discovered in 2005 as a novel flavin adenine dinucleotide (FAD) dependent amine oxidase, it is produced mainly by the kidneys and is excreted into blood directly in contrast to well-known amine oxidases containing FAD (5). It metabolizes circulating catecholamines therefore; renalase may regulate cardiac function, blood pressure and sympathetic tone (6). Other FAD dependent amine oxidases include amine oxidase [monoaminooxidase (MAO)] and polyamide oxidase. It was found that renalase enzyme does not deactivated by clorgyline and pargyline which are known MAO inhibitors. Due to these differences, renalase is called (MAO-C) (7). Renalase enzyme protein was found to be encoded by a gene with 10 exons located on chromosome 10q23.33. There are many isoforms of renalase but the major one contains 342 amino acids with signal peptide, FAD binding domain, and MAO domain (8).

It was found that rise levels of catecholamines, that results in subsequent rise in systolic blood pressure (SBP), is the main stimulant of activation of renalase enzyme, through at least 3 distinct mechanisms, catecholamines regulate renalase: catecholamines acutely (within 1 minute) stimulate enzymatic activity in blood circulation, increase preformed renalase secretion within 15 minutes, and cause activation of gene transcription within 12 hours. Renalase activity does not correlate with diastolic and mean blood pressure (9).

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Insufficiency of renalase predispose to hypertension (10). Patients with ESRD have a significant renalase enzyme deficiency that result in decrease degeneration of catecholamines and, as a result, leads to increase their levels causing elevated stimulation of the sympathetic nervous system, which is related to a high risk of many cardiovascular complications. These observations were confirmed by animal studies in rats after 5/6 nephrectomies (7). Also, parenteral injection of renalase enzyme in rats decreases blood pressure, cardiac contractility and heart rate (10). Renalase also can reduce cell damage caused by ischemia, improve cell tolerance to ischemia and reduce myocardial cell apoptosis (11).

Many polymorphisms of renalase gene has been shown to cause abnormal gene expression and has been reported in association with different diseases. Abnormal gene expression can affect enzymatic activity of renalase leading to dysfunction of renalase and hence catecholamine metabolism (12). rs2296545 single-nucleotide polymorphism is associated with cardiac hypertrophy, dysfunction and ischemia (8), polymorphism of rs10887800 was found to be associated with stroke (13), association of hypertension with Single nucleotide polymorphisms of rs10887800, rs2296545 and rs2576178 was discussed in different studies with variable results (6,7,12-15)

In this study, we investigate whether the two known renalase gene polymorphisms rs2296545 and rs10887800 are associated with developing ESRD and occurrence of hypertension in Egyptian prevalent hemodialysis (HD) patients.

Implication for health policy/practice/research/ medical education

In a study on 337 subjects, which divided into two groups; group I included 252 ESRD patients on regular hemodialysis in Ain Shams University Hospitals, they were subdivided into : group Ia that included 187 patients with hypertension and group Ib included 65 subjects without hypertension. Group II is the control group that included 85 apparently healthy individuals that match in age and sex, we found renalase gene polymorphisms might have role in pathophysiology of ESRD especially in hypertensive patients.

Materials and Methods

Our study was conducted in the period from September 2017 to September 2018 as case control study, on 337 subjects, divided into two groups; group I included 252 ESRD patients on regular hemodialysis in Ain Shams University Hospitals, they were subdivided into : group Ia that included 187 patients with hypertension and group Ib included 65 subjects without hypertension. Group II is the control group that included 85 apparently healthy individuals that match in age and sex. Following the instructions of ethical committee of Ain Shams university, informed consent was taken from all participants.

Full history was taken from all the participants as well as full clinical examination were done to all of them. Hypertension was diagnosed, as according to K/DOQI 2005 guidelines on cardiovascular disease in dialysis patients, as SBP ≥140, diastolic blood pressure (DBP) ≥90 (where Predialysis blood pressure goal is <140/90, measured in sitting position) (16), or receiving antihypertensive medications. Blood pressure measurement was done at least 5 minutes before the needles for dialysis access are placed, we reported the average values of predialysis systolic and DBP readings for about one month. The standard equation used to calculate mean arterial pressure was:

Diastolic blood pressure + 1/3 (SBP - DBP)

We genotyped Rs2296545 polymorphism and rs10887800 polymorphism in 337 subjects, by using polymerase chain reaction (PCR), followed by cleavage with Eco81 I and Pst I restriction endonucleases.

By using EDTA whole blood samples, genomic DNA was extracted using Promega DNA purification kit (Promega Corporation, USA). The NanoDrop™ 1000 spectrophotometer was used to assess the purity and integrity of the extracted DNA, by using the 260 and 280 nm filters. Genotypes of the studied polymorphisms were determined by polymerase chain reaction with primers specific for renalase gene polymorphisms. The composition of a typical 30 µL PCR reaction included: 300 ng genomic DNA, 10 mM TRIS–HCl buffer (pH 8.3), 50 mM KCl, 1.5 mM MgCl2, 200 µM each of ditag primer, 2 U Taq of DNA polymerase. Reagents were brought from MBI Fermentas Company (St Leon-Rot, Germany). Amplification of DNA was done in a PTC200 thermocycler (MJ Research, Inc. Waltham, MA, USA).

Polymerase chain reaction steps were as follow: initial DNA denaturation step for 6 min at 94–96°C, followed by 30–35 cycles of amplification, DNA denaturation for 1 min at 96°C, annealing of primers for 1 minute in the temperature dependent on used primers, DNA chain elongation (extension) for 1–2 minutes at 72°C. The last step of DNA chain elongation lasted 7–10 minute at 72°C. Then, the products of PCR were digested with the Eco81 I and Pst I restrictive endonucleases at a temperature of 37°C for 6–10 hours. The reaction products were separated by using electrophoresis in 2 % agarose gel.

Rs2296545 polymorphism in the renalase gene

This polymorphism consisted of a substitution of a SNP G→C rs2296545 in exon 2 that leads to substitution of aspartic acid amino acid to glutamic acid amino acid at codon 37 (Asp37Glu) and this might affect the function of gene product. To identify this polymorphism, we amplified the gene using primers: forward 5'-GGAAGTCCCCGATCACGTGAC -3' and reverse 5'-

T GCTGTGTGGGACAAGGCTGA-3' using 5 U of Eco81 I as a restriction enzyme.

Rs10887800 polymorphism in the renalase gene

In this polymorphism, there is a substitution of a SNP guanine replacing adenine (A→G) in intron 6 of the gene. The primers used in the amplification step: forward: 5'- CAGGAAA GAAAGAGTTGACAT-3' reverse: 5'- AAGTTGTTCCAGCTACTGT- 3'. The temperature used for binding of the primers in PCR reactions was 60°C. Polymerase chain reaction product length was 554 bp and after digestion with restrictive endonuclease Pst I, fragments 554 bp for AA genotype and 415 + 139 bp for the GG genotype were observed.

Ethical issues

The study was in accordance with the Declaration of Helsinki. All participants gave their informed consent to enter the study. The study has been approved by the ethical committee of Faculty of Medicine, Ain Shams University.

Statistical analysis

Statistical analyses were performed using the SPSS Statistics for Windows, version 20 (SPSS, NY, USA). Data are presented as mean, standard deviation (SD) and ranges when parametric and median with inter-quartile range (IQR) when non-parametric. Qualitative variables were presented as number and percentages. Differences between two independent groups were evaluated using the chi-square test (for categorical variables) and the Student's *t* test for quantitative parametric data while with non-parametric data was done by using Mann-Whitney test. Hardy–Weinberg equilibrium was assessed by a goodness-of-fit chi-square test. The risk for developing ESRD and hypertension in presence of an allele was assessed by calculating the odds ratio with 95% confidence interval. *P* value < 0.05 was considered statistically significant.

Results

Mean age of ESRD group was 50.00 ± 9.25 years, while in the control group 49.58 ± 7.09 years, *P* value = 0.703. ESRD group included 141 males, 111 females, control group included 48 males and 37 females, *P* value = 0.933. Table 1 shows the demographic, clinical data and laboratory data of the ESRD patients which were divided into ESRD with hypertension (n=252) and ESRD without hypertension (n=65).

Results for rs2296545 genotype

The studied groups were classified by genotype and allele frequency at rs2296545 locus and comparison study was done. Genotype CC was higher significantly in dialysis group when compared with healthy subjects with Odds ratio 1.8967 (95% CI: 1.0705-3.3604) while GG genotype was increased in control group than dialysis group with odd ratio 0.4312 (95% CI: 0.2486-0.7479) (Table 2). CC genotype showed also significant increase in dialysis patients with hypertension than those without hypertension; The Odds ratio for the hypertensive group was 2.7387 (95% CI: 1.3956-5.3747), Whereas GG genotype might had protective effect as it was increased in dialysis patient without hypertension than dialysis patients with hypertension with odd ratio 0.4086 (95% CI: 0.2086-0.8003) (Table 3). Dialysis patients with hypertension has higher CC genotype than control group with odds ratio 2.3784 (95% CI: 1.3213-4.2813) (Table 4, Table 5).

Results for rs10887800 genotype

The studied groups were classified by genotype and allele frequency at rs10887800 locus and comparison study was done. Genotype AA was significantly higher in-group I (dialysis patients) when compared with healthy subjects, odds ratio for AA genotype in dialysis group was 2.462 (95% CI: 1.3656-4.4369), while GG genotype had protective effect with odd ratio 0.548 (95% CI: 0.3217-

Table 1. Demographic, clinical and laboratory data of the ESRD groups

	ESRD with hypertension n = 187	ESRD without hypertension n = 65	Test value	P value
Age (y)	50.39 ± 9.03	48.88 ± 9.84	1.248[a]	0.455
Male (n, %)	35 (53.8%)	106 (56.7%)	0.158[b]	0.921
Duration of dialysis (y)	4.49 ± 1.71	4.29 ± 1.35	-0.863[a]	0.389
Dry weight (kg)	80.64 ± 11.68	83.92 ± 14.41	1.835[a]	0.068
SBP (mm Hg)	151.62 ±13.09	130.15 ± 6.97	-12.606[a]	**0.000**
DBP (mm Hg)	91.84 ± 6.98	75.32 ± 5.76	-17.152[a]	**0.000**
MBP (mm Hg)	111.75 ± 8.57	93.58 ± 5.50	-15.965[a]	**0.000**
Hg (gm/dL)	8.96 ± 1.49	8.73 ± 1.43	-1.097[a]	0.274
Corrected Ca (mg/dL)	8.67 ± 0.74	8.55 ± 0.67	-1.201[a]	0.231
Po4 (mg/dL)	4.98 ± 0.83	5.11 ± 0.52	1.199[a]	0.232
Intact PTH (pg/mL), median (IQR)	390 (225 540)	421 (350 - 530)	-1.127[c]	0.260

[a] Independent t-test, [b]Chi-square test, [c]Mann-Whitney test.

Table 2. The distribution of genotypes and alleles frequencies of rs2296545 polymorphism in ESRD group and control group

		ESRD (n = 252)	Healthy control (n = 85)	Odds ratio	(95% CI)	*P* value
RS545	CC	89 (35.3%)	19 (22.4%)	CC/(CG+GG) 1.8967	(1.0705-3.3604)	0.028
	CG	117 (46.4%)	37 (43.5%)	CG/(CC+GG) 1.1243	(0.6853-1.8447)	0.642
	GG	46 (18.3%)	29 (34.1%)	GG/(CC+CG) 0.4312	(0.2486-0.7479)	0.003
Allele	C	295 (58.5%)	75 (44.1%)	1.7879	(1.2589-2.5392)	0.001
	G	209 (41.5%)	95 (55.9%)	0.5593	(0.3938-0.7944)	0.001

Table 3. The distributions of genotypes and alleles frequencies of rs2296545polymorphisms in hypertensive and normotensive ESRD groups

		ESRD with hypertension (n = 187)	ESRD without hypertension (n = 65)	Odds ratio	(95% CI)	*P* value
RS545	CC	76 (40.6%)	13 (20.0%)	CC/(CG+GG)2.7387	(1.3956-5.3747)	0.003
	CG	84 (44.9%)	33 (50.8%)	CG/(CC+GG) 0.7908	(0.4494-1.3917)	0.416
	GG	27 (14.4%)	19 (29.2%)	GG/(CC+CG) 0.4086	(0.2086-0.8003)	0.009
Allele	C	236 (63.1%)	59 (45.4%)	2.0580	(1.3738-3.0829)	0.001
	G	138 (36.9%)	71 (54.6%)	0.4859	0.3244-0.7279	0.001

Table 4. The distributions of genotypes and alleles frequencies of rs2296545 polymorphisms in hypertensive ESRD group and control group

		ESRD with hypertension (n = 187)	Healthy control (n = 85)	Odds ratio	(95% CI)	*P* value
RS545	CC	76 (40.6%)	19 (22.4%)	CC/(CG+GG)2.3784	(1.3213-4.2813)	0.004
	CG	84 (44.9%)	37 (43.5%)	CG/(CC+GG) 1.0580	(0.6311-1.7736)	0.830
	GG	27 (14.4%)	29 (34.1%)	GG/(CC+CG) 0.3259	(0.1777-0.5974)	0.000
Allele	C	236 (63.1%)	75 (44.1%)	2.1662	(1.4985-3.1313)	0.000
	G	138 (36.9%)	95 (55.9%)	0.4616	(0.3194-0.6673)	0.000

Table 5. The distributions of genotypes and alleles frequencies of rs2296545 polymorphisms in non-hypertensive ESRD group and control group

		ESRD without hypertension (n = 65)	Healthy control (n = 85)	Odds ratio	(95% CI)	*P* value
RS545	CC	13 (20.0%)	19 (22.4%)	CC/(CG+GG)0.8684	(0.3927-1.9204)	0.728
	CG	33 (50.8%)	37 (43.5%)	CG/(CC+GG) 1.3378	(0.6996-2.5584)	0.379
	GG	19 (29.2%)	29 (34.1%)	GG/(CC+CG) 0.7976	(0.3970-1.6025)	0.525
Allele	C	59 (45.4%)	75 (44.1%)	1.0526	(0.6650-1.6661)	0.827
	G	71 (54.6%)	95 (55.9%)	0.9500	(0.6002-1.5038)	0.827

0.9339) (Table 6). Allele A was higher in dialysis group than control with odd ratio 1.8445 (95% CI: 1.2975-2.6221) whereas Allele G was lower in dialysis group than control with odd ratio 0.5422 (95% CI: 0.3814-0.7707) (Table 6). AA genotype showed significant increase in dialysis patients with hypertension in comparison to control group, with odd ratio 2.800 (95% CI: 1.5274-5.1328) (Table 8). Allele A expression was increased in both groups of dialysis patients (hypertensive and non-hypertensive) in comparison to control group (Tables 8 and 9). There was no significant increase in AA genotype when comparing ESRD with hypertension to ESRD without hypertension (Table 7).

Discussion

Hemodialysis patients are at higher risk of developing hypertension. There are many factors that contributing to hypertension in this population: hypervolemia, increased sympathetic activity, erythropoietin and recently studied genetic factors (3). In the last decade, renalase enzyme and its role in blood pressure regulation have been studied widely (3).

In this study, we analyzed genotype and allele frequencies of rs2296545 polymorphism and rs10887800 polymorphism of renalase gene in patients on regular hemodialysis and control group of healthy individuals in order to study the association between renalase gene rs2296545 polymorphism and rs10887800 polymorphism with ESRD and hypertension in hemodialysis patients.

Our study showed that rs2296545 CC genotype was significantly increased in hemodialysis patients when compared to healthy control with odds ratio 1.8967 (95% CI: 1.0705 - 3.3604), while GG genotype was higher in healthy control than hemodialysis patients. In addition,

Table 6. The distribution of genotypes and alleles frequencies of rs10887800 polymorphism in ESRD group and control group

		ESRD (n = 252)	Healthy control (n = 85)	Odds ratio	(95% CI)	*P* value
RS800	AA	96 (38.1%)	17 (20.0%)	AA/(GA+GG) 2.462	(1.3656-4.4369)	0.003
	GA	98 (38.9%)	38 (44.7%)	GA/(AA+GG) 0.787	(0.4788-1.2937)	0.345
	GG	58 (23.0%)	30 (35.3%)	GG/(AA+GA) 0.548	(0.3217-0.9339)	0.027
Allele	A	290 (57.5%)	72 (42.4%)	1.8445	(1.2975-2.6221)	0.001
	G	214 (42.5%)	98 (57.6%)	0.5422	(0.3814-0.7707)	0.001

Table 7. The distributions of genotypes and alleles frequencies of rs10887800 polymorphisms in hypertensive and normotensive ESRD groups

		ESRD with hypertension (n = 187)	ESRD without hypertension (n = 85)	Odds ratio	(95% CI)	*P* value
RS800	AA	77 (41.2%)	19 (29.2%)	AA/(GA+GG)1.6947	(0.9220-3.1150)	0.089
	GA	66 (35.3%)	32 (49.2%)	GA/(AA+GG) 0.5625	(0.3177-0.9960)	0.048
	GG	44 (23.5%)	14 (21.5%)	GG/(AA+GA) 1.1209	(0.5672-2.2149)	0.743
Allele	A	220 (58.8%)	70 (53.8%)	1.2245	(0.8195-1.8297)	0.323
	G	154 (41.2%)	60 (46.2%)	0.8167	(0.5465-1.2203)	0.323

Table 8. The distributions of genotypes and alleles frequencies of rs10887800 polymorphisms in hypertensive ESRD group and control group

		ESRD with hypertension (n = 187)	Healthy control (n = 85)	Odds ratio	(95% CI)	*P* value
RS800	AA	77 (41.2%)	17 (20.0%)	AA/(GA+GG) 2.800	(1.5274 - 5.1328)	0.001
	GA	66 (35.3%)	38 (44.7%)	GA/(AA+GG) 0.675	(0.4002 -1.1374)	0.140
	GG	44 (23.5%)	30 (35.3%)	GG/(AA+GA) 0.564	(0.3227 - 0.9862)	0.045
Allele	A	220 (58.8%)	72 (42.4%)	1.9444	(1.3466 - 2.8077)	<0.001
	G	154 (41.2%)	98 (57.6%)	0.5143	(0.3562 - 0.7426)	<0.001

Table 9. The distributions of genotypes and alleles frequencies of rs10887800 polymorphisms in non-hypertensive ESRD group and control group.

		ESRD without hypertension (n = 65)	Healthy control (n = 85)	Odds ratio	(95% CI)	*P* value
RS800	AA	19 (29.2%)	17 (20.0%)	AA/(GA+GG) 1.6522	(0.7775 -3.5109)	0.192
	GA	32 (49.2%)	38 (44.7%)	GA/(AA+GG) 1.1994	(0.6277 to 2.2918)	0.582
	GG	14 (21.5%)	30 (35.3%)	GG/(AA+GA) 0.5033	(0.2401 to 1.0548)	0.069
Allele	A	70 (53.8%)	72 (42.4%)	1.5880	(1.0026 to 2.5151)	0.049
	G	60 (46.2%)	98 (57.6%)	0.6297	(0.3976 - 0.9974)	0.049

we found that rs2296545 CC genotype showed significant increase in hemodialysis patients with hypertensions than those without hypertension with Odds ratio 2.7387(95% CI: 1.3956-5.3747) and that GG genotype was higher in hemodialysis patients without hypertensions than those with hypertension. Thus, renalase gene polymorphism rs2296545 CC genotype is a risk factor for both developing ESRD, and occurrence of hypertension in ESRD patients.

Our study comes in concordance with the study by Ahlawat et al (4) in this study on 287 subjects from the North Indian population; they found a relation between renalase gene polymorphism rs2296545 CC genotype with hypertension with nephrosclerosis. The odds ratio for rs2296545 CC genotype in hypertensive nephrosclerosis were2.11 (95% CI, 1.01 to 4.42; $P = 0.03$) (CC versus CG + GG) and 2.55 (95% CI, 1.03 to 6.42; $P = 0.02$) (CC versus GG) compared to controls

It was postulated that the renalase enzyme activity is probably regulated by its genotypes and the polymorphism rs2296545 CC genotype and its effect in amino acids substitution is related to renalase enzymatic activity (low activity in CC genotype and high activity in GG genotype). Thus, single nucleotide polymorphism rs2296545 CC genotype is related to lower renalase activity, has a potentially higher sympathetic nervous system activity and poor CVD prognosis (4,8), might affect the development of CKD especially hypertensive nephrosclerosis (8).

Our results also are in agreement with Zhao et al, who studied the association of single nucleotide polymorphisms of the renalase gene with the primary hypertension in the northern Han Chinese population, in a group of 2586 subjects (1317 patients with essential hypertension and 1269 healthy controls) and found association between rs2296545 CC genotype and essential hypertension (14).

Buraczynska et al also found that the occurrence of the

C allele of rs2296545 polymorphism was also more in diabetes patients with hypertension than in patients with normal blood pressure and controls (13).

Whereas Fava C et al studied more than 5000 subjects in a Swedish urban-based cohort, found no relation between rs2296545 gene polymorphism and cardiovascular events as hypertension suggesting that in Caucasian population these polymorphisms are of negligible importance (17).

Regarding rs10887800: we found that AA genotype was higher significantly in patients on dialysis (group I) when compared to the healthy subjects, Odds ratio for AA genotype in dialysis group was 2.462 (95% CI: 1.3656-4.4369). While GG genotype was more prevalent in healthy subjects than dialysis group with odd ratio 0.548 (95% CI: 0.3217-0.9339), so GG genotype might have protective effect. There was no significant difference in AA or GG genotype prevalence when comparing hypertensive ESRD patients with normotensive ESRD patients.

Allele A expression was increased in both groups of dialysis patients (hypertensive and non-hypertensive) in comparison to control group. AA genotype was higher significantly in patients on dialysis with hypertension when compared to control group, with odd ratio 2.800 (95% CI: 1.5274-5.1328).

Our results are in agreement with Kandil et al. (15) in their study on 281 Egyptian subjects divided equally into two groups; ESRD patients on hemodialysis with or without hypertension, and healthy control group, they found that the risk of developing ESRD was more among AA genotype for the rs10887800 with odds ratio 3.05, (95 CI %: 1.558-5.971) and that no difference in genotypes between hypertensive and normotensive ESRD groups.

On the other hand, Stec et al (7) in a study on 421 Polish Caucasian ESRD patients (278 hypertensive patient, 143 non hypertensive) found that G allele carriers for rs10887800 were significantly higher in hypertensive ESRD patients in comparison to non hypertensive ESRD patients with odds ratio 1.76 (95% CI: 1.159-2.667). Higher frequency of AA genotype was found in normotensive patients (44.1% versus 30.9% in hypertensive ESRD, P = 0.008) highlighting its possible protective rule. No comparison was control group was done in this study.

Whereas in study of Abdallah et al (12) on 139 Egyptian patients on regular hemodialysis and 50 healthy subjects as a control group, it was found that a statistically higher significant frequency of GG genotype for the rs10887800 was found in ESRD patients group (26% vs 12% in control group; p-value 0.04), while in our study GG genotype was higher in healthy group and AA genotype was risky for ESRD. But similar to our results there was no difference in genotypes between hypertensive and normotensive ESRD

As regards essential hypertension, Zhao et al (14) did not find correlation with rs10887800 gene polymorphism with essential hypertension in the northern Han Chinese population.

Conclusion

Our results showed that rs2296545 CC genotype and rs10887800 AA genotype might be unidentified risk factors for developing ESRD and that rs2296545 CC genotype is a risk factor for hypertension among Egyptian ESRD patients.

Limitations of the study

Limitations of our study are the relative small sample size that not covers different geographic areas and lake of measurement of renalase activity. So, we recommend that further studies should be conducted on a larger sample size in different geographic areas, with measurement of renalase level or its enzymatic activity to confirm our results.

Authors' contribution

HAZ supervised, reviewed and validated the final manuscript and was responsible for conceptualization. TMM and RS both of them contributed to the writing and editing of the manuscript and contributed to setting the research methodology, while MSH contributed to the manuscript review and sample collection. Finally, MAZ was responsible for original draft preparation and writing, sample collection and research methodology. All authors read, revised and approved the final manuscript.

Conflicts of interest

The authors declare that they have no conflicting interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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References

1. Fox CS, Yang Q, Cupples LA, et al. Genomewide linkage analysis to serum creatinine, GFR, and creatinine clearance in a community-based population: the Framingham Heart Study. J Am Soc Nephrol. 2004;15(9):2457-61. doi: 10.1097/01.ASN.0000135972.13396.6F.
2. Satko SG, Sedor JR, Iyengar SK, Freedman BI. Familial clustering of chronic kidney disease. Semin Dial. 2007;20(3):229-236. doi: 10.1111/j.1525-139X.2007.00282.x.
3. Kazancioğlu R. Risk factors for chronic kidney disease: an update. Kidney Int Suppl (2011). 2013;3(4):368-371. doi: 10.1038/kisup.2013.79.
4. Ahlawat R, Gupta S, Kapoor S, Kar P. Polymorphism of renalase gene in patients of chronic kidney disease. Open J Nephrol. 2012;2:136-143. doi: 10.4236/ojneph.2012.24021
5. Xu J, Li G, Wang P, Velazquez H, Yao X, Li Y, et al. Renalase is a novel, soluble monoamine oxidase that regulates cardiac function and blood pressure. J Clin Invest. 2005;115:1275-80. doi:10.1172/JCI24066.
6. Kiseljakovic E, Mackic-Djurovic M, Hasic S, Beciragic A, Valjevac A, Alic L, Resic H. Renalase gene rs2576178 polymorphism in hemodialysis patients: study in Bosnia and Herzegovina. Med Arch. 2016;70:31-4. doi: 10.5455/medarh.2016.70.31-34.
7. Stec A, Semczuk A, Furmaga J, Ksiazek A, Buraczynska M. Polymorphism of the renalase gene in end-stage renal disease patients affected by hypertension. Nephrol Dial Transplant.

2012;27:4162-6. doi: 10.1093/ndt/gfr293.
8. Farzaneh-Far R, Desir GV, Na B, Schiller NB, Whooley MA. 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. Published 2010 Oct 20. doi:10.1371/journal.pone.0013496.
9. Li G, Xu J, Wang P, Velazquez H, Li Y, Wu Y, et al. Catecholamines regulate the activity, secretion, and synthesis of renalase. Circulation. 2008;117(10):1277-82. doi:10.1161/CIRCULATIONAHA.107.732032.
10. Xu J, Desir GV. Renalase, a new renal hormone: its role in health and disease. Curr Opin Nephrol Hypertens. 2007;16:373-8. doi:10.1097/MNH.0b013e3281bd8877.
11. Li X, Huang R, Xie Z, Lin M, Liang Z, Yang Y, Jiang W. Renalase, a new secretory enzyme: Its role in hypertensive-ischemic cardiovascular diseases. Med Sci Monit. 2014;20:688-92. doi: 10.12659/MSM.890261.
12. Abdallah E, Sabry D. Renalase gene polymorphisms in end stage renal disease patients: an Egyptian study. J Am Sci. 2013;9:346-349.
13. Buraczynska M, Zukowski P, Buraczynska K, Mozul S, Ksiazek A. Renalase gene polymorphisms in patients with type 2 diabetes, hypertension and stroke. Neuromolecular Med. 2011;13:321-327. doi:10.1007/s12017-011-8158-6
14. Zhao Q, Fan Z, He J, Chen S, Li H, Zhang P, 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(8):877-85. doi:10.1007/s00109-006-0151-4.
15. Kandil NS, El Sharkawy RM, Desouky LM, Kandil LS, Masoud IM, Amin NG. Renalase gene polymorphisms (rs2576178 and rs10887800) in Egyptian hypertensive end stage renal disease patients. Egyptian Journal of Medical Human Genetics. 2018;19:379-83. doi:10.1016/j.ejmhg.2018.02.004.
16. K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis. 2005;45:S1-S153.
17. Fava C, Montagnana M, Danese E, Sjögren M, Almgren P, Engström G, 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. doi:10.1186/1471-2350-13-57.