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ORIGINAL ARTICLE

Impact of Renalase Gene Polymorphism rs10887800 in Patients having Metabolic Syndrome with Ischemic Heart Disease

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ABSTRACT

Background: The metabolic syndrome (MetS) is a collection of disorders that elevate the possibility of atherosclerotic disorder, such as peripheral vascular illnesses, peripheral vascular disorders, insulin resistance, myocardial infarction, and type II diabetes mellitus. The current study aimed to study the impact of renalase rs10887800 gene polymorphisms in patients having metabolic syndrome with ischemic heart disease (IHD).**Methods:** This case control study included 81 participants allocated into 3 groups: Group I: 27 MS cases, Group II: 27 MS & IHD cases, and Group III: 27 healthy controls. All patients of the studied groups were subjected to laboratory tests and the detection of renalase (rs10887800) single nucleotide gene polymorphism by high resolution melting (HRM) curve analysis technique for genotyping. **Results:** The distribution of renalase gene AA and AG genotypes were increased in group I (Ms) cases than group II (MS with IHD). There was a remarkable relationship of elevated diastolic blood pressure (DBP) values with AG genotypes of renalase gene among Ms cases (P=0.031) and increased all lipid profile values with GG genotypes of renalase gene. There was a substantial relationship of elevated 2hPPG and HbA1c and all lipid profile values with the carrier of AG and GG genotypes of renalase gene among the cases of Ms with IHD (P=0.01 & 0.007 respectively). **Conclusion:** Metabolic syndrome and ischemic heart diseases have a complex etiopathogenesis and multifactorial origin. Single nucleotide polymorphisms (SNPs) are potential risk factors for these Diseases. renalase (rs10887800) gene polymorphisms may have an impact role in patients having metabolic syndrome with ischemic heart disease.
Keywords: Renalase gene polymorphism, Metabolic syndrome, Ischemic heart disease

INTRODUCTION

The metabolic syndrome (MetS) is a group of diseases comprising hypertension, abdominal obesity, hyperglycemia, and dyslipidemia. These illnesses raise the risk of cardiovascular conditions, diabetes, and stroke. MetS has been identified as a secondary risk reduction target after being linked to an elevated possibility of cardiovascular mortality [1].

From myocardial infarction (MI) to unstable angina pectoris (USAP), and asymptomatic ischemia, ischemic heart disorders encompass a wide range of illnesses. There have been reports of an increase in catecholamine levels in CVDs. Additionally, it has been demonstrated that catecholamines specifically, dopamine, epinephrine, and norepinephrine play a role in controlling blood pressure (BP) [2].

The breakdown of catecholamine is aided by monoamine oxidase-A (MAO-A) and MAO-B. Renalase is a soluble dinucleotide-dependent amine oxidase flavin adenine and a genuinely novel monoamine oxidase enzyme. Investigations revealed that elevated plasma catecholamine concentrations significantly boost renalase activity, supporting renalase's role in catecholamine breakdown circulation, blood pressure regulation and heart

activity [3].Renalase is a flavoprotein enzyme that aids in the decomposition of catecholamines. It is also known as MAO-C [4].

RNLS is found on chromosome 10 at q23.33 (length 309 469 bp). This gene has ten exons and at least 4 differentially spliced isoforms. Renalase 1 is predominantly expressed in plasma, cardiac, renal, hepatic and skeletal muscle tissues. The RNLS gene contains several SNPs, including rs2296545, rs10887800, rs2114406 and rs2576178, which have been linked to hypertension, vascular disease, diabetes and stroke in numerous investigations [5].

Although the RNLS rs10887800 SNP was studied under diverse situations and in a variety of populations, the precise mechanism by which the polymorphism influenced the possibility of IHD and MetS is unknown. SNP analysis reveals that renalase rs10887800 is located along the exon/intron border in a potential functional area. Therefore, it may have affected gene expression and regulation, resulting in alterations in renalase concentrations [6].

Multiple investigators discovered that the downregulation of renalase was linked with a substantial reduction in the nicotinamide adenine dinucleotide (NAD) that controls the function of SIRT1, which contributes in cellular survival pathways and metabolic homeostasis [7].

Thus, increased NAD concentrations would boost SIRT1 activity, resulting in subsequent targets such as peroxisome proliferator-activated receptor-c coactivator1a and transcription factors (FOXO1 and FOXO3a). A drop in the NAD/NADH ratio induced by an absence of renalase would be expected to worsen damage of the Myocardium throughout ischemia and impede cardiac contraction following reperfusion [8].

The present work aim was to study the impact of renalase rs10887800 gene polymorphisms in cases having metabolic syndrome with ischemic heart disease (IHD).

METHODS

Patients :

This case control study was performed at Medical Biochemistry & Molecular Biology and Internal medicine Departments, Faculty of Medicine, Zagazig University. The included cases were diagnosed as MetS with or without IHD who were attending outpatient clinics at Internal Medicine Department, Zagazig University Hospitals for regular care after obtaining approval from Institutional Review Board (IRB#10572/14/3/2023) and written informed consent from all cases. The research was conducted under the World Medical Association's Code of Ethics (Helsinki Declaration) for human research.

The cases who were allocated into three equal groups: Group (1) "Patients having MetS without having IHD": This group included 27 obese, hypertensive, non-insulin dependent diabetic patients with (BMI) > 30 kg/m2, blood pressure over 85/130 mmHg. Group (2) "Patients having MetS with IHD" This group included 27 obese, hypertensive, non-insulin dependent diabetic patients with (BMI) > 30 kg/m2, blood pressure over 85/130 mmHg and abnormal coronary angiography. Group (3) "healthy participants as control group" This group included (27) healthy, non-obese individuals who had no diagnosis of type 2 diabetes mellitus or other chronic illness and had no family history or any other disease that may interfere with this study.

Cases with the following criteria were included; cases with MetS concerning the NCEP ATP lll definition, MetS exists when 3 or more of these parameters are accomplished: Waist circumference >35 inches (females) or 40 inches (males), fasting HDL cholesterol <50 mg/dl (females) or 40 mg/dl (males), fasting TG level over 150 mg/dl, BP >85/130 mmHg, and fasting blood glucose (FBG) over 100 mg/dl.

Cases with the following characteristics were excluded; cases who had cardiac, respiratory and hepatic conditions in control group. Cases who had drug intoxication, infection and malignant tumors. Cases who had severe renal and hepatic failure. We also excluded cases who had acute infectious disease or chronic inflammatory disease or any cases involving intense exercise within a 24-hour period or having any inflammatory conditions for 1 month. Patients with thyroid disease or glucocorticoid treatment were excluded as well.

Sample size:

Assuming that, the mean renalase level in metabolic syndrome patients with IHD is 23.28+/- 4.09 mg/dl, and in healthy people is 20.81+/- 2.73 mg/dl. So, the sample size was calculated to be 81(27 in each group), calculated using OpenEpi at power 80% and CL 95%.

Methods:

All patients of the studied groups were subjected to: complete history taking, complete clinical and physiological assessment, and laboratory tests (FBG, HbA1c, and lipid profile).

Blood sampling

After 12 hours of overnight fasting, 5 ml of venous blood were collected form each participant under

complete aseptic condition by sterile vein-puncture and allocated into three samples: Two ml were collected in sterile EDTA, dipotassium salt, dihydrate (K2EDTA-2H2O) treated tubes and were stored at -20 °C for genomic DNA extraction. One ml collected in sodium fluoride/potassium oxalate for estimation of fasting blood glucose level. Two ml were collected in plain tubes then left for 20 minutes until clot retraction then separation of serum and stored at -20 °C for estimation of fasting lipid profile.

Laboratory assessment

FBG level was determined by glucose oxidase enzymatic technique regarding to Trinder [9]. Assessment of total cholesterol (TC) was according to Rifai and Warnick [10], HDL-c according to Naito and Kaplan [11], and triacylglycerol (TAG) values were determined by colorimetric technique employing commercial kits from (Spinreact, Spain) [12]. LDL-c was assessed regarding to the Friedewald and Fredrickson formula: [13] LDL-c = Total cholesterol – HDL-c – (TAG/5)

DNA extraction:

Genomic DNA was extracted from whole blood utilizing Applied Bio Technology Genomic DNA Extraction kit (spin-column), as instructed in the user manual [14].

Quantification and purity of DNA:

To measure the amount of DNA and assess its purity, 20 µl of each extracted DNA sample was mixed with 1 ml of deionized water in a quartz cuvette. The Milton Roy Spectronic 3000 Array was used to detect absorbance at 260 and 280 nm wavelengths.

The absorbance of DNA is highest at 260 nm. The concentration of DNA is 50 µg/ml when the absorbance is 1.0 at 260 nm. Proteins that contain tyrosine, tryptophan, and phenylalanine absorb most at 280 nm. Proteins in DNA samples can be detected using this wavelength of absorption. The A260/A280 ratio is calculated to do this. The range of this ratio for pure double-stranded DNA was 1.7 to 1.9 [14].

Detection of renalase (rs10887800) single nucleotide gene polymorphism (SNP) by high resolution melting (HRM) curve analysis method for genotyping.

Detection of renalase (rs10887800) single nucleotide gene polymorphism was carried out by High resolution melting curve analysis (HRM) method for genotyping, using Real-Time PCR detection system (Rotor-Gene Q 2 Plex (Qiagen, Hilden, Germany)) employing the following primers: Forward: 5’ -CAGGAAAGAAAGAGTTGACAT-3’ and Reverse: 5’ -AAGTTG TTCCAGCTACTGT-3’

HRM curve analysis method for genotyping:

As directed by the manufacturer, DNA was extracted utilizing the Genomic DNA Extraction kit (spin-column). A fluorescent dye was used to create a PCR mixture with 10 ng of template DNA and 0.7 lM forward and reverse oligonucleotide primers. Data was obtained during the 72 °C step of the PCR amplification process, which involved initial denaturing at 95 °C for 5 min, then 45 cycles at 95 °C for 10 s, at 52 °C for 30 s, and at 72 °C for 10 s. Amplified samples attached to the fluorescent dye were heated between 65 and 95 °C for HRM analysis. Rotor-Gene Q was used to raise the temperature by 0.1 °C at a time, covering the whole range of the anticipated melting temperatures. Rotor-Gene Q software was used for the analysis of HRM data. By establishing linear baselines prior to and following each sample's melting transition, fluorescence intensity data were normalized between 0% and 100%. With a confidence level of 80%, the fluorescence of each acquisition was determined by calculating the proportion of fluorescence at the top and bottom baseline of each acquisition temperature using HRM curves.

PCR Protocol:

DNA thermal cycler 480, PERKIN ELMER (Norwalk, CT 06856, USA), Serial No. P16462, was used for the amplification.

Denaturation at 95°C for 2 minutes was followed by 29 denaturation cycles at 95°C for 25 seconds, annealing at 58°C for 30 seconds, and extension at 72°C for 1 minute. The final extension stage lasted for 5 minutes at 72°C. Following 2% agarose gel electrophoresis, ethidium bromide staining, and UV transilluminator visualization, the PCR products were examined.

Statistical analysis:

Data were analyzed utilizing SPSS software version 20 (IBM, USA). Parametric data is presented as mean ± SD or percentage (%) for categorical data. Parametric data were compared utilizing the independent student t test for two groups and the one-way ANOVA test followed by Turkey's test for multiple comparisons for the three groups. Chi square test or odds ratio was carried out for categorical data. Data with $P<0.05$ considered significant

RESULTS

There was no substantial variance among three studied groups as regard age and gender of studied cases. While there was a substantial variance as regard BMI with more increased among group I (MetS cases). (Table 1)

The distribution of renalase gene AA genotypes was not substantial variance between Ms cases and healthy controls, but both AG and GG genotypes were higher with elevated risk for MetS (OR, 3.66; 95% CI, 0.93–14.4; p − 0.06 for AG; and OR, 4.81; 95% CI, 0.89–25.7; p − 0.06 for GG, respectively), but not reach significant level. Also, the G allele frequency was elevated in MetS than in healthy controls (55.6% vs. 37%, respectively), with no significant difference. (Table 2)

The GG genotypes of renalase gene distribution was substantially varied between MetS with IHD cases and controls. When the AA genotype was used as the guidance, GG genotypes have been shown to be related with an elevated risk of MetS and IHD (OR, 9.16; 95% CI, 1.63–51.4; p − 0.01). Both AG and GG genotypes were shown to be higher with elevated risk for MetS and IHD. Furthermore, the prevalence of G allele was considerably greater in MetS with IHD cases compared to controls (63% vs. 37%, respectively). (Table 3)

The distribution of renalase gene AA and AG genotypes were more increased in group I (MetS) cases than group II (MS with IHD). (Table 4)

There was a substantial relationship of increased diastolic blood pressure values with the carrier of AG genotypes of renalase gene among MetS cases (P=0.031) and increased all lipid profile concentrations with the carrier of GG genotypes of renalase gene. (Table 5)

There was a substantial relationship of increased 2hPPG and HbA1c and all lipid profile values with the carrier of AG and GG genotypes of renalase gene among the cases of MetS with IHD (P=0.01 & 0.007 respectively). (Table 6)

Table (1): Basic characteristics of the studied group.

		Group I N=27		Group II N=27		Group III N=27		F test	P
Age\ years Mean ±SD Range		51.9 ± 6.39 39-62		56.3 ± 9.44 38-70		56.8 ± 9.74 39-75		2.86	0.08
BMI Mean ±SD Range		35.9 ± 3.42 [A,B] 30.5-41.1		35 ± 3.94 30.3-41.1		27.8 ± 1.74 23.7-29.7		58.8	<0.001
		N	**%**	**N**	**%**			**X^2**	**P**
Gender	**Male**	8	17.4	13	48.1	17	63	2.67	0.102
	Female	19	82.6	14	51.8	10	37		

A: Significant difference between group I & II, B: Significant difference between group I & III

Table (2): Different genotypes and allele distribution of Renalase gene among the studied groups**.**

		Group I N=27		Group III N=27		OR (95% CI)	X^2	P
		N	**%**	**N**	**%**			
Renalase gene	**AA**	4	14.8	11	40.7	------	Ref.	-------
	AG	16	59.3	12	28.6	3.66 (0.93-14.4	1.85	0.06 NS
	GG	7	25.9	4	14.8	4.81 (0.89-25.8)	1.58	0.06 NS
Allele distribution	**A**	24	44.4	34	63.0	2.13 (0.98-4.59)	1.91	0.05 NS
	G	30	55.6	20	37.0			

NS: P-value>0.05 is not significant

Table (3): Different genotypes and allele distribution of Renalase gene among the studied groups.

		Group II N=27		Group III N=27		OR (95% CI)	X^2	P
		N	%	N	%			
Renalase gene	**AA**	3	11.1	11	40.7		Ref.	-------
	AG	14	51.9	12	28.6	4.28 (0.96-19.1)	1.93	0.06 NS
	GG	10	37.0	4	14.8	9.16 (1.63-51.4)	2.51	0.01 S
Allele distribution	**A**	20	37.0	34	63.0	2.89 (1.32-6.31)	2.65	0.008 S
	G	34	63.0	20	37.0			

S: P-value<0.05 is significant

Table (4): Different genotypes and allele distribution of Renalase gene among the studied groups.

		Group I N=27		Group II N=27		OR (95% CI)	X^2	P
		N	%	N	%			
Renalase gene	**AA**	4	14.8	3	11.1	------	Ref.	-------
	AG	16	59.3	14	51.9	0.86 (0.16-4.54)	0.185	0.856 NS
	GG	7	25.9	10	37	0.525 (0.09-3.18)	0.708	0.476 NS
Allele distribution	**A**	24	44.4	20	37.0	0.713 (0.38-1.51)	0.761	0.434 NS
	G	30	55.6	34	63.0			

NS: P-value>0.05 is not significant

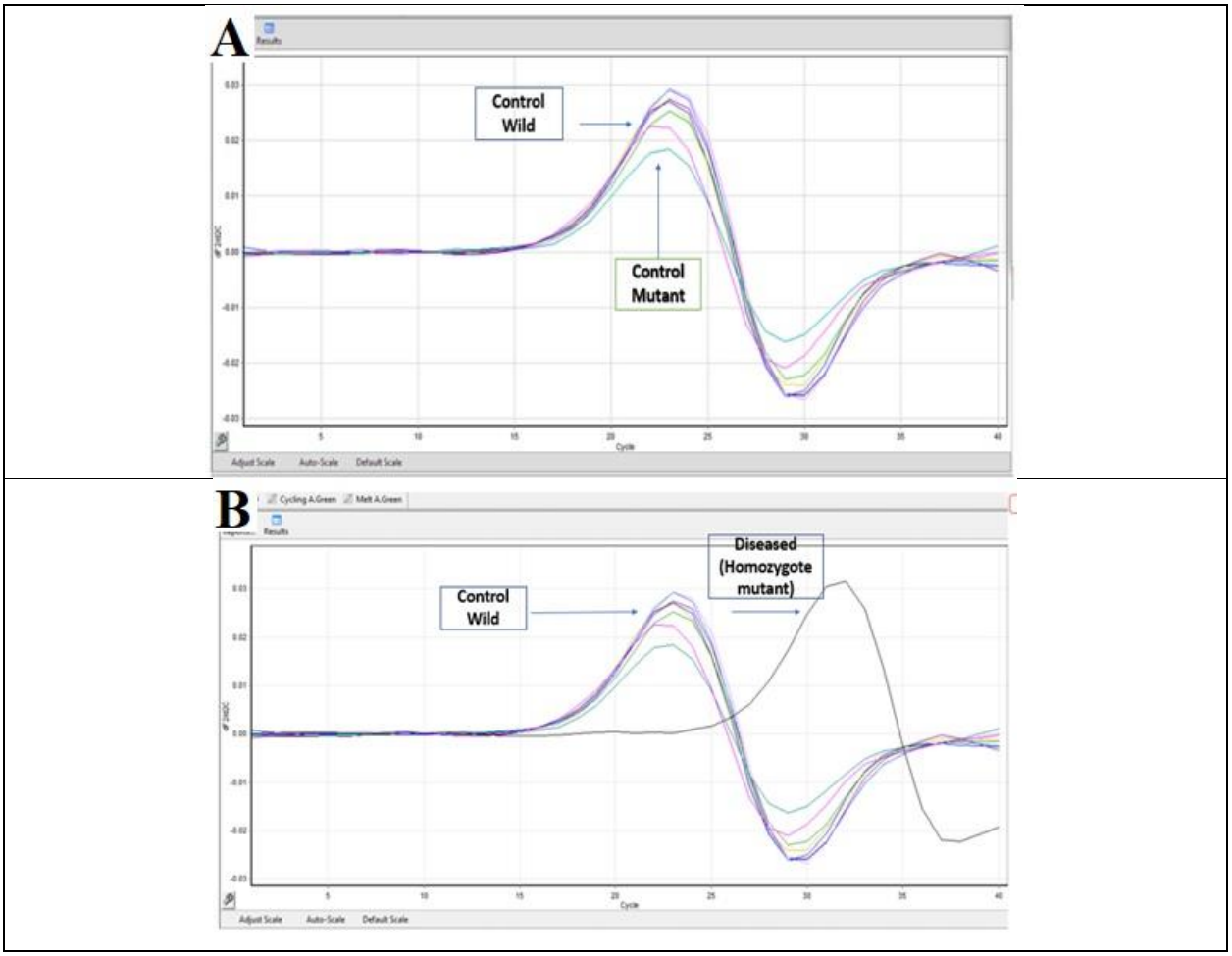
Table (5): Relation between Renalase gene polymorphism and biochemical data among Ms cases (group I).

	Renalase gene polymorphism			F test	P value
	GG N=7	AG N=16	AA N=4		
BMI	**36.6 ± 3.75**	**35.3 ± 3.87**	**35.8 ± 2.51**	0.234	0.501
SBP	**151.6 ± 10.7**	**157.7 ± 10.8**	**150 ± 9.15**	0.234	0.501
DBP	**96.4 ± 3.75**	**103.3 ± 8.17**	**95 ± 4.19**	**4.11**	**0.031**
FBG	**177.4 ± 42.3**	**192 ± 35.7** [AC]	**157 ± 17.3**	0.462	0.636
2 hours PP	**286.8 ± 48.2**	**300.2 ± 33.7**	**266.8 ± 48.8**	1.31	0.291
HbA1c	**8.92 ± 1.36**	**8.72 ± 1.51**	**8.5 ± 0.35**	0.235	0.527
TG	**267.6 ± 24.5**	**240.3 ± 48.7**	**231.8 ± 38.1**	0.234	0.501
HDL-c	**33.3 ± 3.98**	**34.9 ± 3.81**	**34.3 ± 3.69**	0.234	0.501
TC	**263.3 ± 6.18**	**256.9 ± 9.81**	**256.3 ± 7.69**	1.62	0.219
LDL-c	**206.3 ± 7.98**	**202.9 ± 10.71**	**198.3 ± 8.69**	0.934	0.405

NS: P-value>0.05 is not significant, S: P-value<0.05 is significant, A: Significant difference between group I & II, C: Significant difference between groups II & III

Table (6): Relation between Renalase gene polymorphism and biochemical data among Ms & IHD cases (group II).

	Renalase gene polymorphism			F test	P value
	AA N=3	AG N=14	GG N=10		
BMI	**36.1 ± 4.45**	**35.7 ± 4.17**	**33.8 ± 3.45**	0.774	0.421
SBP	**165 ± 8.76**	**161.3 ± 7.47**	**158.5 ± 7.15**	1.02	0.381
DBP	**106.6 ± 15.8**	**104.3 ± 9.77**	**102.5 ± 8.58**	0.234	0.801
FBG	**170 ± 65.9**	**184 ± 38.9**	**183 ± 37.03**	0.162	0.866
2 hours PP	**253.8 ± 52.8**	**288.8 ± 30.7**	**275.8 ± 45.1**	1.11	0.351
HbA1c	**7.77 ± 1.29**	**8.28 ± 0.91**	**7.65 ± 0.687**	1.35	0.247
TG	**235.3 ± 75.3**	**259.9 ± 46.7**	**263.8 ± 50.3**	0.324	0.831
HDL-c	**34.6 ± 3.26**	**35.6 ± 3.37**	**34.8 ± 3.26**	0.934	0.411
TC	**296.7 ± 48.5**	**302.1 ± 24.8**	**306.3 ± 31.1**	0.134	0.871
LDL-c	**248.3 ± 18.2**	**251.9 ± 10.5**	**254.3 ± 14.2**	0.123	0.885



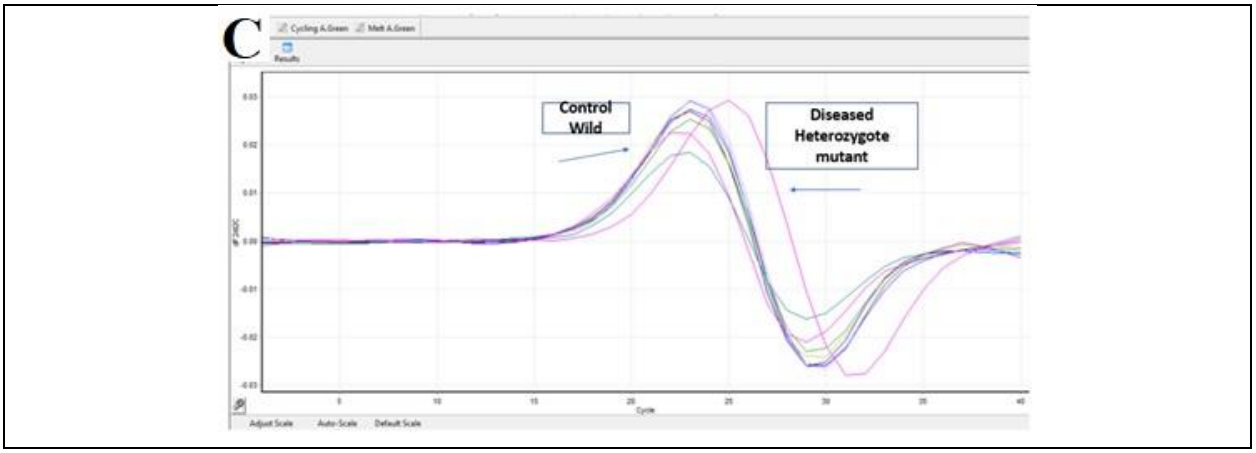


Figure (1): Melting curve analysis of Renalase (rs10887800) single nucleotide gene polymorphism using real time PCR. (A) Show control wild and control homozygous mutant. (B) Show diseased homozygous mutant (its curve not intersected with control wild curve). (C) Show diseased heterozygous mutant (its curve intersected with control wild curve).

DISCUSSION

A condition known as MetS can result from metabolic alterations brought on by changes in lifestyle, genetic predisposition, dietary habits, and physical inactivity. These changes raise the risk of age-related disorders like diabetes, obesity, and hypertension. A group of metabolic disorder correlated to an elevated risk of T2DM and cardiovascular conditions are together referred to as MetS [16].

In recent years, the incidence of MetS has rapidly risen worldwide, impacting 20% to 30% of the general population. As a result, MetS has emerged as a significant global public health concern. It is generally accepted that central obesity and insulin resistance are essential characteristics of MetS. Based on research on twins and families, a genetic predisposition seems to be the most likely cause. Currently, research on the genetic components of MetS has concentrated on potential genes linked to energy, lipid, and glucose metabolism [17].

Hereditary genetic predisposition, in conjunction with environmental and metabolic factors, determines the onset, progression, and extent of MetS. Therefore, it is crucial to identify genetic and metabolic risk factors for MetS in order to forecast the risk of USAP and other serious illnesses. Renalase is considered an innovative indicator that disrupts several metabolic pathways [6].

Isomaa et al. [18] illustrated that since it has been linked to a higher risk of cardiovascular mortality, MetS has been recognized as a secondary risk decline goal. The incidence of MetS rises to about 50% in individuals with acute coronary syndrome (ACS), and it enables these patients to have higher levels of complications.

The present study aimed to determine the influence of renalase gene polymorphisms (rs10887800) in cases having metabolic syndrome with or without ischemic heart disease.

The study included 81 participants divided into 3 groups: Group I: 27 MS cases, Group II: 27 MS & IHD cases, and Group III: 27 healthy controls.

In the current study there was no remarkable variation among three studied groups as regard age and gender of studied cases. While there was a substantial variance concerning BMI with more increased among group I (metabolic syndrome cases).

Izadpanah et al., [5] when investigated 134 cases with USAP+MetS and 134 normal subjects, reported that The BMI was substantially greater in USAP +MetS cases than in control cases ($P < 0.001$), but there were no substantial distinctions in gender or age between the case and control groups ($p<0.05$).

Mohtavinejad et al. [19] study demonstrated that gender, age, smoking status, ethnicity, hypertension, history of CVD, and diabetes mellitus were among the demographic features of CVD cases and controls that were shown to differ significantly.

Our study showed that both AG and GG genotypes have been shown to be greater with a higher risk for MetS, but not to a significant degree. Renalase gene AA genotypes did not vary substantially between MetS cases and controls.

Also, the G allele prevalence was elevated in MetS cases than in controls (55.6% vs. 37%, respectively), with no significant difference.

Between Ms with IHD cases and controls, there was a substantial difference in the prevalence of GG genotypes of the renalase gene. The GG genotype was linked to higher risk for Ms and IHD when the AA genotype was used as the reference (OR, 9.16; 95% CI, 1.63–51.4; p − 0.01).

It was discovered that elevated MetS and IHD risk was linked with both the GG and AG genotypes.

Additionally, metabolic syndrome with IHD patients had a considerably greater frequency of the G allele than did controls (63% vs. 37%, respectively).

The distribution of renalase gene AA and AG genotypes were more increased in group I (Ms) cases than group II (MS with IHD).

Izadpanah et al., [5] found that When 134 cases with USAP+MetS and 134 normal participants were analyzed, rs10887800 AG and GG genotypes prevalence of the RNLS gene was substantially elevated in USAP+MetS cases than in normal participants. This showed that both AG and GG genotypes of the RNLS rs10887800 polymorphism showed a risk factor influence with a higher risk of USAP and MetS in 2.114 and 2.057 times, respectively. Additionally, USAP+MetS cases had a greater incidence of the RNLS rs10887800 G allele than the control group.

In a case-control study by Stec et al. [6] renalase gene rs10887800 and rs2576178 SNPs were genotyped in 309 hemodialyzed cases (107 with and 202 without CAD). The most intriguing result was that the rs10887800 renalase gene polymorphism suggested a potential role in the pathophysiology of CAD in hemodialyzed cases, while the rs2576178 polymorphism had no effect on the risk of CAD.

In our study, there was a remarkable relationship of elevated DBP values with the carrier of AG genotypes of renalase gene among MetS cases (P=0.031), and increased all lipid profile values with the carrier of GG genotypes of renalase gene.

There was a substantial link of elevated 2hPPG and HbA1c and all lipid profile values with the carrier of AG and GG genotypes of renalase gene among the cases of MetS with IHD (P=0.01 & 0.007 respectively).

Previous investigations by Teimoori et al. [21] and Desir et al. [22] illustrated that the mean of SBP, DBP, and FBG were the most important MetS metrics associated with renalase functioning. In this regard, the analysis of the RNLS rs10887800 SNP in conjunction with MetS components revealed no correlation between the genotype distributions of rs10887800 and MetS components.

There is no published research on the probable relationship between MetS, IHD and RNLS gene polymorphism, despite the fact that many investigations have discovered a relationship between other RNLS SNPs and other disorders.

Although the results are still unclear, both clinical research and experimental have verified the connection between renalase and BP and other metabolic variables.

Findings obtained from the Izadpanah et al. [5] revealed that compared to healthy persons, USAP+MetS cases had much greater concentrations of circulating renalase. Buraczynska et al. [23] noted that in cases with T2DM, hypertension, and stroke, the link between renalase rs2296545, rs2576178, and rs10887800 SNPs and gene polymorphism was examined.

Conclusions

Metabolic syndrome and ischemic heart diseases have a complex etiopathogenesis and multifactorial origin. Single nucleotide polymorphisms (SNPs) are potential risk factors for these diseases. Renalase (rs10887800) gene polymorphisms may have an impact role in patients having metabolic syndrome with ischemic heart disease. Studies of other polymorphisms in the renalase gene and their relationships with metabolic syndrome and ischemic heart diseases should be carried out.

Conflict of interest:

The authors declare no conflict of interest.

Financial Disclosures:

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