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Serum Renalase and its Relation to Left Ventricular Hypertrophy in Patients on Hemodialysis

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ABSTRACT

Background: Renalase is a blood-secreted protein produced only by the kidney; its blood level approximately 3–5 µg/ml. The Left ventricular hypertrophy (LVH) is defined by an augmented left ventricular mass that may be measured via echocardiography or magnetic resonance imaging (MRI). The aim of the present study was to study whether Renalase is a marker or has a potential role in developing myocardial hypertrophy in CKD patients under hemodialysis (HD) treatment.

Patients and methods: To achieve this target, 90 patients on maintenance HD were incorporated in the present study.

Results: The mean renalase levels were 61.7±67.5 ng/mL in HD patients. The cutoff value of Renalase was >57.9 ng/ml with a sensitivity of 92.3% and a Specificity of 84.0%. The mean LVMI of the studied dialysis patients was 138 g/m2. The majority of cases were severely abnormal (60%). There was a statistically significant difference between the age groups and the LVMI among dialysis patients. The level of Renalase was significantly increased with the moderately and severely abnormal LVMI among dialysis patients. The present study disclosed statistically significant relations between the duration of dialysis and Renalase, HDL, CRP, and LVMI. There were significant relations between the serum renalase and s. creat, bl. Urea, Ph, LVMI and dialysis vintage. Also, there were significant positive relations between LVMI and Hb, CRP, and dialysis vintage.

Conclusion: Renalase could be a novel predictive biomarker in the assessment of LVH, which is closely associated with the increased risk of death in HD patients.

Keywords: End stage renal disease, Hemodialysis, Cardiovascular, Left ventricular hypertrophy, Renalase.

1. INTRODUCTION

Cardiovascular major issues contribute significantly to the substantial morbidity and mortality of individuals with end-stage renal disease (ESRD) [1].Individuals with a wide range of problems are included, involving vascular disorders, particularly LVH. Heart failure (HF) is a frequently occurring complication of such processes. Owing to breathing difficulties, edema, and fatigue, HF impairs the quality of life of ESRD patients [2].

LVH occurs mostly throughout milder stages of CKD, affecting up to 20% of individuals with Stages of CKD 1-3 [3] and 80% of individuals with ESRD [4]. Eccentric LVH is caused by cyclic water overload as well as anemia, whereas concentric hypertrophy is caused by arterial hypertension. Both processes are prevalent in individuals with ESRD, and hence the stronger one defines the overall phenotype [5].

Renalase is a kidney-produced protein that is released into the bloodstream at a level of around 3–5 g/ml. It acts as a cytokine that protects cells, tissues as well as organs mostly by interaction with its receptor in order to trigger protein kinase B, JAK/STAT, and mitogen-activated protein kinase pathways [6]. The mean serum Renalase concentration was 75.8 34.8 g/mL. Renalase is linked to monoamine oxidase A and shares 13% of its amino acids [7]. It was shown to have a considerable affinity for noradrenaline (NA), adrenaline (ADR), as well as dopamine (DA), but only a negligible affinity for serotonin, tyramine, benzylamine, and spermidine [8].

On chromosome 10, there is a 311,000-bp gene that encodes human Renalase (RNLS). This gene is highly polymorphic and is responsible for the production of Renalase in humans [9]. While some old studies argued that patients with end-stage renal disease have a significant Renalase deficiency, which could be one of the mechanisms explaining the high prevalence of hypertension in these patients, recent studies found that a high level of serum and urine concentrations of Renalase was found in cases with chronic kidney diseases **[10].**

The Renalase gene is expressed most abundantly inside the kidneys, and whenever released, it circulates throughout the blood, affecting systolic blood pressure (BP) in addition to cardiac function via catecholamine modulation [11]. Additionally, it has been demonstrated that recombinant Renalase reduces blood pressure and also improves cardiovascular functions [12]. Inadequate treatment of high blood pressure is a significant risk factor for LVH [13]. The purpose of this study is to determine the association between serum renalase and LVH in individuals with ESRD whic are on hemodialysis.

2. PATIENTS AND METHODS

2.1. Ethical Clearance

Individuals who took part in this trial were asked to provide written informed consent before participating. Faculty of Medicine, Zagazig University's research ethics committee gave its approval to the study's implementation. According to the World

Medical Association's Code of Ethics (Declaration of Helsinki) for studies involving humans, the research was carried out in compliance with these guidelines.

2.2. Study design and population

A Cross-sectional study was carried out at Nephrology Units in Zagazig University Hospitals in ESRD patients on maintenance hemodialysis. The study included 90 hemodialysis patients who were divided into two groups, **a group I** (which included 15 patients on hemodialysis for less than or equal to 5 years) and **group II** (which included 75 patients on hemodialysis for more than five years).

2.3. Inclusion criteria:

Firstly, age older than 18 years and not exceeding 60 years. Secondly, sex, males, and females were included. Finally, at least one year of previous chronic HD treatment three times per week, with each session lasting for 4 hours.

2.4. Exclusion criteria:

Patients with the following criteria had been excluded; malignancies, infections, pregnancy, extremes of age, and patients who were known to have cardiomyopathy or documented coronary artery disease.

2.5. Methods

All patients were subjected to the following measures:

2.5.1. Clinical Evaluation*:* detailed history and clinical examination with special emphasis on age, gender, duration of dialysis, and cardiovascular disease.

2.5.2. Investigations: the routine laboratory investigations were done according to the Clinical Pathology department and laboratories of Zagazig University Hospitals' protocol and include: *Complete blood count (CBC)*, *Serum creatinine, Blood urea*, *Lipid profile*: *(LDL, HDL, total serum cholesterol, serum Triglyceride), Serum Albumin*, *Electrolytes (Ca, Ph), C-reactive protein and Blood glucose*.

2.5.3. Specific investigations

***a)Renalase by ELISA technique*:** The technique of this ELISA kit is Sandwich-ELISA. The Microelisa strip plate in this kit was pre-coated with a Renalase-specific antibody. In the relevant Microelisa strip plate wells, standards or samples are introduced and mixed with a particular antibody. Subsequently, every Microelisa strip plate well is treated with Horseradish peroxidase (HRP)-conjugated antibody specific for Renalase. Constituents that are not required are swept up. Every well is then filled with the TMB substrate solution. Just those wells containing Renalase plus HRP conjugated Renalase antibody will show blue and subsequently change yellow when the stop solution is added. At a wavelength of 450nm, the optical density (OD) is determined spectrophotometrically. The OD value is proportional to the renalase level. By comparing the OD of the samples to the standard curve, you may determine the level of Renalase in the samples.

***b)Echocardiography*:** All participants underwent transthoracic color Doppler echocardiography in two dimensions using a Philips IE-33 system and S5-1 transducer (1e5 MHz, Philips, Bothell, WA). The same cardiologist examined all of the individuals and conducted echocardiography on all of them.

2.6. Statistical analysis

The collected data were coded and analyzed using SPSS (Statistical Package for the Social Sciences) version 21 for windows (SPSSINC, Chicago, IL, USA) and medcalc 13 for windows (medcalc Software bvba, Ostend, Belgium). At the level of significance $p < 0.05$, and 95% confidence interval. The quantitative data were summarized by mean and Standard Deviation (SD) for normally distributed data, median for non-parametric data, and analyzed using Mann Whitney U test (comparing the median of two non-parametric data), Student test (comparing means of two groups), Analysis Of Variance (ANOVA, F test) (comparing means of more than two groups of normally distributed data), and Kruskal Wallis test (comparing the median of more than two groups of non-parametric data), while the qualitative data were summarized using frequency (F) and percentages (%), while Chi-square (X^2) test was used for analysis.

To test the association between two continuous variables, correlation coefficient Persons correlation was used, r = k0-1. There was a negative relationship and/or direct positive relationship.

To test the role or new tool or test in diagnosis or predicting the LVMI, ROC curve was used, and the ability of the test to determine true positive (sensitivity), while excluding true negative cases (Specificity).

3. RESULTS

Table (1): The demographic data of the standard population**.**

	Mean±SD	**Range**
Age (y)	46.2±9.3	23-59
Age groups	No.	%
20-<30y	5	5.6
30-<40y	20	22.2
40-<50y	27	30.0
50-<60 y	8	42.2
Sex	No.	%
Male	50	55.6
Female	40	44.4

Dialysis duration (y)		
Median	(6)	
	5.01±2.6	1-13

The mean age of the studied dialysis patients was 46y; they dialyzed median six years ago, the majority were males (55.6%) with mean±SD age of 46.2±9.3 years, as shown in table1 of demographic data distribution.

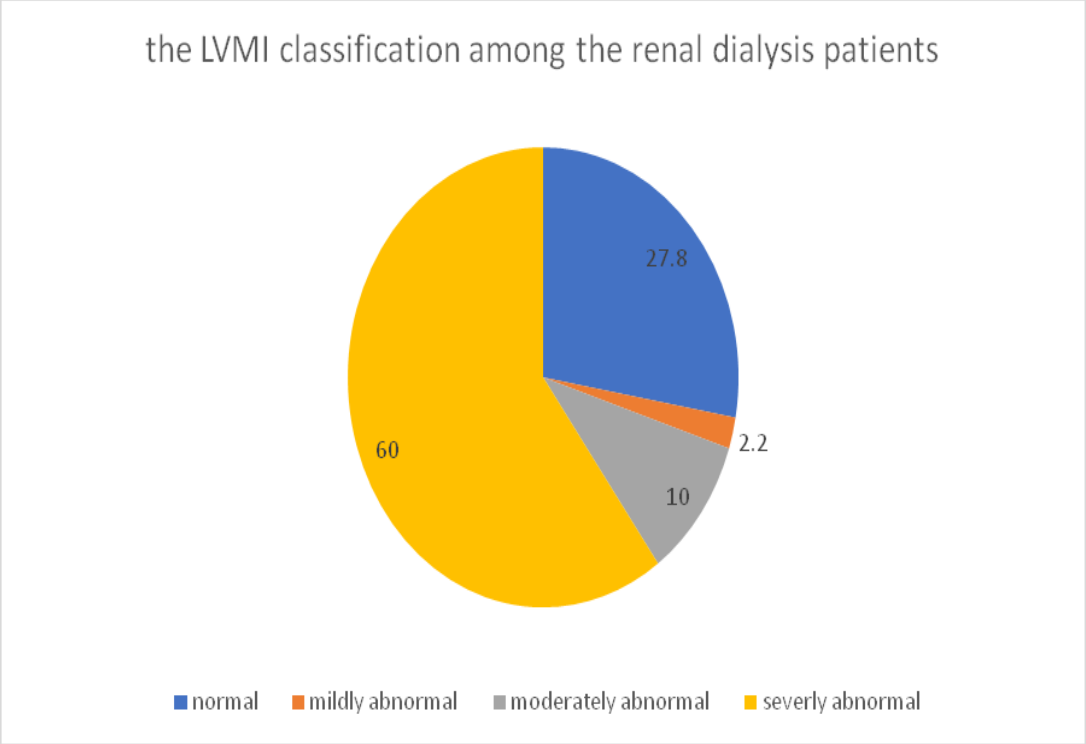

Figure (1): The Left Ventricle Mass index (LVMI) to Body Surface Area (g/m2) among renal dialysis patients.

The mean LVMI of the studied dialysis patients was 138 (g/m2), the majority of cases were severely abnormal (60%), 27.8% were normal, and only 10% have moderate abnormal readings, as presented by figure1

Table (2): The sex relationship with the renalase and left ventricle mass index (LVMI) among dialysis patients

	Females No =40	**Males No=50**	Test	p
THE LVMI classification	No.(%)	No. (%)	X2=2.07	0.41
➢ **Normal**	10(25.0)	15(30.0)		
➢ **Mildly abnormal**	1(2.0)	1(2.0)		

➢ **Moderately abnormal**	2(5.0)	7(14.0)	
➢ **Severely abnormal**	27(67.5)	27(54.0)	
Renalase (ng/ml)			Mann –whitnet U 0.39
Median	25.5	28.1	
Range	13-283	13.4-261	

Table (3): The relationship between the age groups and renalase and left ventricle mass index (LVMI) among dialysis patients

	20-<30y No= 5	**30-<40 No=20**	**40-<50y No=27**	**<60 No=38**	**p**
Renalase (ng/ml)					
Median	20.9	25.1	26.8	26.5	0.45
Range	17-147	17-240.4	14.3-268.0	13.4-228	
LVMI mean+_SD	145.4±39	131.2±39.4	130.9±39.4	148.4±32.1	0.00*
Range	83-182	82-182	82-182	83-185	
THE LVMI classification	No.(%)	No.(%)	No.(%)	No.(%)	
➢ Normal	1(20.0)	8(40.0)	8(29.6)	8(21.1)	
➢ Mildly abnormal	0(0.0)	2(10.0)	0(0.0)	00(0.0)	0.00*
➢ Moderately abnormal	0(0.0)	2(10.0)	5(18.5)	2(5.3)	
➢ Severely abnormal	4(80.0)	8(40.0)	14(51.9)	28(73.7)	

*p<0.05 there is a statistical significant difference

There was no statistically significant difference between sex groups as regards the LVMI and the renalase level among dialysis patients, as shown in table2. At the same time, there was a statistically significant difference between the age groups and the LVMI among dialysis patients, as 73.7% of older age group (50-<60y) had a severely abnormal LVMI and no statistically significant difference between age groups as regards renalase level among dialysis patients as shown in table3.

Table (4): The relationship between the renalase and the left ventricle mass index (LMVI) among Dialysis patients

	Normal No=25	**Mildly abnormal No=2**	**Moderately abnormal No=9**	**Severely abnormal No=54**	**P**
Renalase					
Median	(25.1)a	(26.5)a	(37.0)b	(71)c	0.00*
Range	14.3-170	17.8-200	16.5-268	13.4-281	

*P<0.05 there was a significant difference

Table (5): Diagnostic value of renalase in diagnosis of left ventricle mass index (LVMI) among heamodialysis patients

	abnormal LVMI	**normal LVMI**	
RENALASE >57.9	60	4	64
RENALAASE<57.9	5	21	26
TOTAL	65	25	

	%
Sensitivity	92.3
Specificity	84.0
Ppv[1]	93.8
Npv[2]	80.8

The cutoff value >57.9

[1] Positive predictive value

[2] Negative predictive value

The level of Renalase was significantly increased with the moderately and severely abnormal LVMI among dialysis patients, as shown in table4. The cutoff value of Renalase in this study was >57.9 ng/ml with a Sensitivity of 92.3%, Specificity of 84.0%. +ve predictive value 93.8% and –ve predictive value 80.8% as shown in table 5.

Table (6): The relationship between the duration of dialysis and the laboratory findings

	≤ 5 years (No=15) **Mean±SD** **Range**	**> 5 years (No=75)** **Mean+_SD** **Range**	T	P
Renalase(ng/ml)	26.9 13.9-281.6	78.5 13..4-240.4	2.20	0.03*
S.creat[1](mg/dl)	8.2 3-16	8 4-16.4	0.70	0.48
Bl .urea[2](mg/dl)	123.6±38.4 45-200	119.1±43.6 64-228	0.39	0.69
Ca[3](mg/dl)	8.6±0.8 7-10.2	8.7±0.6 7.1-10.0	0.06	0.96
Bl.Glucose[4](mg/dl)	103.4±14.4 83-139	107.3±18.1 86-147	0.46	0.64
PH[5](mg/dl)	4.9±1.4 3-10	5.3±1.9 3-10	0.86	0.40
HDL[6](mg/dl)	45.1±8.1 30-57	38.4±7.9 27-55	3.3	0.00*
TC[7](mg/dl)	201.6±29.2 156-255	199.5±25.4 159-247	0.27	0.79
LDL[8](mg/dl)	94±21.6 57-139	93.7±19.8 69-139	0.21	0.83
CRP[9](mg/l)	6.5±1.6	7.5±0.7	2.35	0.00*

	3-5.9	6-8.4		
Albumin(g/dl)	3.7±1.0	3.5±1.3	0.87	0.39
	1.7-5.5	2-5.3		

*p <0.05 here was a statistical significant difference.

[1] Serum creatinine

[2] Blood urea

[3] Calcium

[4] Blood glucose

[5] Phosphorus

[6] High density lipoproteins

[7] Total cholesterol

[8] Low density lipoproteins

[9] C- reactive protein

There was no significant relationship between the duration of dialysis and s.creat, bl. Urea, Ca, blood Glucose, Ph, Tc, LDL, and Albumin, but there was a significant relationship between the duration of dialysis and Renalase, HDL, and CRP, as shown in table6.

Table (7): The relationship between the duration of dialysis and the left ventricle mass index (LVMI)

	≤ 5 years (No=15) **Mean±SD** **Range**	**> 5 years (No=75)** **Mean+_SD** **Range**	T	P
LVMI	133.7±33.6 82-185	162.3±16.9 137-185	T=4.90	0.00*
THE LVMI classification	No.(%)	No.(%)	X2=11.8	0.00*
➢ **Normal**	10(66.7)	15(19.5)		
➢ **Mildly abnormal**	1(6.7)	1(1.3)		
➢ **Moderately abnormal**	1(6.7)	8(10.7)		
	3(20.0)	51(68.0)		

- **Severely abnormal**

*p <0.05 there was a statistical significant difference

Table (7) shows that there was a statistically significant difference between the duration of dialysis and LVMI.

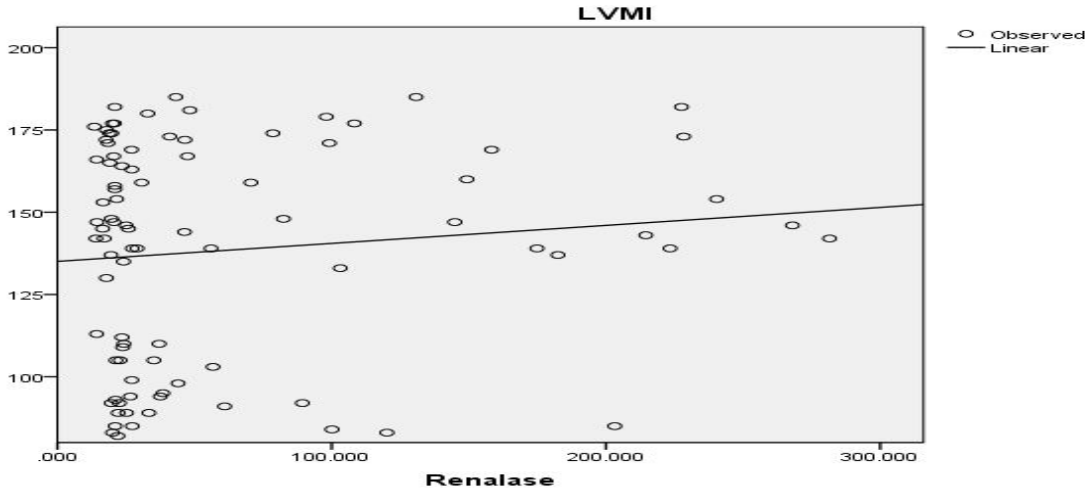

Figure (2): The correlation between the serum renalase and left ventricle mass index LVMI

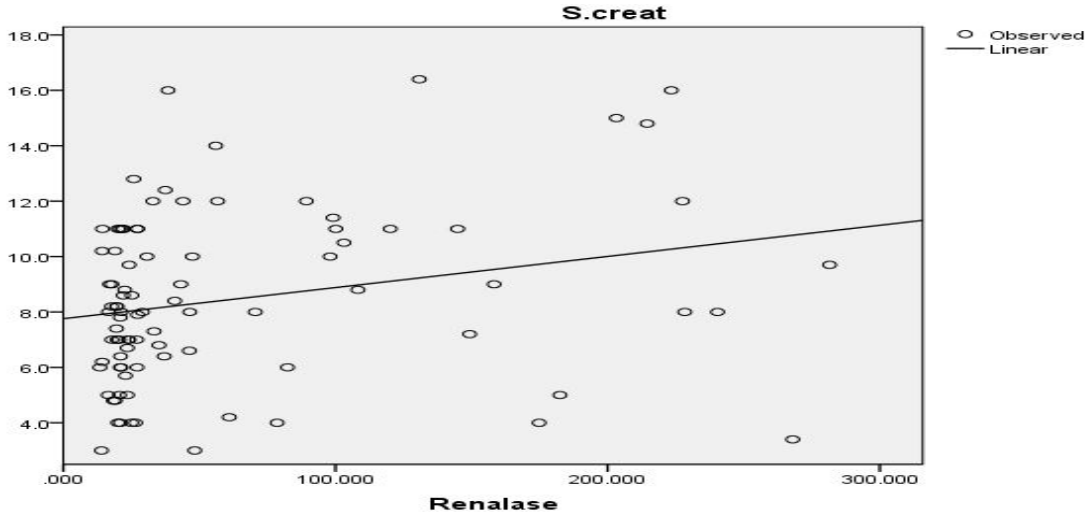

Figure (3): The correlation between the serum renalase and serum creatinine (s.creat)

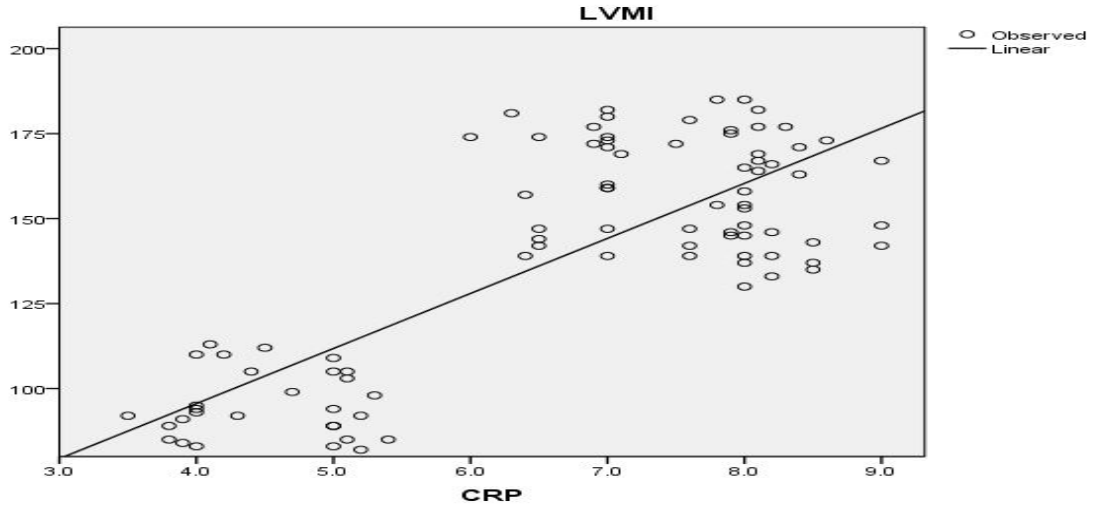

Figure (4): Correlation between left ventricle mass index (LVMI) and C-reactive protein (CRP)

There were significant relations between the serum renalase and s.creat and LVMI as presented in figures2 and 3. There was a significant positive relation between LVMI and CRP, as shown by figure4.

4. DISCUSSION

Renalase is a kidney secreted enzyme that was discovered in 2005 and has a vital role in controlling blood pressure [14]. Since its discovery, Renalase has been studied for its impact on blood pressure regulation and cardiovascular diseases. Firstly, a study in 2008 [15] tried to discover the relation between renalase level and chronic kidney diseases as well as cardiovascular complications. In that study, Renalse was found to be able to degrade catecholamines and consequently regulate blood pressure. Moreover, the same study suggested that, as a result of kidney function deficiency in patients with chronic kidney diseases, the level of renalase enzyme that was secreted from the kidney will decrease, and hence those patients have a higher tendency to have elevated blood pressure and cardiovascular complications.

This study has been argued by a recently published one [10]. The new study showed that the lower renalase synthesis by the kidney in CKD is reflected as a decreased renalase levels in erythrocytes. On the other hand, the same cases were found to have a high level of serum and urine concentrations of Renalase. This rise was attributed to compensatory production of Renalase in extra-renal organs, such as the heart, skeletal muscles, and the nervous system [16], as a result of changes in the cardiovascular system and hypertension. So, to sum up, the overall level of renalase enzyme was increased as a result of chronic kidney diseases. In addition to this study, another recent study [17] found a strong association between the circulating renalase enzyme and the renal function, which proposed utilizing renalase enzyme level as a biomarker to investigate renal dysfunction pre-dialysis patients. The same outcome was also supported by [2].

The approach of relating the high level of renalase enzyme and left ventricular hypertrophy in patients with kidney problems has been proposed by several studies. The study [18] showed that left ventricular hypertrophy is one of the most common cardiac abnormalities in patients with chronic kidney disease, and at the same time, those patients have a high level of renalase enzyme due to their kidney disease therefore from the previous two points, the study concluded that there might be a direct correlation between the increased level of renalase enzyme and LVH in patients with chronic kidney diseases. Another study [19] demonstrated that high renalase enzyme levels are positively correlated with LVH, where the left ventricular mass index was markedly increased.

The current study was performed on 90 hemodialysis patients whose mean age was 46, the majority of them were males (55.6%), and their mean renalase level was 61.7. Furthermore, most cases were severely abnormal 60%, 27.8% were normal, and only 10% had moderate abnormal readings, and the overall mean LVMI was found to be 138 (g/m2). Correlation between age groups and LVMI showed that 73.7% of the older age group (50-<60y) had a severely abnormal LVMI. On the other hand, there was no statistically significant difference between age groups as regards renalase level among dialysis patients.

The major outcomes of the current study can be shown as the following; the level of Renalase was significantly increased with the moderately and severely abnormal LVMI among dialysis patients. Considering the correlation between renalase levels and the other parameters, the current study detected no significant relationship between serum renalase and age, blood glucose, Ca, Hb, Tc, HDL, LDL, TG, CRP, and Albumin. But, there were significant relations between the serum renalase and s. creat, bl. Urea, Ph, LVMI, and dialysis vintage. Considering the correlation between LVMI and the other parameters, the current study detected no significant relations between LVMI and age, s. creat, bl. Urea, blood glucose, Ca, Ph, Tc, HDL, LDL, TG, and Albumin. But, there were significant positive relations between LVMI and Hb, CRP, and dialysis vintage.

Oguz EG et al. (2016) [18] was an important study that examined the association between renalase levels and LVH. Such a study discovered a positive correlation between LVMI and dialysis vintage and C-reactive protein (CRP) levels and a negative correlation between LVMI and residual diuresis and haemoglobin levels. Additionally, serum renalase levels were significantly greater in HD patients (212 ± 127 ng/mL) than in controls (116 ± 67 ng/mL) ($p<0.001$), and Renalase levels were positively related to serum creatinine and dialysis vintage. One of the primary limitations of such a study was really the limited sample size; a higher sample size is required for compelling statistical significance, which was avoided in our investigation.

Another important study that analyzed the relationship between renalase level and LVH [20] found that the median serum renalase level was significantly higher in the dialysis patients than in the control group, and renalase level was positively correlated

with C-reactive protein ($r = 0.705$, $p < 0.001$). A third study [21] showed that a high serum renalase level could predict a higher risk for the composite endpoint of myocardial infarction, stroke, and death. In addition to that, renalase level was also associated with other cardiovascular complications. The study [22] showed that In children having chronic kidney diseases, there is an apparent positive association between renalase level and CKD stage. In addition to that finding, the same study proposed that Renalase does not correlate with the blood pressure but may be a marker of arterial stiffness. The previous findings were supported by [23], which found that children with chronic kidney disease renalase levels are higher compared to healthy ones, and that can be a marker of arterial stiffness.

5. CONCLUSION

Our study revealed that Renalase might be a potential prognostic biomarker for LVH, which would be strongly linked with an elevated risk of mortality in individuals with HD. The primary determinants of renalase levels, dialysis time, and serum creatinine, might also be linked with LVH in long-term HD patients, implying that monitoring serum renalase levels could be a possible way to detect LVH development and therefore enhance HD patient survivability.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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