STUDY THE ASSOCIATION BETWEEN SERUM ASYMETRICAL DIMETHYLARGININE LEVEL AND CARDIAC FUNCTIONS IN CHRONIC KIDNEY DISEASE PATIENTS

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ABSTRACT

Background: *It is well known that cardiovascular disease is the leading cause of death for those who suffer from chronic renal disease, making it a pressing global public health concern. Human blood contains a naturally occurring modified amino acid called asymmetric dimethylarginine (ADMA). It may have a significant role in the development of atherosclerosis by preventing the body from producing nitric oxide, a gas essential for maintaining healthy vascular tone.*

Aim of the work: *This research aimed to examine the correlation between ADMA levels in the blood and heart function as measured by tissue Doppler imaging in patients with chronic renal disease.*

Patients and methods: *Ninety individuals were enrolled in our study from the National Institute of Nephrology and Urology's outpatient clinics and inpatient units. All patients underwent a thorough history and physical examination as well as laboratory tests, echocardiography, and Tissue Doppler imaging.*

Results: *There are a highly significant difference among three groups as regard as serum Creatinine level, estimated glomerular filtration rate (eGFR), serum calcium, Parathyroid hormone, serum ADMA, interventricular septal diameter (IVSD), left atrial diameter (LAD), Septal Peak E' and Lateral Peak E'. There is a positive correlation with between ADMA and serum phosphorus, and a negative correlation between ADMA and lateral peak E'.*

Conclusion: *Tissue Doppler imaging is considered to be more accurate than echocardiography in estimating diastolic function, and serum ADMA is inversely correlated with diastolic function in chronic kidney disease (CKD) patients.*

Key words: *Tissue Doppler imaging, diastolic dysfunction, ADMA.*

INTRODUCTION:

Minor to moderate renal insufficiency has also been documented to be related with unfavorable cardiovascular events, adding further weight to the idea that chronic kidney illness is a risk factor for cardio-vascular disease. Moreover, cardiovascular disease is the leading cause of death in CKD patients, which is not fully explained by the clustering of the conventional cardiovascular risk factors[(1)].

The amino acid asymmetric dimethyl-larginine (ADMA) occurs naturally in human blood. Reduced nitric oxide production, a major regulator of arterial tone, may have a significant role in the

development of atherosclerosis. ADMA has been linked to several markers of preclinical atherosclerosis, such as carotid intima-media thickness and flow-mediated dilatation. High levels of circulating ADMA have also been linked to an increased risk of cardiovascular disease (CVD), according to growing research[(2)].

Patients with chronic renal disease are at increased risk for nitric oxide insufficiency, which has been linked to a hastened course of the disease, hypertension, and cardiovascular problems. There appears to be a significant role played by an uptick in endogenous nitric oxide inhibitors like asymmetric dimethylarginine. The accumu-lateion of asymmetric dimethylarginine is a predictor of the development of cardiovascular problems in CKD patients as well as an increased risk of mortality from renal failure[(3).]

Studies have shown that high levels of ADMA foretold a more rapid decline in renal function and increased the development of renal impairment by causing glomerular hypertension, salt buildup, cell structure damages as well as endothelial damages[(4)].

ADMA may contribute to renal impairment through a number of different molecular processes[(5)].

AIM OF THE WORK:

This research aimed to examine the correlation between ADMA levels in the blood and heart function as measured by tissue Doppler imaging in patients with chronic renal disease.

PATIENTS AND METHODS:

This was a cross sectional trial and was performed in National Institute of Nephrology outpatient clinic and inpatient department from December 2019 till June 2020. Ain Shams University's ethical board has given its stamp of approval to this work. Ninety patients with chronic kidney disease participated in the research (CKD) stage 3”4”5 (30 patients in each group)

Inclusion Criteria: The patients should be ≥ 18 years old and admitted or maintained on regular follow up in National institute of nephrology. The patients had CKD stage 3 or stage 4 or stage 5.

Exclusion Criteria: Active infection, Cancer, Active autoimmune disease, decompensated liver disease and Class III and IV heart failure.

Sampling method:

- A consecutive sampling methodology was used for CKD participant.

Sample Size:

90 CKD patients divided to 3 groups: (eGFR was measured by Cockcroft and Gault formula.)

Group I: Thirty CKD patients stage 3

Group II: Thirty CKD patients stage 4

Group III: Thirty CKD patients stage 5

All patients will be subjected to: Full thorough history taking including medical co-morbidities, etiology of renal disease, also comprehensive Clinical examination was done. Venous samples will be taken for: urea, creatinine, complete blood picture, serum albumin, serum electrolytes (Calcium - Phosphorus- Parathyroid hormone), lipid profile (Triglyceride, Cholesterol, LDL, and HDL), and serum ADMA level. **Echocardiography with tissue Doppler study.**

Methods of Measuring ADMA:

The blood plasma was separated using centrifugation. Prior to analysis, plasma samples were frozen at 20 degrees Celsius. The concentration of ADMA was determined using a commercial ELISA kit (YL Biotech Co., Ltd., Shanghai) using the

supplied protocol. The results are given in (µmol/ml) with a reference range (0.5-1). Serum samples were also collected at the same time to measure other parameters.

Statistical Analysis:

Personal computers with a social sciences statistical software suite were used for the analysis (IBM SPSS VERSION 20. 0). Each parameter's data was presented and analyzed appropriately for its type of data. P-value: Significant (S) at P< 0.05, non-Significant (NS) at P > 0.05 and highly significant (HS) at P<0.01 (HS). Multi-variate linear regression analysis for factors associated with serum ADMA level

RESULTS:

Table 1: Comparison between 3 groups of study as regard basic descriptive data

		Group I (GFR 30-59)	Group II (GFR 15-29)	Group III (GFR<15)	Test value	P-value	Sig.
		No. = 30	No. = 30	No. = 30			
Age (years).	Mean ± SD	42.33 ± 11.83	39.77 ± 13.95	38.67 ± 10.71	0.709•	0.495	NS
	Range	17 – 67	18 – 78	22 – 67			
Gender	Female	19 (63.3%)	17 (56.7%)	13 (43.3%)	2.509	0.285	NS
	Male	11 (36.7%)	13 (43.3%)	17 (56.7%)			
BMI (kg/m²)	Mean ± SD	20.33 ± 3.80	21.30 ± 3.72	21.53 ± 4.24	0.787•	0.458	NS
	Range	14 – 29	16 – 29	15 – 32			
BWT (kg)	Mean ± SD	73.20 ± 15.55	75.27 ± 16.47	81.00 ± 16.24	1.892•	0.157	NS
	Range	38 – 101	41 – 104	59 – 132			

Table 1: non-significant difference among the 3 groups in descriptive data.

BMI: Body Mass Index BWT: Body Weight

Table 2: Comparison between 3 groups of study as regard different laboratory findings :

		Group I (GFR 30-59)	Group II (GFR 15-29)	Group III (GFR<15)	Test value	P-value	Sig.
Urea mg/dl	Mean ± SD	98.50 ± 37.18	88.70 ± 28.92	99.90 ± 33.27	1.008	0.369	NS
	Range	45 – 178	42 – 158	39 – 161			
Creatinine mg/dl	Mean ± SD	2.06 ± 0.34	2.88 ± 0.62	4.12 ± 0.43	141.302	<0.001	HS
	Range	1.5 – 3	1.9 – 4.2	3.1 – 5			
▪ GFR (ml/min/1.73)	Mean ± SD	36.77 ± 5.41	22.80 ± 3.51	12.97 ± 0.85	304.220	<0.001	HS
	Range	31 – 51	15 – 29	11 – 14			
*ADMA ng/L	Median (IQR)	12701 (4356 - 18756)	14853.5 (6734 - 25367)	18481 (12244 - 30342)	6.570	0.037	S
	Range	2156 – 36710	2537 – 53872	2642.3 – 54623			
Uric Acid mg/dl	Mean ± SD	5.73 ± 1.39	5.64 ± 1.53	5.43 ± 1.37	0.351	0.705	NS
	Range	3.8 – 9.5	3.7 – 9	3.8 – 10.8			
Albumin g/dl	Mean ± SD	3.81 ± 0.42	3.66 ± 0.59	3.93 ± 0.45	2.259	0.111	NS
	Range	2.9 – 5	2.4 – 4.7	2.9 – 5			
Hemoglobin g/dl	Mean ± SD	9.54 ± 1.18	9.60 ± 1.20	9.94 ± 0.89	1.156	0.319	NS
	Range	7.2 – 12.1	7.4 – 12	8.6 – 11.8			
Hematocrit %	Mean ± SD	26.90 ± 3.17	26.86 ± 3.53	27.67 ± 2.29	0.670	0.514	NS
	Range	18 – 33	18 – 37	24 – 33			
Total Leucocytic Count K/ul	Mean ± SD	6.43 ± 1.83	6.59 ± 1.72	6.92 ± 1.86	0.578	0.563	NS
	Range	2.7 – 10.1	3.7 – 10	3.5 – 11			
Platelets K/ul	Mean ± SD	227.97 ± 70.52	248.10 ± 67.71	229.53 ± 84.64	0.675	0.512	NS
	Range	110 – 367	145 – 432	109 – 410			

Calcium mg/dl	Mean ± SD	8.79 ± 1.05	8.40 ± 1.07	7.67 ± 0.82	10.049	<0.001	HS
	Range	6.7 – 11	6.2 – 10.2	5.8 – 9.8			
Phosphorus (mg/dl)	Mean ± SD	5.42 ± 0.85	5.07 ± 0.77	5.24 ± 1.45	0.824	0.442	NS
	Range	4.3 – 8.7	3.9 – 7.2	3.7 – 9.3			
Vitamin D3(ng/m)l	Median(IQR)	18.85(7.66 – 34.6)	15.53(4.15 - 27.58)	8.21(4.23 - 14.3)	7.081	0.029	S
	Range	0.64 – 61.3	0.59 – 55.4	1.46 – 42.1			
Parathyroid Hormone (mg/dl)	Mean ± SD	255.10 ± 63.59	271.77 ± 83.86	371.33 ± 133.46	12.307	<0.001	HS
	Range	160– 387	165-501	187 – 651			

Post hoc analysis

Parameters	P1	P2	P3
Creatinine mg/dl	<0.001	<0.001	<0.001
ADMA ng/L	0.323	0.025	0.197
GFR (ml/min 1.73)	<0.001	<0.001	<0.001
Calcium mg/dl	0.009	<0.001	0.142
Vitamin D3ng/ml	0.32	<0.001	<0.001
Parathyroid Hormone mg/dl	<0.001	<0.001	0.702

P1: Comparing of Group I to Group II
P2: Comparing of Group I to Group III
P3: Comparing of Group II to Group III

In terms of blood Creatinine, estimated GFR, serum calcium, and PTH, there are statistically significant differences between the three groups. When comparing serum ADMA levels amongst the three groups, there is a substantial difference.

*ADMA: asymmetric dimethyl arginine

▪ GFR: Glomerular Filtration Rate

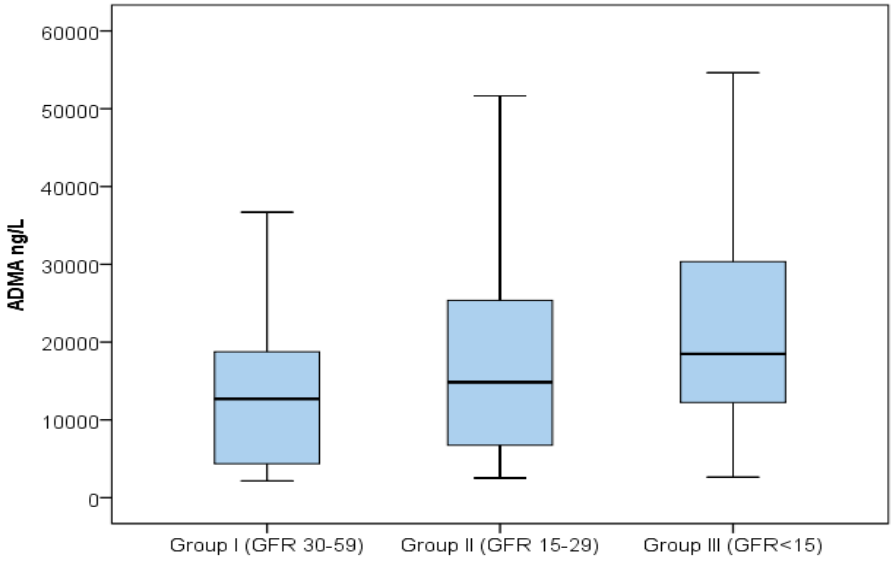

Diagram 1: Comparison between the three studied groups as regard ADMA

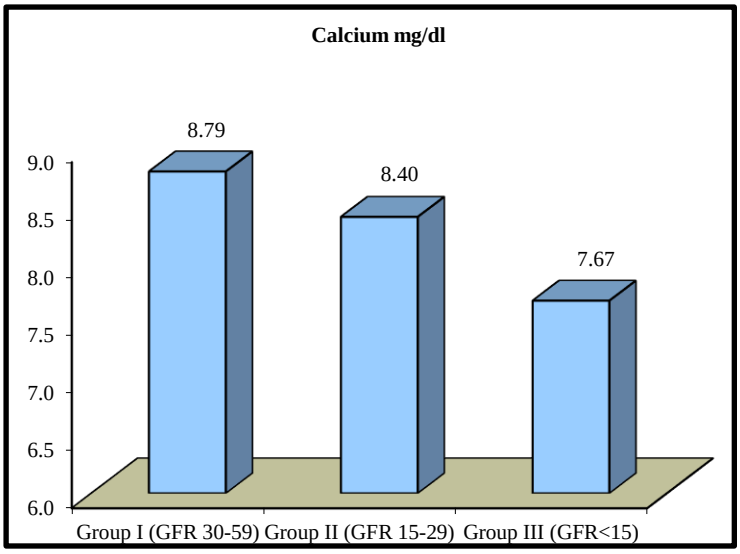

Diagram 2: Comparison between the 3 studied groups as regard serum calcium.

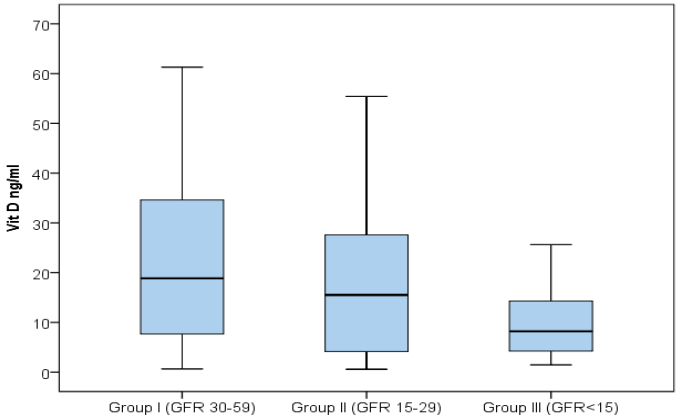

Diagram3: Comparison between the three groups of study as regard Vit. D.

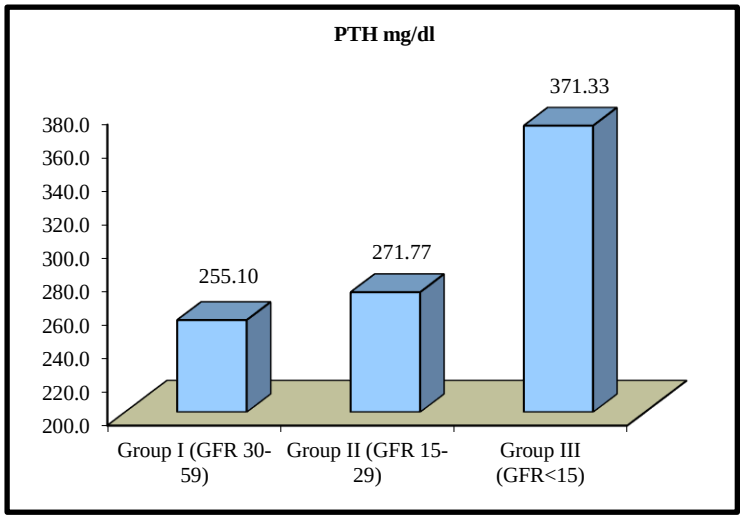

Diagram4: Comparison between the three studied groups as regard PTH.

Table 3: Comparison between 3 groups of study as regard lipid profile markers

		Group I (GFR 30-59)	Group II (GFR 15-29)	Group III (GFR<15)	Test value•	P-value	Sig.
Cholesterol mg/dl	Mean ± SD	194.90 ± 30.95	181.23 ± 38.02	184.40 ± 39.89	1.153	0.320	NS
	Range	135 – 256	78 – 264	119 – 316			
HDL Cholesterol mg/dl	Mean ± SD	32.73 ± 6.52	29.90 ± 5.60	28.23 ± 7.81	3.455	0.036	NS
	Range	22 – 44	21 – 44	21 – 61			
Triglyceride mg/dl	Mean ± SD	186.73 ± 47.15	190.20 ± 65.53	200.57 ± 47.10	0.534	0.588	NS
	Range	57 – 273	59 – 301	101 – 300			
LDL Cholesterol mg/dl	Mean ± SD	174.20 ± 25.62	163.07 ± 34.36	167.07 ± 27.36	1.107	0.335	NS
	Range	101 – 211	79 – 231	109 – 211			

Table 4: Comparison between 3 groups of study as regard echocardiography findings

		Group I (GFR 30-59)	Group II (GFR 15-29)	Group III (GFR<15)	Test value•	P-value	Sig.
IVSD cm	Mean ± SD	1.08 ± 0.17	1.14 ± 0.18	1.32 ± 0.20	14.005	<0.001	HS
	Range	0.7 – 1.35	0.87 – 1.52	0.95 – 1.61			
EF %	Mean ± SD	61.97 ± 6.81	60.40 ± 5.39	58.90 ± 6.76	1.747	0.180	NS
	Range	49 – 75	48 – 70	41 – 71			
PWDD cm	Mean ± SD	1.17 ± 0.22	1.22 ± 0.27	1.23 ± 0.21	0.537	0.586	NS
	Range	0.8 – 1.6	0.8 – 1.7	0.9 – 1.7			
LVEDD cm	Mean ± SD	5.35 ± 0.66	5.43 ± 0.59	5.18 ± 0.43	1.547	0.219	NS
	Range	4 – 7.1	4 – 6.4	4.2 – 6.2			
LVESD cm	Mean ± SD	3.46 ± 0.44	3.69 ± 0.37	3.55 ± 0.32	2.784	0.067	NS
	Range	2.7 – 4.2	2.8 – 4.3	3 – 4.1			
E/A	Mean ± SD	1.04 ± 0.14	1.06 ± 0.13	1.01 ± 0.16	0.905	0.408	NS
	Range	0.85 – 1.4	0.8 – 1.3	0.7 – 1.3			
LVMI g/m2	Mean ± SD	126.53 ± 20.36	131.50 ± 19.71	132.83 ± 16.53	0.922	0.402	NS
	Range	86 – 168	97 – 172	99 – 171			
LVM g	Mean ± SD	214.97 ± 25.01	221.47 ± 24.02	229.17 ± 43.82	1.456	0.239	NS
	Range	169 – 272	179 – 262	153 – 316			
LAD cm	Mean ± SD	3.80 ± 0.29	3.97 ± 0.35	4.04 ± 0.36	3.879	0.024	S
	Range	3 – 4.4	3.22 – 5.2	3 – 5			

Post hoc analysis			
Parameters	P1	P2	P3
IVSD cm	0.492	<0.001	<0.001
LAD cm	0.553	0.013	0.068

Table 4: While comparing the three groups on IVSD, there is a statistically significant difference between them; when comparing the three groups on LAD, there is a statistically significant difference between them also.

IVSD: Inter ventricular septum diameter
EF: Ejection fraction
PWDD: Posterior Wall Diastolic Diameter
LVEDD: Left Ventricular End Diastolic Diameter
LVESD: Left Ventricular End Systolic Diameter
LVMI: Left Ventricular Mass Index
LVM: Left Ventricular Mass
LAD: Left Atrial Diameter

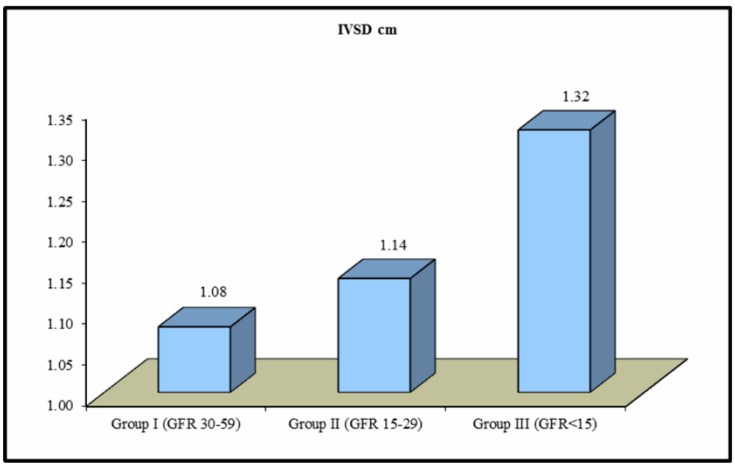

Diagram 5: Comparison between the 3 studied groups as regard IVSD

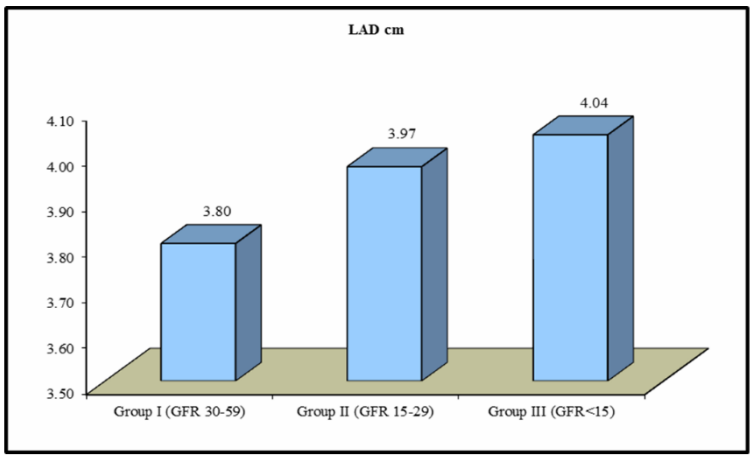

Diagram 6: Comparison between the 3 studied groups as regard LAD.

Table 5: Comparison between three groups of study as regard Tissue Doppler findings

		Group I (GFR 30-59)	Group II (GFR 15-29)	Group III (GFR<15)	Test value•	P-value	Sig.
Septal Peak E'	Mean±SD	7.13 ± 0.78	6.50 ± 0.73	5.77 ± 0.43	31.850	<0.001	HS
	Range	6 – 8	5 – 8	5 – 6			
Lateral Peak E'	Mean±SD	8.47 ± 1.01	7.17 ± 1.05	6.40 ± 0.50	41.386	<0.001	HS
	Range	6 – 11	6 – 10	6 – 7			
Post hoc Analysis							
Parameters		**P1**		**P2**		**P3**	
Septal Peak E'		0.002		<0.001		<0.001	
Lateral Peak E'		<0.001		<0.001		0.001	

There are highly significant differences among three groups as regard as Septal Peak E' and Lateral Peak E'.

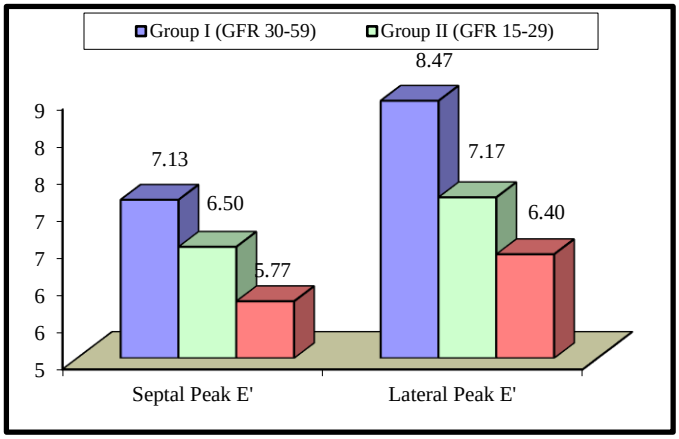

Diagram7: Comparison between the three studied groups as regards Tissue Doppler findings**.**

Table 6: Correlation coefficient (r) between serum ADMA and other biomarkers.

	ADMA ng/L	
	R	P-value
Age (year)	0.095	0.374
m2)/Body Mass Index (kg	0.233*	0.027
Body Weight (kg)	0.263*	0.012
Systolic Blood Pressure (mmHg)	0.112	0.294
Diastolic Blood Pressure (mmHg)	-0.008	0.937
Urea (mg/dl)	-0.098	0.357
Creatinine (mg/dl)	0.215*	0.042
Glomerular Filtration Rate (ml/min 1.73)	-0.251*	0.017
Uric Acid (mg/dl)	-0.173	0.102
Albumin (g/dl)	0.170	0.109
Hemoglobin (g/dl)	0.024	0.823
Hematocrit %	0.032	0.764
Total Leucocytic Count (K/ul)	0.041	0.698
Platelets (K/ul)	0.069	0.521
Calcium (mg/dl)	-0.517**	<0.001
PO4 (mg/dl)	0.352**	0.001
K (mmol/l)	0.046	0.670
Parathyroid Hormone (mg/dl)	-0.075	0.482
Total Cholesterol (mg/dl)	0.166	0.117
HDL Cholesterol (mg/dl)	-0.020	0.854
Triglyceride (mg/dl)	0.179	0.092
LDL Cholesterol (mg/dl)	0.143	0.180
IVSD cm	0.004	0.973
EF %	0.080	0.455
PWDD cm	-0.066	0.536
MWT cm	-0.124	0.244
LVEDD cm	-0.204	0.053
LVESD cm	-0.072	0.497
E/A	0.075	0.483
LVMI cm	+0.233	0.027
LVM cm	0.127	0.001
LAD cm	0.040	0.709
Septal Peak E'	-0.219	0.038
Lateral Peak E'	-0.262	0.016

IVSD: Inter ventricular septum diameter EF: Ejection fraction
PWDD: Posterior Wall Diastolic Diameter LVEDD: Left Ventricular End Diastolic Diameter
LVESD: Left Ventricular End Systolic Diameter LVMI: Left Ventricular Mass Index
LVM: Left Ventricular Mass LAD: Left Atrial Diameter

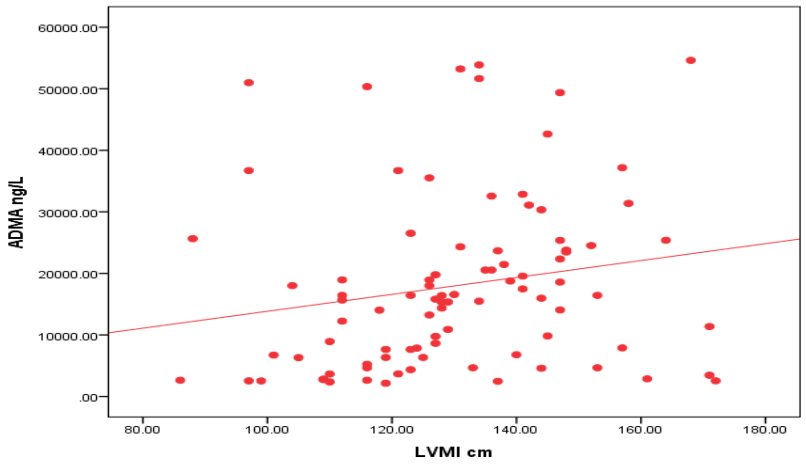

Diagram 8: Correlation between serum ADMA and LVMI

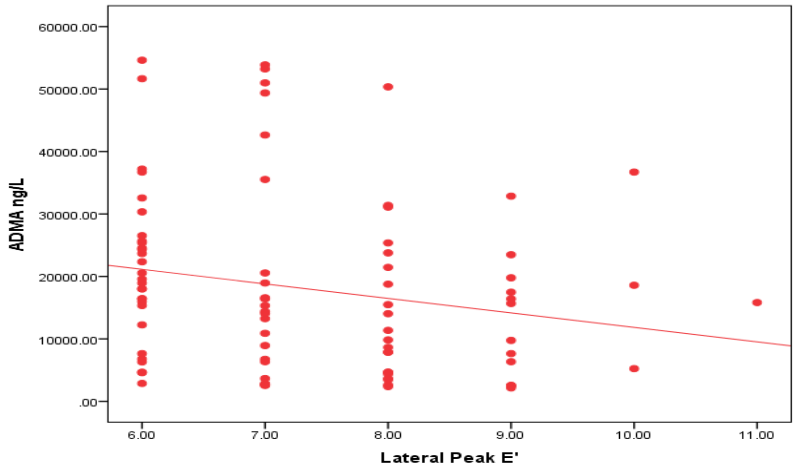

Diagram 9: Correlation between serum ADMA and lateral peak E

There is a negative correlation with between ADMA and lateral peak E.

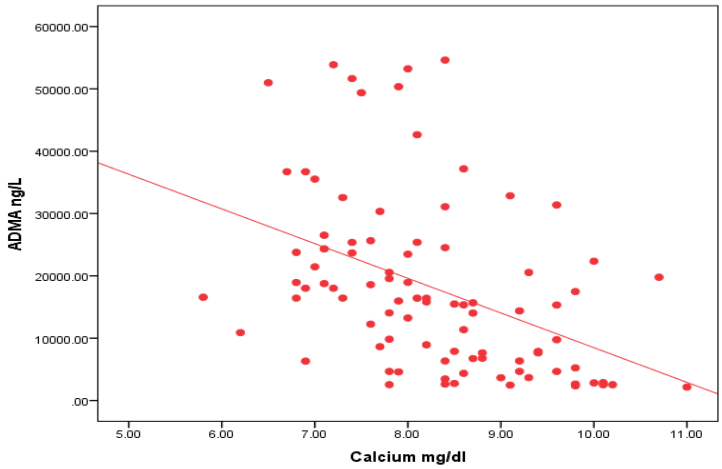

Diagram 10: Correlation between serum ADMA and calcium

There is a negative correlation with between ADMA and serum calcium.

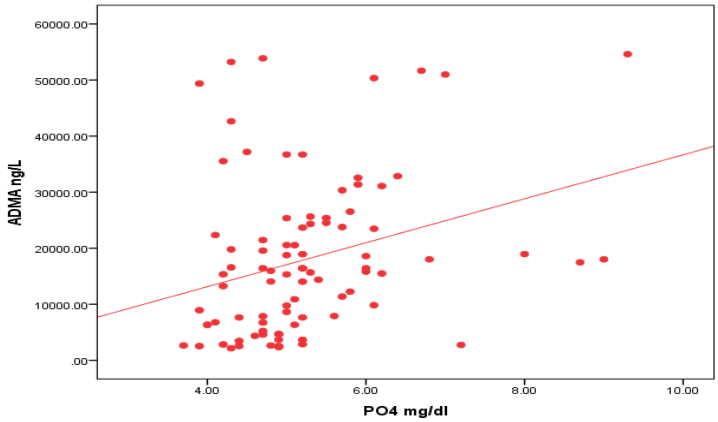

Diagram11: Correlation between serum ADMA and PO_4.

There is a positive correlation with between ADMA and serum PO_4

Table 7: Multivariate linear regression analysis for factors associated with serum ADMA level

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	-36019.488	20984.211		-1.717	0.090
Body Mass Index (kg/m2)	291.262	56.450	0.483	5.160	0.000
Body Weight (kg)	211.226	45.624	0.401	4.630	0.000
Creatinine mg/dl	3217.466	1850.791	0.210	1.738	0.086
Glomerular Filtration Rate (ml/min 1.73)	-23.528	191.681	-0.018	-0.123	0.903
Calcium mg/dl	-776.128	1146.383	-0.060	-0.677	0.500
Phosphorus mg/dl	1484.762	995.327	0.127	1.492	0.140
Left Ventricular Mass Index cm	133.482	65.965	0.170	2.024	0.046
Septal Peak E'	-1669.193	1714.209	-0.107	-0.974	0.333
Lateral Peak E'	1691.780	1345.159	0.146	1.258	0.212

DISCUSSION:

Increasing evidence suggests that CKD is a significant independent risk factor for CVD. It's becoming increasingly obvious that cardiovascular disease is a greater killer than end-stage renal illness. Initial evidence linking renal failure with CVD outcomes emerges in the dialysis population, where an increased mortality rate from cardiovascular causes was observed [(3)].

Inhibition of NO by asymmetric dimethylarginine is linked to oxidative stress, which in turn causes endothelial dysfunction and vascular damage and exacerbates atherosclerosis**[(6)].**

Our study was a cohort cross sectional study included 90 patients with chronic kidney disease divided into 3 groups stage 3,4 and 5 according to KDIGO classification each group contain 30 patients.

The mean age in our study was (42.33, 39.7, 38.6) years old in stage 3, 4 and 5 respectively with no significant difference among three groups (p=0.495). (Table1).

Our research showed that serum Creatinine levels varied significantly across the three groups that we compared (p<0.001) with mean range of creatinine (2.06, 2.88, 4.12) mg /dl in stage 3, 4 and 5 respectively (Table 2). These results were in line with *Thadhani et al [(7)]*.

Both Our study and the *Thadhani et al.* ***(2012)*** study have the same target population who have stage 3, 4 and 5 CKD with same risk factors e.g. (Diabetes, Hypertension, etc..)[(7)].

In this investigation, we found that serum calcium levels varied significantly between the groups. (p<0.001) (Table 2) (Diagram 2) which decrease with the progression of disease with mean range (8.79, 8.4, 7.67) mg /dl in stage 3, 4 and 5 respectively(in the post hoc analysis, the significant difference appears between group I and group III , this result was in agreement with *Schwarz et al.*[(8)].

Bone and mineral metabolism are severely disrupted in patients with chronic kidney disease, leading to a complicated illness known as chronic kidney disease - mineral bone disorder (CKD-MBD). Disturbances emerge at the onset of CKD and increase as the disease progresses. A decrease in 1,25-dihydroxyvitamin D (1,25D), an increase in serum phosphate, and a decrease in serum calcium are all biochemical changes associated with CKD-MBD. Heterogeneous bone disease and excessive vascular and soft tissue calcification also occur alongside decreased calcium absorption and decreased urine calcium excretion. Increased risk of cardiovascular disease and death from cardiovascular causes has been linked to CKD-MBD. **[(9)]**

However, *Freethi et al.*[(10)] reported that calcium levels were not significantly different across stages 3, 4, and 5 of chronic kidney disease, according to the mean range (9.2, 9.1, 8.9) mg/dl respectively (p =0.06).

In our investigation, we discovered no statistically significant difference in serum phosphorus (po4) levels across the three groups (p=0.442)(Table 2) (Diagram 3).This was against *Freethi et al.*[(10)] who found that serum po4 increase with progression of CKD stages with mean range (3.9, 4.44, 5.2)mg/dl for CKD stage 3, 4 and 5 respectively (p=0,002)

We found in this study that there is a significant difference among three groups as regard serum vitamin D level which was decreased with the progression of chronic kidney disease with the median value of vitamin D among 3 groups (group 1 M= 18.85, group 2 M= 15.53, group 3 M= 8.21**(p= 0.029**)(Table 2) (Diagram 3). These result in agreement with *Levin A, et al., 2007.*

Levin and his colleagues [11] found that patients at high risk for renal problems might be identified by their 25(OH) D status.

Serum 1, 25-dihydroxyvitamin D levels have been shown to decrease in tandem with glomerular filtration rate (GFR) reductions in multiple investigations. A decrease in renal mass is a primary factor in poor 1,25-dihydroxyvitamin D production because it leads to a decrease in the amount of 1α hydroxylase available for converting 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D [12]

Results from our study showed that serum PTH levels varied significantly across the three groups we compared which increases with the progression of disease with mean range (271.7, 255.1, 371.33) mg/dl in stage 3, 4 and 5 respectively (p<0.001) (Table 2) (Diagram 4). This result didn't go with *Palmer et al* [13].

Palmer and his colleagues [13] found that Patients' serum PTH levels tend to decline in tandem with advancement in CKD stages (As chronic kidney disease advances, the body's PTH levels drop). However, our study and Palmer study found that Many of the problems of end-stage renal disease (ESRD) can be traced back to PTH's association with disturbances in the metabolism of electrolytes such calcium, magnesium, phosphorus, and potassium. In order to prevent CKD patients from problems, it is important to monitor PTH at an early stage and to take any necessary actions regarding these electrolytes.

In our study, in terms of serum uric acid levels, there was no discernible difference between the three groups (p=0,705) (Table 2). This was against *Doualla et al.* [14] who found that there was a statistically significant difference in mean blood uric acid levels amongst CKD severities. (p value < 0.001).

In our study was found that the average range of ADMA differed significantly which were 12701,14853, and 18481 ng/L in CKD stages 3, 4, and 5, respectively Differences in ADMA levels between the groups were statistically significant. (p=0.037) (Table 2) (Diagram 1)

Our study supported by *Asmarawati et al* [15]. This study conducted on 75 patients three groups stage 3, 4 and 5 CKD Stage 3 had the lowest mean ADMA level (0.62 (+/- 0.11) IU/mL), stage 4 had the second lowest (0.72 (+/- 0.16) IU/mL), and stage 5 had the highest (0.73 (+/- 0.18) IU/mL). Differences in ADMA levels across groups were statistically significant (p=0.04) with the largest difference occurring between stages 3 and 5.

In our study there was no differences between three groups as regard mean values of LVMI (p=.402) with mean range in CKD 3, 4 and 5 were (126.53, 131.50, 132.83) g/m^2 respectively (Table 4), this was supported by *Gromadzinski and Pruszczyk* [16] study conducted on 70 patients with CKD at stages 3-5 and 26 control group which found that there was no significant difference between CKD stages only between CKD stage 4,5 and control group (p=0.015).

Regarding E/A, our investigation found no significant differences among the three groups (p=0.4)as well as EF %(P=0.180) (Table 4), this was against *Gromadzinski and Pruszczyk*[16] which found borderline significance between CKD stage 3,4 and 5 as regard E/A ratio(p=0.05).

Beata Franczyk-Skóra[17] study conducted on 118 CKD patients divided in to 4 groups stage II, III, IV and V he found that EF decrease with progression of CKD with mean range (56.0, 50.0, 50.0, 45.0)% for CKD stage II, III, IV and V respectively (p<0.001) and Using the E/A ratio, we found that results were constant between CKD stage II and IV patients (0.80), indicating that this ratio is in line with current recommendations. But with stage V dialysis

patients, this ratio was dramatically higher. (0.96) (p=0.007).

Three groups were significantly different from one another in our study in terms of IVSD (P<0.001) with mean range in CKD stage 3, 4 and 5 were (1.08, 1.14, 1.32) cm respectively (Table 4) (Diagram 5) and significant difference in LAD (p=.024) with mean range in CKD stage 3, 4 and 5 (3.80, 3.97, 4.04) cm respectively (Table 4) (Diagram 6). This was supported by *Beata Franczyk-Skóra*[17] who found that significant difference as regard IVSD (p<0.001) and LAD (p<0.001) with higher level in stage V.

Additionally, we found highly significant differences between the three groups with respect to the mean values of the lateral peak E (EmLvlat) with (p <0.001) and septal peak E (EmLvsept) with (p <0.001) (Table 5&Diagram7). *Gromadzinski and Pruszczyk* [16] showed that there was no difference between the CKD stages as regard the $EmLV_{lat}$ and $EmLV_{sept}$ but the mean range in $EmLV_{lat}$ in CKD 4 and CKD 5 was 6 cm/ s which lower than 8 cm /s which indicate diastolic dysfunction.

Cerasola et al. [18] confirmed these findings by assessing diastolic function in 156 hypertension individuals (both with and without CKD) using mitral inflow evaluation and tissue Doppler imaging. Diastolic function was shown to be significantly impaired in CKD patients. Furthermore, diastolic function was found to be independently related to renal function in a multiple regression analysis.

We demonstrated that ADMA is positively correlated with body mass index (Table 6) and this was against *Krzyzanowska et al.* [19] study was conducted on 103 diabetic patients, they found no correlation between ADMA and BMI.

We found no association between ADMA in the blood and uric acid levels (r=0.173, p=0.102). This was against *Kanbay et al.*[20], specifically, they discovered that uric acid levels in the blood were positively linked with ADMA levels (r = 0.73, p < 0.0001).

Plasma ADMA concentrations in our study did not correlate with systolic, diastolic blood pressure (Table 6), the findings were consistent with those of *Fleck et al.* [21], who examined plasma ADMA concentrations in 221 CKD patients and found no association between ADMA and either systolic or diastolic blood pressure.

Our results showed a modestly unfavorable relationship between ADMA concentration and glomerular filtration rate (r=-0.251, p=0. 042) and positive correlation with serum creatinine (r=0.251, p=0.017) (Table 6).A study conducted by *Ronden et al.* [22], on 171 patients divided in to three groups normal GFR, stage 2 and stage 3 who found that eGFR inversely correlated with ADMA level (standardized regression coefficient = -0.22, p=0.019).

Kielstein et al.[23] found, on the other hand, that ADMA levels rose in CKD patients regardless of renal function and had no correlation with GFR (r= -0.26, p=0.09). Plasma ADMA concentrations in renal patients were substantially linked with serum creatinine and GFR, despite the fact that *Fliser et al.*[2] evaluated plasma ADMA concentrations in 227 patients with non-diabetic kidney disorders and mild to moderate renal failure.

In our study there were no significant correlation between the ADMA level and cholesterol, LDL and Triglycerides levels. (Table 6).

ADMA levels were positively correlated with patients' LVMI in our study (r=.233, p=.027) (Table 6) (Diagram 8). This supported by *Shi et al.* [24], study conducted on 76 CKD patients and 15 controls who found significant correlation between ADMA and LVMI in CKD group (r=0.597, p=0.001).

Our study was corroborated by research by *Zoccali et al.* [3] that was conducted on 198 HD patients and found that 147 of them had LVH. Using multivariate analysis, he found that plasma ADMA was independently linked with LVMI (r=0.17, p=0.006) and significantly related to LVM (r=0.26, p <0.001).and direct related to RWT (r=0.35, p <0.001).

Nonetheless, ADMA levels were significantly correlated negatively with Em lateral and septal (Table 6) . According to these findings, CKD patients who have increased ADMA levels may have impaired left ventricular diastolic functioning. This supported by *Fatma* [25] study in 2008 that was conducted on fifty-four continuous peritoneal dialysis found that ADMA has a strong inverse relationship with Em (r=-0.28, p=0.01) as well as a positive association with LVMI (r=0.29, p=0.01).

In our study there was no correlation between ADMA and EF (r=0.080, p=0.455) (Table 6).this was against *Zoccali et al.* [3], who found significant negative correlation (r=-0.35, p <0.001).

We found that ADMA had an inverse relationship with serum Ca levels (r=-0.517, p<0.001) (Table 6) (Diagram 10) and also positive correlation between ADMA and po4 level(r=0.352, p=0.001) (Table 6) (Diagram 11).

In a multivariate linear regression analysis of factors influencing serum ADMA level, body mass index (BMI) and left ventricle mass index (LVMI) were emerged as the most significant markers affecting ADMA level. (Table7).

Conclusion:

ADMA levels were significantly higher in advanced CKD patients than early CKD stages. Tissue Doppler showed Diastolic function decrease with progression of the CKD disease. Echocardiography showed disturbance in cardiac structure (IVSD, LAD) with progression of CKD disease, as electrolyte disturbance and fluid retention. ADMA level positively correlates with serum creatinine. As ADMA accumulate with progression of CKD disease. ADMA level positively correlates with LVMI. ADMA level negatively correlated with lateral and septal peak E this indicate the relationship between ADMA level and diastolic function by tissue Doppler. Tissue Doppler Imaging is a more precise method of estimating diastolic function.

Ethical considerations:

The authors have taken care to avoid any ethical disruption (such as plagiarism, data manipulation, or multiple publications) at all costs.

Authors' contributions:

All of the authors were involved in the research's design. As a group, AHA, WMS, SA, and MAM worked together to analyze and interpret data. The initial draught was prepared by MAM. It was AHA, WMS and SA's job to revise the first version. The final version of the manuscript was approved by all of the writers.

Limitation of the Study: The study follows a cross-sectional design, includes a relatively small sample size and is influenced by substantial residual confounding

Conflicts of Interest: The authors state that the publishing of this paper is free of any conflicts of interest.

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العلاقة بين مستوي الثنائي ميثيل ارجينين الغير متماثل في الدم ووظائف القلب لدي مرضي القصور الكلوي المزمن

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المقدمة: من المعروف أن أمراض القلب والأوعية الدموية هي السبب الرئيسي للوفاة لمن يعانون من أمراض الكلى المزمنة ، مما يجعلها مصدر قلق عالمي ملحاً للصحة العامة. يحتوي دم الإنسان على حمض أميني معدل طبيعيًا يسمى ثنائي ميثيل أرجينين غير متماثل. قد يكون له دور مهم في تطور تصلب الشرايين عن طريق منع الجسم من إنتاج أكسيد النيتريك ، وهو عامل ضروري للحفاظ على قوة الأوعية الدموية الصحية.

الأهداف: يهدف هذا البحث إلى فحص العلاقة بين مستويات ثنائي ميثيل الأرجينين غير المتكافئة في الدم ووظيفة القلب كما تم قياسها عن طريق التصوير الدوبلري للأنسجة في المرضى المصابين بأمراض الكلى المزمنة.

. المرضى والأساليب: تم تسجيل تسعين فردًا في دراستنا من المعهد الوطني لأمراض الكلى وعيادات المسالك البولية الخارجية ووحدات المرضى الداخليين. خضع جميع المرضى لتاريخ شامل وفحص جسدي بالإضافة إلى الاختبارات المعملية وتخطيط صدى القلب وتصوير الأنسجة دوبلر.

النتائج: هناك فرق كبير بين ثلاث مجموعات فيما يتعلق بمستوى الكرياتينين في الدم ، وهرمون جارات الدرقية في مصل الدم ، وثنائي ميثيل الأرجنين غير المتماثل في الدم ، وقطر الحاجز البيني ، وقطر الأذين الأيسر ، وذروة الحاجز ، والذروة الجانبية. كما توجد علاقة ايجابية بين ثنائي ميثيل الأرجنين ومصل الفوسفور ، وارتباط سلبي بين ثنائي ميثيل الأرجنين غير المتماثل والذروة الجانبية.