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A Study of Cardiac Autonomic Neuropathy among Non-Diabetic Chronic Kidney Disease Patients

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Abstract

Background: The primary etiologies of morbidity and death in people with chronic renal disease are cardiovascular consequences. Having cardiovascular autonomic neuropathy increases your chance of dying suddenly from heart failure.

Aim of Study: To assess the CAN pattern in non-diabetic chronic kidney disease (CKD) who are not receiving dialysis.

Patients and Methods: Fifty non-diabetic, non-dialysis CKD patients participated in this case-control study and were split into two groups: 25 with CKD in stages 3 and 4 made up Group I, 25 with CKD stage 5 made up Group II, in addition to 25 healthy volunteers as a control group. Full history and clinical examination with stress on autonomic neuropathy manifestations, routine laboratories and resting echocardiography were done. The heart rate reaction to the Valsalva ratio, the heart rate fluctuation during deep breathing, and the heart rate response to the standing 30:15 ratio test.

Results: Cardiovascular autonomic neuropathy dysfunctions were significantly different in CKD patients (n=50) in comparison to the control group (MCp< 0.001). 29 had cardiac autonomic dysfunctions, the pattern that was detected in Group I was: 5 early parasympathetic, 4 definitive parasympathetic, 2 combined damage, 1 sympathetic damage. In Group II : 8 early parasympathetic, 6 definitive parasympathetic, and 3 combined damage. Patients with abnormal heart rate (R-R interval) variation during the deep breathing (beat/min) test had higher serum creatinine and lower serum calcium levels (FP=0.02).

Conclusion: Cardiac autonomic dysfunction is common in non-diabetic, non-dialysisCKD without significant association with the occurrence of autonomic neuropathy clinical symptoms.

Key Words: *Cardiac autonomic neuropathy – Chronic kidney disease - Cardiovascular diseases.*

Introduction

CARDIAC Autonomic Neuropathy (CAN) is a condition where the cardiovascular system's autonomic regulation is compromised. Between 2.5 percent to 50 percent of people have it [1]. It is associated with a reduction in heart rate variability leading to an increased risk of dysrhythmia such as paroxysmal atria tachycardia and ventricular ectopic, unstable blood pressure, postural hypotension, nocturnal hypoxemia, cardiac hypertrophy, and dialysis-induced hypotension. The identification of CAN is therefore very important since the presence of CAN in diabetic patients indicates a bad prognosis. According to certain reports, parasympathetic damage happens more frequently than sympathetic damage [2].

The etiology of CAN is not known, either in diabetic oruremic patients. However, there are many theories about the pathophysiology underlying autonomic neuropathy, including metabolic nerve injury, neurovascular insufficiency, autoimmune damage, or hyperglycemia as a pathogenic factor [3]. Both the onset and progression of cardiac autonomic neuropathy and diabetic peripheral neuropathy occur more quickly under the influence of the concurrent uremic condition and its constellation of specific metabolic/physiologic changes. Several toxins, notably Parathyroid Hormone (PTH)

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List of Abbreviations:

CAN : Cardiac autonomic neuropathy.
CKD : Chronic kidney disease.
ESRD : End stage renal disease.
PTH : Parathyroid hormone.
CVD : Cardiovascular disease.
SBP : Systolic blood pressure
DBP : Diastolic blood pressure.
LVH : Left ventricular hypertrophy.
HRV : Heart rate variability.
GFR : Glomerular filtration rate.
ANS : Autonomic nervous system.
HTN : Hypertension.
DM : Diabetes mellitus.
CRF : Chronic renal failure.

and 2-microglobulin (whose levels are higher in ESRD patients), may contribute to the development of uremic neuropathy, according to some research [4]. Cardiovascular impairment may be related to CAN via several pathological pathways. As a result, individuals with and without documented cardiovascular illness may employ CAN evaluation to stratify their cardiovascular risk [5].

It is generally known that the majority of renal insufficiency patients, regardless of stage, pass away from cardiovascular disease (CVD) before receiving hemodialysis or a kidney transplant. Numerous studies have attempted to identify factors that raise the risk of morbidity and death in individuals with CKD, especially those who have end-stage renal failure (ESRF). Anaemia, LVH, higher Systolic Blood Pressure (SBP), lower Diastolic Blood Pressure (DBP), Left Ventricular Hypertrophy (LVH), lower Systolic Blood Pressure (SBP), higher Systolic and Pulse Pressure, and all of these have been found to be independent risk factors for CV morbidity and death in ESRF patients. Furthermore, CKD is associated with diminished cardiac autonomic function. A drop in HRV has been shown to be a reliable predictor of mortality in studies on HRV in ESRF patients and its usage as a marker for CAN [6].

This study investigated CAN patterns and risk factors in non-diabetic people with late-stage chronic kidney disease (CKD) who weren't on dialysis.

Patients and Methods

This case-control research included 50 CKD patients who were selected from the Internal Medicine and Nephrology Departments of the Ain Shams University Hospital in Cairo, Egypt.

The research was conducted through one year from January 2016 till January 2017.

25 individuals had CKD in stages G3-4, while 25 others had CKD G5 but weren't receiving dialysis. Thestages are mainly builton calculation of estimated Glomerular Filtration Rate (eGFR) using the MDRD Equation: GFR (mL/min/1.73 m^2) = 175 x (Scr)-1.154 x (age) - 0.203 x (0.742 if female) x (1.212 if African American) [7]. 25 healthy volunteers who could serve as the control group according to their age and sex were also included.

There was no clinical indication of diabetes mellitus in any of the individuals., severe congestive heart failure, coronary heart diseases, cerebrovascular stroke or demyelinating disease, collagen disease, acute infection, decompensated liver disease (child c), thyroid disease, or malignancy. Neither the patients nor the controls were on medications that could influence the cardiovascular andautonomic nervous systems.

All subjects underwent full clinical history andexamination with emphasis on signs and symptoms of autonomic neuropathy which included impotence in males, bowel dysfunction with diarrhea, colonic distension, dysphagia, constipation, bladder problems as urine retention, hyposialism, hypohidrosis, numbness [8].

The Mean Arterial Pressurewas measured:MAP = (SBP + 2 (DBP))/3, where MAP = Mean arterial pressure, SBP = Systolic blood pressure, andDBP = Diastolic blood pressure [9].

Tests of cardiac autonomic neuropathy:

A- *Tests reflecting parasympathetic damage:*

1- Rhythm of the heart (R-R interval) The patient was told to take six breaths per minute for one minute while exhaling fully. The ECG paper, which was continually recorded, shows the length of deep breathing as well as the start of each inspiration and expiration. Using a ruler and conversion to beats per minute, the maximum and lowest R-R intervals of each respiratory cycle were determined. The results of the test were expressed as the difference between the maximum and lowest heart rates for the six recorded cycles in beats per minute [10].

Equation: Beats per minute = (25mm/s/shortest interval (mm)) x 60s/min.) - (25mm/s/ longest interval (mm)) x 60s/min.).Normal was >15, borderline 11-14, and abnormal <10 [10].

2- To test the heart rate response to the Valsalva manoeuvre, the patient was advised to hold motionless while blowing into a mouthpiece connected to a manometer for 15 seconds at a pressure of 40 mmhg (Valsalva ratio). At one-minute intervals, the manoeuvre was repeated three times. The results were as follows: The components of the Valsalva ratio are the longest R-R period following the move and the shortest R-R interval during the manoeuvre. The ultimate outcome was calculated by averaging the three Valsalva ratios. 1.11 to 1.20 was within the range of normal, 1.21 and above was abnormal [10].

3- 30:15 ratio test for immediate heart rate response to standing: During the test, the patient remains motionless on a sofa while an electrocardiograph continuously monitors their heart rate. The ECG pad was then used to record the moment the patient began to stand alone. The initial test's

15th pulse had the lowest R-R interval and the ECG paper's 30th beat had the greatest R-R interval. The 15th beat after starting to stand had the lowest R-R interval and the 30th beat after starting to stand had the largest R-R interval, as determined using a ruler. The 30:15 ratio served as an expression for the typical heart rate response. Borderline 1.01-1.03 was considered normal, abnormal was 1. 00 **[10]**.

B- *Examinations of sympathetic damage:*

1- Blood pressure reaction to standing: A sphygmomanometer was used to take the patient's blood pressure both while they were lying still and for one minute after they stood up. The postural decline in blood pressure was calculated using the difference between the systolic pressure while lying down and the systolic pressure while standing. The test was run three times, and the mean was calculated after each run. The normal range was between 10 and 29, whereas the pathological range was greater than 30 **[10]**.

In case of normal full test, the patients were classified as "normal". In case of occurrence of 1 of the 3 parasympathetic revealed an issue it is classified as with "early parasympathetic", "definite parasympathetic" is assessed when 2 or more of the parasympathetic functions tests were abnormal, and if, in addition to parasympathetic damage, one or both tests for sympathetic functioning were abnormal it is classified as with "combined damage". The borderline tests were considered normal for the categorization.

Echocardiography: Left ventricular mass and left ventricular mass indexed to body surface area were evaluated for Left Ventricular (LV) mass index and Ejection Fraction (EF percent) based on the LV cavity size and LV mass at end-diastole (g) = 0.8 {1.04 [([LVEDD + IVSd + PWd] 3 - LVEDD 3)]} + 0.6.

LV mass index (g/m^2) = lv mass / BSA, LVEDD = PWD is for posterior wall thickness at the end of diastole (mm), LVSD stands for interventricular septal thickness at the end of diastole (mm), and BSA stands for body surface area (g/m^2) **[11]**.

Laboratory tests: The tests included serum potassium (mmol/l), hemoglobin level (g/dl), serum creatinine (mg/dl), parathyroid hormone level (pg/ml), serum albumin (g/dl), blood urea (mg/dl), serumcalcium (mg/dl), protein/creatinine ratio (mg/g), serum phosphorus (mg/dl), cholesterol (mg/dl), triglycerides (mg/dl) and fasting blood glucose (mg/dl).

Statistical analysis:

Using the IBM SPSS software application, version 20.0, data were imported into the computer and evaluated. In terms of numbers and percentages, the qualitative data were reported. The mean, standard deviation, range (minimum and maximum), and median were used to characterize quantitative data. The results' significance was determined at the 5% level.

To compare outcomes between groups, categorical data were subjected to the Chi-square test. Fisher's Exact or Monte Carlo techniques were used to make adjustments for the Chi-square value when it exceeded 20% of the cells and a count of less than five was predicted. The Student *t*-Test: For normally quantitative variables, the Student t-test was utilised to compare the two research groups. In contrast to the post-hoc test (Tukey), the F-Test (ANOVA) was employed to compare between more than two groups for generally quantitative variables. To compare the two research groups for exceptionally quantitative variables, use the Mann-Whitney test. With exceptionally quantitative data, the Kruskal Wallis test was employed to compare more than two research groups. Using the Spearman coefficient, two exceptionally quantitative variables were associated.

Results

In the 50 non-diabetic CKD patients who were not on dialysis (30 males, 20 females) with a mean ageof 44.78±13.11 years (18-65 years) and mean duration of CKD 21.92±17.92 months (4.0-84.0 months), the following was found: Etiology of renal disease was hypertensive glomerulosclerosis in 16 (32%), chronic glomerulonephritis in 16 (32%), analgesics nephropathy in 5 (10.0%), obstructive uropathy in 3 (6.0%), adult polycystic kidney disease among 3 (6.0%), while unknown causes in 7 (14.0%) patients. The study included 25 volunteers matched in age and gender as the control group. Patients with CKD were split into two groups: 25 patients were in Group I (14 (28%) stage-3 CKD and 11 (22%) stage-4 CKD) with a mean GFR of 31.95±7.04 ml/min /$1.73m^2$, and-Group II had 25 patients (CKD stage 5) with mean GFR of10.96±3.13 ml/min/$1.73m^2$. Mean GFR 130.02±37.70 ml/minwas found in the control group. 30(60%) patients were hypertensive, 16 (53.3%) in Group I, and 14 (46.6%) in Group II. Table (1) displays the demographics and clinical characteristics of the groups under investigation.

Table (1): Comparison between the three studied groups according to demographic and clinical characteristics.

Parameters	Group I (n=25)		Group II (n=25)		Control (n=25)		Test of sig.	*p*
	No.	%	No.	%	No.	%		
Sex:	16	64.0	14	56.0	16	64.0	X^2=0.450	0.799
Male	9	36.0	11	44.0	9	36.0		
Female								
Age (years) Mean ± SD	44.28±13.99		45.28±12.44		44.52±10.63		F=14.807*	<0.759
BMI (kg/m^2) Mean±SD	24.48±3.42		24.13±4.05		22.28±2.97		F=2.832	0.065
Systolic Mean±SD.	130.0±17.85		131.40±15.04		111.20±7.94		F=15.698*	<0.001 *
Sig. bet. Grps	p_1=0.729, p_2<0.001 *, p_3<0.001 *							
Diastolic Mean±SD	83.20±10.40		86.20±10.44		76.20±9.82		F=6.302*	0.003 *
Sig. bet. Grps	p_1=0.303, p_2=0.018*, p_3=0.001 *							
MAP (mmHg) Mean±SD	98.78±12.44		101.26±11.25		87.86±8.78		F=10.643 *	<0.001 *
Sig. bet. Grps	p_1=0.425, p_2=0.001 *, p_3<0.001 *							
Duration of the disease (month) Mean±SD	24.72±21.51		19.12±13.29				U=280.0	0.528

$X2$, $^{p:}X^2$ and p values for Chi square test for comparing between the three groups and each two groups.
F, p: F and *p*-values for ANOVA test, Sig. bet. groups was done using Post Hoc Test (LSD) .
*p*1: *p*-value for comparing between group I and group II, *p*2: *p*-value for comparing between group I and Control,
*p*3: *p*-value for comparing between group II and Control U, *p*: U and *p*-values for Mann Whitney test for comparing between the two groups.
*: Statistically significant at *p* 0 05.

In Table (2), studied laboratory tests are displayed.

Table (2): Comparison between the two studied groups according to laboratory data.

Laboratory data	Group I (n=25)	Group II (n=25)	Control (n=25)	Test of sig.	*p*
Serum creatinine (mg/dl):					
Min. - Max.	1.80-3.70	3.60-10.80	0.50-1.0	H=65.820*	<0.001 *
Mean ± SD.	2.33±0.46	5.74± 1.76	0.74±0.15		
Median	2.20	5.20	0.80		
Sig. bet. Groups	p_1=0.001 *, p_2<0.001 *, p_3<0.001 *				
Serum potassium (mmol/l):					
Min. - Max.	3.60-5.60	3.80-5.90	3.70-4.50	F=11.667*	<0.001 *
Mean ± SD.	4.44±0.48	4.66 ± 0.46	4.12±0.20		
Median	4.40	4.80	4.10		
Sig. bet. Groups	p_1=0.053, p_2=0.006*, p_3=<0.001*				
Serum calcium (mg/dl):					
Min. - Max.	7.20-10.60	7.30-10.0	8.40-10.60	F=8.740*	<0.001 *
Mean ± SD.	8.86±0.92	8.61±0.75	9.47±0.52		
Median	9.0	8.60	9.40		
Sig. bet. Groups	p_1=0.237, p_2=0.005*, p_3<0.001*				
Serum phosphorus (mg/dl):					
Min. - Max.	3.40-6.80	3.50-6.0	3.40-5.0	H=12.838*	0.002*
Mean ± SD.	4.07±0.73	4.62±0.69	4.12±0.39		
Median	3.90	4.50	4.10		
Sig. bet. Groups	p_1=0.018, p_2=0.249, p_3<0.001 *				
Serum albumin (g/dl):					
Min. - Max.	2.90-4.40	3.10-4.50	3.90-4.80	H=16.744*	<0.001 *
Mean ± SD.	3.86±0.37	3.90±0.37	4.24±0.23		
Median	3.90	4.0	4.20		
Sig. bet. Groups	p_1=0.001 *, p_2=0.688, p_3<0.001*				

Table (2): Count.

Laboratory data	Group I (n=25)	Group II (n=25)	Control (n=25)	Test of sig.	*p*
Parathyroid hormone level (pg/ml):					
Min. - Max.	32.0-50.0	40.60-627.0	22.0-84.0	H=35.263 *	<0.001 *
Mean ± SD.	123.06±79.55	129.89±113.35	42.44±12.58		
Median	89.0	115.0	43.0		
Sig. bet. Groups	p_1=0.753, p_2<0.001 *, p_3<0.001 *				
Protein/Creatinine ratio (mg/g):					
Normal	14 56.0	8 32.0	25 100.0	χ^2=28.239????	MC p
Micro albuminuria	8 32.0	12 48.0	0 0.0		<0.001 *
Macro albuminuria	3 12.0	5 20.0	0 0.0		
Sig. bet. Groups	p_1=0.254, p_2=0.001 *, p_3<0.001 *				
Min. - Max.	9.90-475.20	12.30-654.20	3.70-9.12	H=51.237*	<0.001 *
Mean ± SD.	112.01 ± 144.14	188.99±196.69	6.16± 1.54		
Median	24.40	115.10	5.90		
Sig. bet. Groups	p_1=0.169, p_2<0.001 *, p_3<0.001 *				
Hemoglobin level (g/dl):					
Min. - Max.	8.90-15.20	6.80-14.0	12.60-15.50	F=41.205*	<0.001 *
Mean ± SD.	11.95± 1.83	10.28±1.78	14.24±0.82		
Median	12.20	10.20	14.20		
Sig. bet. Groups	p_1<0.001 *, p_2<0.001 *, p_3<0.001 *				
Blood Urea (mg/dl):					
Min. - Max.	28.0-100.0	52.0-200.0	12.0-27.0	H=60.984*	<0.001 *
Mean ± SD.	56.49±19.37	116.52±42.38	19.0±3.51		
Median	50.0	110.0	19.0		
Sig. bet. Groups	p_1=0.001 *, p_2<0.001 *, p_3<0.001 *				
Total cholesterol:					
Min. - Max.	125.0-232.0	86.0-248.0	96.0-220.0	F=9.513*	<0.001 *
Mean ± SD.	177.40±28.62	172.56±39.86	140.72±26.88		
Median	176.0	172.0	140.0		
Sig. bet. Groups	p_1=0.598, p_2<0.001 *, p_3<0.001 *				
Triglycerides (mg/dl):					
Min. - Max.	66.0-178.0	60.0-189.0	64.0 - 165.0	F=1.527	0.224
Mean ± SD.	116.60±36.05	115.44±37.93	101.80±24.26		
Median	102.0	116.0	96.0		
Fasting blood glucose (mg/dl):					
Min. - Max.	78.0-113.0	74.0-105.0	75.0-100.0	F=0.247	0.782
Mean ± SD.	89.36±8.68	88.08±8.89	89.60±6.98		
Median	88.0	87.0	90.0		

F, p : F and p-values for ANOVA test, Sig. bet. groups was done using Post Hoc Test (LSD).
χ^2, p : χ^2 and p-values for Chi square test for comparing between the two groups.
MC : Monte Carlo for Chi square test for comparing between the two groups.
F, p : F and p-values for ANOVA test, Sig. bet. groups was done using Post Hoc Test (LSD).
H, p : H and p-values for Kruskal Wallis test, Sig. bet. groups was done using Post Hoc Test (Dunn's multiple comparisons test).
p_1 : p-value for comparing between group I and group II.
p_2 : p-value for comparing between group I and Control.
p_3 : p-value for comparing between group II and Control.
* : Statistically significant at p 0.05.

16 cases (32%) had left ventricular hypertrophy (LVH), with 7 instances (43.75%) in Group I and 9 cases (56.25%) in Group II. LVMI did not differ significantly between groups. The CKD patient groups, however, significantly differed from the control group. (Table 3).

29 of the total cases were free of clinical symptoms concerning autonomic neuropathy, constipation was found in 4 patients, colonic distension in 7 patients, diarrhea in 2 cases, dysphagia in 2 cases, hyperhidrosis in 2 cases,and impotence in 2 cases. There was one case with numbness and another with urinary retention (Fig. 1).

Table (3): Comparison between the three studied groups according to ECHO.

ECHO	Group I (n=25)		Group II (n=25)		Control (n=25)		Test of sig.	*p*
	No.	%	No.	%	No.	%		
Left ventricular hypertrophy:								
No LVH	18	72.0	16	64.0	25	100.0	χ^2=10.646*	0.005*
LVH	7	28.0	9	36.0	0	0.0		
Sig. bet. Groups	p_1=0.544, p_2=0.010*, p_3=0.002*							
Left ventricular mass index (g/m ^{2}):								
Mean ± SD.	85.68±16.60		82.96±21.34		57.20±4.82		F=24.548*	<0.001*
Sig. bet. Groups	p_1=0.546, p_2<0.001 *, p_3<0.001*							
Ejection Fraction %:								
Mean ± SD.	61.64±3.19		61.48±2.66		66.96±2.51		F=30.989*	<0.001*
Sig. bet. Groups	p_1=0.841, p_2<0.001 *, p_3<0.001*							

χ^2, p : χ2 and p-values for Chi square test for comparing between the two groups.
F, p : F and p-values for ANOVA test, Sig. bet. groups was done using Post Hoc Test (LSD).
p_1 : p-value for comparing between group I and group II.
p_2 : p-value for comparing between group I and Control.
p_3 : p-value for comparing between group II and Control.
* : Statistically significant at p0.05.

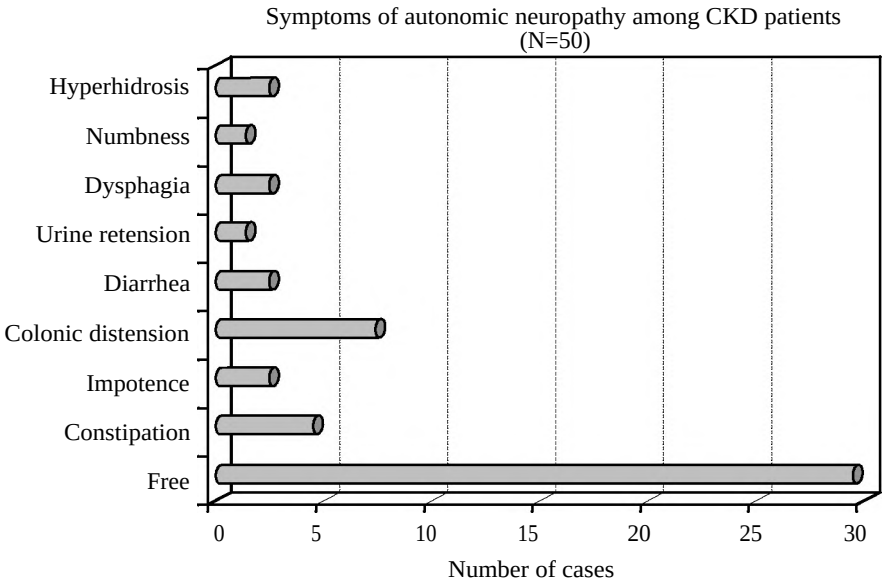

Fig. (1): Symptoms of autonomic neuropathy among non-diabetic CKD patients' groups (N=50).

Cardiovascular autonomic neuropathy dysfunctions were significantly different between CKD patients (n=50) and the control group (χ^2 =17.427, p_{MC}<0.001 (Cardiac autonomic dysfunctions were observed among total CKD patients as follows: 13 (26.0%) early parasympathetic, 10 (20.0%) definite parasympathetic, 1 (2%) sympathetic damage, 5 (10.0%) combined damage, and 21 (42.0%) of the studied patients were with normal cardiac autonomic function (Fig. 2).

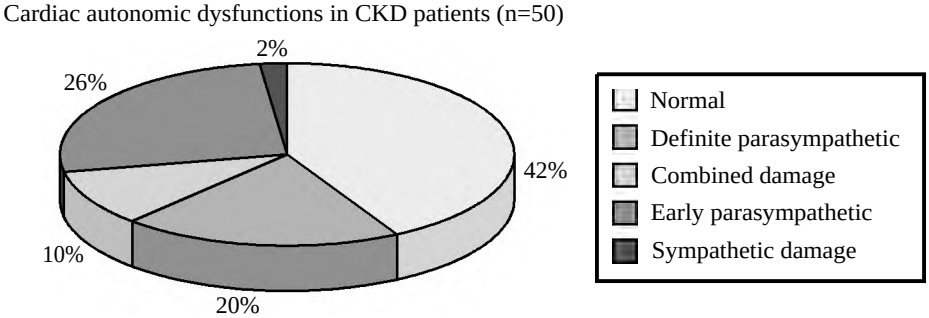

Fig. (2): Cardiac autonomic neuropathy dysfunctions among Non-diabetic CKD patients.

Among the healthy control group, 2 (8.0%) of them exhibited early parasympathetic dysfunction. A comparison was devised between GroupsI andII versus the control group regarding cardiac autonomic dysfunctions, which showed a significant difference, Nevertheless, individuals with CKD stage 5 (Group II) had a greater prevalence of early and obvious parasympathetic cardiac autonomic dysfunction than did Group I patients. The post-hoc analysis revealed no statistically significant distinction between Groups I and II. (Table 4).

Significant correlation between cardiac autonomic dysfunction types and hemoglobin and total cholesterol level ($p<0.05$) as definite parasympathetic dysfunction associated significantly with lower hemoglobin and higher cholesterol level, as shown in Table (5), but No relationship was found between the examined parameters of LVH, EF percent, or cardiac autonomic dysfunction.

Table (4): Comparison between the three studied groups according to cardiac autonomic dysfunction.

Cardiac Autonomic dysfunction	Group I (n=25)		Group II (n=25)		Control (n=25)		χ^2	MC p
	No.	%	No.	%	No.	%		
Normal	13	52.0	8	32.0	23	92.0	22.031 *	<0.001*
Definite Parasympathetic	4	16.0	6	24.0	0	0.0		
Combined damage	2	8.0	3	12.0	0	0.0		
Early Parasympathetic	5	20.0	8	32.0	2	8.0		
Sympathetic damage	1	4.0	0	0.0	0	0.0		
Sig. bet. grps	p_1=0.525, p_2=0.011 *, p_3<0.001 *							

χ^2, p : $\chi 2$ and p-values for Chi square test for comparing between the two groups.
MC : Monte Carlo for Chi square test for comparing between the two groups.
p_1 : p-value for comparing between group I and group II.
p_2 : p-value for comparing between group I and Control.
p_3 : p-value for comparing between group II and Control.
* : Statistically significant at p0.05.

Table (5): Relation between autonomic dysfunction with laboratory data and ECH0 cardiography of the patients groups.

Laboratory data	Cardiac autonomic dysfunction					p
	Normal (n=21)	Definite Paras-ympathetic (n=10)	Combined damage (n=5)	Early Para-sympathetic (n=13)	Sympathetic damage (n=1)#	
- Serum Creatinine (mg/dl) Median	2.60	4.20	5.30	4.50	2.50	Hp=0.599
- Serum Potassium (mmol/l) Mean ± SD	4.52±0.46	4.41±0.46	4.90±0.33	4.58±0.57	4.50	Fp=0.319
- Serum Calcium (mg/dl) Mean ± SD	8.70±0.94	8.71±0.96	8.28±0.46	8.98±0.69	8.90	Fp=0.481
- Serum Phosphorus (mg/dl) Median	4.10	4.40	4.30	4.0	4.50	Hp=0.729
- Serum Albumin (g/dl) Median	4.0	3.85	4.0	3.80	4.10	Hp=0.899
- Parathyroid hormone level (pg/ml) Median	86.0	120.0	116.0	100.0	89.0	Hp=0.489
- Protein/Creatinine ratio (mg/g) Median	98.30	154.30	28.20	25.32	20.50	Hp=0.222
- Hemoglobin level (g/dl) Mean ± SD	11.75±2.19	9.62±2.05	10.82±0.80	11.28±1.38	12.20	Fp=0.042*
- Blood Urea (mg/dl) Median	66.0	106.0	90.0	80.0	62.0	Hp=0.350
- Total cholesterol Mean ± SD	184.67±33.39	188.80±17.0	160.20±39.0	151.46±33.54	213.0	Fp=0.012*
- Triglycerides (mg/dl) Mean ± SD	110.57±29.01	118.40±42.27	127.80±45.86	114.54±41.24	167.0	Fp=0.805
- Fasting blood glucose (mg/dl) Mean ± SD	88.14±9.29	88.80±10.06	90.80±6.22	88.69±8.68	90.0	Fp=0.950
- Left ventricular hypertrophy	15 (71.4%)	6 (60.0%)	2 (40.0%)	10 (76.9%)	1 (100.0%)	MCp=0.564
No LVH LVH	6 (28.6%)	4 (40.0%)	3 (60.0%)	3 (23.1%)	0 (0.0%)	
- Left ventricular mass index (g/m^2) Mean ± SD	87.38±17.33	82.70±19.57	86.60±26.68	80.0±20.10	81.0	Fp=0.733
- Ejection Fraction (%) Mean ± SD	62.0±3.08	61.70±3.13	61.40±2.88	60.92±2.75	60.0	Fp=0.783

Fp: p-value for ANOVA test.
Hp: p-values for Kruskal Wallis test.
*: Statistically significant at p0.05.
#: Excluded from the comparison due to small number of case (n=1).

Clinical symptoms of autonomic neuropathy did not substantially associated with the statistical presence of different cardiac autonomic neuropathy dysfunctions (p>0.05). (Table 6).

The findings of the Valsalva manoeuvre heart rate response test (Valsalva ratio) and the R-R interval heart rate variation test (measured in beats per minute) across patient groups were abnormal in 14 (28.0%), borderline in 5 (10.0%), and normal in 31 (62.0%) cases of the total cases.In the standing 30:15 ratio test, the immediate heart rate response values were abnormal in 39 (78.0%) individuals and borderline in 11. (22.0 percent). Blood pressure response to standing (mm/Hg) test results were abnormal in 33 (66.0%) cases, normal in 6 (12.0%) cases, and borderline in 11 (22.0%) cases of total CKD patients (Tables 7-10).

Table (6): Relation between autonomic dysfunction with Symptoms of autonomic neuropathy in patients group.

Symptoms of autonomic neuropathy	Autonomic dysfunction					MC$_p$
	Normal (n=21)	Definite Para-sympathetic (n=10)	Combined damage (n=5)	Early Para-sympathetic (n=13)	Sympathetic damage (n=1)	
Free	18 (85.7%)	5 (50.0%)	0 (0.0%)	6 (46.2%)	0 (0.0%)	0.001 *
Constipation	1 (4.8%)	1 (10.0%)	1 (20.0%)	1 (7.7%)	0 (0.0%)	0.652
Impotence	0 (0.0%)	0 (0.0%)	1 (20.0%)	1 (7.7%)	0 (0.0%)	0.177
Colonic distension	1 (4.8%)	3 (30.0%)	2 (40.0%)	1 (7.7%)	0 (0.0%)	0.111
Diarrhea	0 (0.0%)	0 (0.0%)	1 (20.0%)	1 (7.7%)	0 (0.0%)	0.176
Urine retention	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000
Dysphagia	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0.020*
Numbness	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	0.586
Hypohidrosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (15.4%)	0 (0.0%)	0.245

MCp: p-value for Monte Carlo for Chi square test.
*: Statistically significant at p0.05.

Table (7): Comparison between the studied groups according to test 1 (valsalva ratio).

Heart rate response to Valsalva maneuver (Valsalva ratio)	Group I (n=25)		Group II (n=25)		Control (n=25)		Test of sig.	p
	No.	%	No.	%	No.	%		
Normal	16	64.0	15	60.0	24	96.0	X^2=10.738	MC$_p$=
Abnormal	7	28.0	7	28.0	1	4.0		0.013*
Border line	2	8.0	3	12.0	0	0.0		
Sig. bet. Grps	p_1=1.000, p_2=0.012*, p_3=0.007*							
Min. - Max.	0.99-1.47		0.92-1.91		1.05-2.10		H=14.067*	0.001 *
Mean ± SD.	1.23±0.13		1.22±0.19		1.37±0.19			
Median	1.28		1.24		1.32			
Sig. bet. Grps	p_1=0.005*, p_2=0.471, p_3<0.001 *							

$\chi 2, p$: $X2$ and p-values for Chi square test for comparing between the two groups.
MC : Monte Carlo for Chi square test for comparing between the two groups.
H, p : H and p-values for Kruskal Wallis test, Sig. bet. groups was done using Post Hoc Test (Dunn's multiple comparisons test).
p_1 : p-value for comparing between group I and group II.
p_2 : p-value for comparing between group I and Control.
p_3 : p-value for comparing between group II and Control.
* : Statistically significant at p0.05.

Table (8): Comparison between the studied groups according to test 2 (R-R interval).

Heart rate (R-R interval) variation during deep breathing (beat/min)	Group I (n=25)		Group II (n=25)		Control (n=25)		Test of sig.	*p*
	No.	%	No.	%	No.	%		
Normal	18	72.0	13	52.0	24	96.0	ξ^2=17.365*	MC$_p$=
Abnormal	3	12.0	11	44.4	1	4.0		<0.001 *
Border line	4	16.0	1	4.0	0	0.0		
Sig. bet. Groups	p_1=0.026*, p_2=0.059, p_3=0.001 *							
Min. - Max.	8.20-27.10		6.90-31.20		9.50-33.75		H=20.131*	<0.001 *
Mean ± SD.	16.37±4.51		14.29±5.23		21.19±5.54			
Median	16.40		15.0		20.0			
Sig. bet. Groups	p_1=0.002*, p_2=0.194, p_3<0.001 *							

ξ^2, p : ξ^2 and p-values for Chi square test for comparing between the two groups.
MC : Monte Carlo for Chi square test for comparing between the two groups.
H, p : H and p-values for Kruskal Wallis test, Sig. bet. groups was done using Post Hoc Test (Dunn's multiple comparisons test).
p_1 : p-value for comparing between group I and group II.
p_2 : p-value for comparing between group I and Control.
p_3 : p-value for comparing between group II and Control.
* : Statistically significant at p0.05.

Table (9): Comparison between the two studied groups according to test 3 (30:15 ratio).

Immediate heart rate response to standing (30:15 ratio test)	Group I (n=25)		Group II (n=25)		Control (n=25)		Test of sig.	*p*
	No.	%	No.	%	No.	%		
Normal	5	20.0	6	24.0	0	0.0	ξ^2=7.651*	MC$_p$=
Abnormal	20	80.0	19	76.0	25	100.0		0.035*
Border line								
Sig. bet. Groups	p_1=1.000, p_2=0.050, p_3=0.022*							
Min. - Max.	0.93-1.36		0.92-1.68		1.04-1.37		H=14.182*	0.001 *
Mean ± SD.	1.11±0.11		1.10±0.15		1.20±0.09			
Median	1.09		1.08		1.20			
Sig. bet. Groups	p_1=0.004*, p_2=0.537, p_3<0.001*							

ξ^2, p : ξ^2 and p-values for Chi square test for comparing between the two groups.
MC : Monte Carlo for Chi square test for comparing between the two groups.
H, p : H and p-values for Kruskal Wallis test, Sig. bet. groups was done using Post Hoc Test (Dunn's multiple comparisons test).
p_1 : p-value for comparing between group I and group II.
p_2 : p-value for comparing between group I and Control.
p_3 : p-value for comparing between group II and Control.
* : Statistically significant at p0.05.

Table (10): Comparison between the two studied groups according to test 4.

Blood pressure response to standing (mm/Hg)	Group I (n=25)		Group II (n=25)		Control (n=25)		Test of sig.	*p*
	No.	%	No.	%	No.	%		
Normal	3	12.0	3	12.0	0	0.0	ξ^2=6.756	MC$_p$=
Abnormal	17	68.0	16	64.0	23	92.0		0.133
Border line	5	20.0	6	24.0	2	8.0		
Min. - Max.	0.93-1.36		0.92-1.68		1.04-1.37		H=12.634*	0.002*
Mean ± SD.	1.11±0.11		1.10±0.15		1.20±0.09			
Median	1.09		1.08		1.20			
Sig. bet. Groups	p_1=0.912, p_2=0.003 *, p_3=0.002*							

ξ^2, p : ξ^2 and p-values for Chi square test for comparing between the two groups.
MC : Monte Carlo for Chi square test for comparing between the two groups.
H, p : H and p-values for Kruskal Wallis test, Sig. bet. groups was done using Post Hoc Test (Dunn's multiple comparisons test).
p_1 : p-value for comparing between group I and group II.
p_2 : p-value for comparing between group I and Control.
p_3 : p-value for comparing between group II and Control.
* : Statistically significant at p0.05.

Discussion

Three tests that demonstrate parasympathetic damage were employed in our study: The R-R interval, the Valsalva maneuver, and the 30:15 ratio test, which measures the initial heart rate response to standing and an assessment of sympathetic damage (blood pressure response to standing). We found 31 (41%) cases from all participants had cardiac autonomic dysfunction. 29 of them were CKD patients in Groups I and II. 15 (45%) cases had early parasympathetic, 10 (31%) cases had definite parasympathetic, 5 (15%) cases had combined damage, 1 (3%) case had sympathetic damage. 2 (6%) of the cases from the control group were early parasympathetic. Between CKD patients and the controls, there is a sizable statistical difference due to cardiac autonomic dysfunction. These findings can be explained by non-traditional risk factors seen in all stages of chronic kidney disease, such asleft ventricular hypertrophy, vascular calcification, inflammation,oxidative stress, as well as anaemia, which may be the root cause of CAN in CKD.

This coincides with Sanya et al., study, where the testshad been done on 60 non-diabetic CKD patients who were not on dialysis. CAN was present in 39 patients (65%) and 5 controls (8.3%). A significant number of CRF patients had abnormalities in four of five CVR tests compared withthe healthy controls. This could be explained by chronic uremia, which is an important cause of autonomic neuropathy. This is also in agreement with Marie Bayerstudy, who reported that the uremic patients had a significantly higher incidence of CAN than the healthy control group (38% versus 8%). This could be explained by the fact that the degree of autonomic dysfunction gets worse as CKD gets worse. This discovery is also in line with the findings of the Thapa et al., research, which found that all CKD diabetic patients (100%) had some sort of autonomic dysfunction. However, there were 7 (or 35% of instances) in the healthy control group. According to a previous report, parasympathetic damage happens more frequently than sympathetic damage. The involvement of the kidneys, the severity of the disease, and the metabolic status all playing moderating roles in diabetic autonomic neuropathy can be used to explain this conclusion that all patients with CKD had autonomic neuropathy. In our study, type of cardiac autonomic dysfunction didn't differ significantly between both groups, apart from a single case of sympathetic damage in Group I. Parasympathetic dysfunction wasmore common than sympathetic. In Group I, 12 (48%) cases had cardiac autonomic dysfunction, 5 (42%) cases had early parasympathetic, 4 (33%) cases had definitive parasympathetic, 2 (17%) cases had combined damage, and one case (8%) had sympathetic damage. In Group II, 17 (68%) cases had cardiac autonomic dysfunction, 8 (47%) cases had early parasympathetic, 6 (35%) cases had definitive parasympathetic, and 3 (17%) cases had combined damage. The malfunctioning of the sympathetic and parasympathetic nerve systems that was seen in CKD patients can be used to explain these findings. All heart rate reflex tests may show substantial impairment in CRF patients' CAN.

These results are consistent with the Sanya et al., research, which indicated that CRF patients had greater parasympathetic dysfunction than sympathetic dysfunction. This can be explained by the fact that autonomic neuropathy occurs often (65%) in pre-dialyzed non-diabetic CRF patients. It involved both parasympathetic and sympathetic functions early in the course of the disease. This differs from the pattern in DM, where the parasympathetic function was majorly impaired, while the sympathetic control was rarely involved or minimally involved late in the course of the disease.This alsoagreeswith Thapa et al., study, who revealed that in 20 diabetic CKD patients' in Group III, in stage-3, 4, and 5 CKD, 2 (10%) cases had early parasympathetic, In 8 (40%) cases, there was obvious parasympathetic damage, and in 10 (50%) cases, there was mixed injury. It was discovered that none of the patients had isolated sympathetic dysfunction. It had been said that parasympathetic rather than sympathetic damage occurred more frequently. The early engagement of sympathetic fibres in the illness process, which is followed by involvement of sympathetic fibres, the limited sample size, and the older age of 37 years or more may all contribute to this.

Our finding wasnot compatible with that of Miyanaga et al., study, who showed an early impairment of the sympathetic nervous system in uremic dysautonomia using radio nuclear MIBG myocardial scintigraphy. This can be explained by decreased renal blood flow, decreased renal salt excretion, and decreased GFR due to vasoconstriction in the kidney.

We reported that the mean GFR in early parasympathetic cases was 18.05±9.40. In definitive parasympathetic cases,it was 17.74±9.48, combined damage 20.14±15.71, and sympathetic damage 27.95; however, we did not find a significant statistical difference between types of cardiac autonomic neuropathy and GFR.The lowest GFR wasdetected in definite parasympathetic.

Our findings did not agree with the findings of the Thapa et al., research, which claimed that most CKD patients had mixed types of autonomic failure. In stage-5 CKD, the mixed form predominated. This can be explained by the fact that the illness process first affects the sympathetic fibres, which then affects the sympathetic fibres.

In our study, we reported that 31 of the cases were CAN positive, and 13 (42%) of them were free of symptoms of cardiacautonomic dysfunction. 18 (58%) patients were symptomaticas follows: 6 (33%) hadcolonic distension, 3 (17%) constipation, 2 (11%) impotence + urinary incontinence, 2 (11%) diarrhea, 2 (11%) dysphagia, 2 (11%) hyperhidrosis, and 1 (6%) numbness. Our results showed no significant correlation between the types of cardiac autonomic dysfunction and the signs of autonomic neuropathy. Most cases with or without CAN were-free of symptoms. Hypohidrosis and numbness were mainly present in early the parasympathetic type, but dysphagia was present mainly with the definite parasympathetic type. Colonic distension and constipation were the most common symptoms present. This can be explained by the fact that in chronic renal failure, the symptoms of autonomic dysfunction and peripheral neuropathy are often overshadowed by uremic symptoms that are commonly seen in CRF and may be unnoticed.

These results were compatible with Sanya et al., study, who found neuropathic symptoms such as constipation, persistent dry mouth, hypohidrosis, loss of sensation, and numbness in the limbs had a significant clinical correlation with CAN in CRF patients. It can be explained by dehydration, which might be responsible for symptoms like constipation and hyposialism observed in the patients. However, this is unlikely as there was no significant difference in the hydration status between the patients and controls.

We noticed that 18 patients with CAN were hypertensive, 9 (50%) had early parasympathetic, 5 (28%) had definite parasympathetic, 3 (17%) had combined damage, and only onecase hadsympathetic damage. None of the control group patients were hypertensive. Thus, there wasa significant correlation between CAN & HTN. This is due, in part, to the sympathetic as well as parasympathetic nervous systems' shared functions of innervating and regulating the heart's heart rate (HR), chronotropic activity, and compression force (inotropic activity). Only the SNS can innervate the vasculature, allowing it to mediate the Baroreceptor Reflex, regulate peripheral resistance, and finally regulate blood pressure (BP).

These results corroborated a research by Marie Bayer et al., that found that as people aged and their systolic blood pressure rose, the incidence of CAN increased. Patients with uremic patients frequently have elevated systolic pressure, which is associated with the existence of autonomic neuropathy. This can be explained by sympathetic overactivity, which in individuals with early autonomic neuropathy boosts the activity of the renin-angiotensin-aldosterone system, accelerates salt reabsorption, and raises peripheral resistance, resulting in hypertension. It is yet unknown if hypertension causes the development of CAN. These results concur with a research by Cordeiro et al., that showed ANS dysfunction has been linked to hypertension, which is prevalent in people with CKD even before diagnosis. This can be explained by the fact that hypertension individuals with CKD have poorer baroreflex sensitivity due to changes in heart rate regulation or possibly because of diminished distensibility and blood artery vascular calcification.

We found that there was no correlation between types of cardiac autonomic dysfunction andleft ventricular hypertrophy. LVH in CAN-positive patients were presentin 10 (32%) cases (5 (16%) in Group I and 5 (16%) in Group II, but no LVH was found in the control group. Mean LVMI was 85.68±16.60 in Group I, 82.96±21.35 in Group II, and 57.20±4.82 in the control group. Mean EF was 61.64±3.19 in Group I, 61.48±2.66 in Group II, and 66.96±2.51 in the control. This can be explained by the fact that CAN causes anomalies in the mainly diastolic and systolic functions of the left ventricle. Studies using echocardiography had revealed that CAN was substantially linked to decreased peak diastolic filling and elevated atrial diastole component. Furthermore, MRI showed that, independent of age, sex, or other factors, CAN was connected to increased LV mass and concentric remodelling as determined by MRI. However, in DM patients, anomalies other than CAN, such as interstitial myocardial fibrosis, microangiopathic alterations, or metabolic changes, may potentially contribute to left ventricular dysfunction. These findings supported the findings of Cordeiro et al., who discovered that left ventricular hypertrophy was seen on the ECG in nine CKD patients (28 percent) but not in the control group. Arrhythmias weren't visible in any of the people's resting ECGs. Compared to patients in the control group, 64 percent of those with CKD had left ventricular hypertrophy as detected by echocardiography. Men in the CKD group had a mean left ventricular mass index of 136.3±39.9 g/m^2, whereas women had 117.7±37.1 g/m^2. These numbers were much lower

in the control group: 86.5±5.1 g/m^2 for women and 98.1±5.4 g/m^2 for males. In this study, LVH was present in 64% of the CKD patients, which may have influenced their lower HRV.

In our study, we found that in all 31 patients with cardiac autonomic neuropathy, there was no significant correlation between types of autonomic dysfunction regardinglaboratory data, except for definite parasympathetic that had a significant correlation with hemoglobin (anemia) andcholesterol levels (hypercholesterolemia). This can be explained by the fact that resting tachycardia is an ambiguous indicator of CAN since it can also occur in a number of other disorders, including anaemia, thyroid problems, and underlying cardiovascular diseases such heart failure, obesity, and poor fitness. The age group and diagnostic standards that were employed both have an impact on CAN prevalence. Other clinical correlations and predictors of CAN include blood pressure, obesity, smoking, cholesterol, and triglyceride levels, which often necessitate a multifaceted approach aiming at lifestyle modification with pharmaceutical correction of hypertension, dyslipidemia, and microalbuminuria.

Our finding was incompatible with Sanya et al., study, who found no correlation between biochemical parameters and autonomic neuropathy in CRF patients, confirming previous reports that showed no relationship between serum calcium, phosphate, and hematocrit and the development of autonomic neuropathy.

Conclusions:

The frequency of Cardiovascular Autonomic Neuropathy (CAN) is significantly high in non-diabetic CKD G stages 3-5compared with the healthy control group, with predominant early and definite parasympathetic dysfunction patterns. Anemia and high cholesterol levelsmay be considered aggravating factors of CAN, especially the definite parasympathetic dysfunction pattern. Left ventricular mass index or ejection fraction percent age was not correlated to the presence of CAN. There was no significant association between CAN degree or pattern and the presence of clinical symptoms of autonomic neuropathy among non-dialysis CKD G stages 3-5 patients, which may reflect the importance of tests for cardiac autonomic dysfunctions assessment among those patients.

Declarations:

Ethics approval and consent to participate: The study was approved by the Ethical Scientific Committee of Internal Medicine, Ain Shams University. The study subjects agreed to participate in the research, after receiving detailed information about the research. Written informed consent for participation in the study was obtained from subjects.

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions: G M and M B and A E designed the idea and the tools of the study and revised step by step the recruitment of patients, and the tools used, M E collected, analyzed, and interpreted the data, F A and M B proposed the methodology of the study and interpreted the results and wrote the manuscript. All authors agreed with the results and conclusions of this article. All authors read and approved the final manuscript.

All data generated or analysed during this study are included in this published article and its supplementary information files.

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اعتلال القلب الا ارادى العصبى فى مرضى القصور الكلوى المزمن غير المصابين بداء السكرى

تعتبر مشاكل اللب من أكثر الأسباب شيوعاً لتدهور أو وفاة مرضى القصور الكلوى المزمن ويعتبر اعتلال القلب الا ارادى العصبى من أكثر أسباب الوفاة المفاجئة نتيجة لفشل عضلة القلب.

هذه الدراسة شملت عدد ٥٠ مريض قصور كلوى مزمن غير مصابين بالسكرى وليسو على غسيل كلوى منتظم (٣٠ ذكور، ٢٠ إناث) فى سن يتراوح من (١٨–٦٥ سنة) ومدة القصور الكوى المزمن ٢١.٩٢±١٧.٩٢ شهراً (المدى من ٤ إلى ٨٤ شهراً).

تم اختيار المرضى من العيادات الخارجية لقسم أمراض الكى والطب الباطنى بمستشفيات جامعة عين شمس. وشملت الدراسة عدد ٥٠ مريض قصور كلوى مزمن غير المصابين بالسكرى مقسمين إلى مجموعتين و ٢٥ متطوعاً أصحاء كمجموعة مراقبة تتراوح أعمارهم بين ١٨ سنة و ٦٥ سنة. وتم أخذ التاريخ المرضى وعمل الفحوصات والتحاليل الطبية لجميع المشاركين.

تم تقسيم المرضى إلى مجموعتين : المجموعة الأ ولى ٢٥ مريضاً (١٤ مريضاً بالمرحلة ٣ من القصور الكلوى المزمن، ١١ مريض بالمرحلة ٤ من القصور الكلوى المزمن)، المجموعة الثانية ٢٥ مريضاً (المرحلة ٥ للقصور الكلوى المزمن).

تم إجراء عدد من الاختبارات لتحديد الاختلال القلبى العصبى اللارادى اختبارات تعكس الاعتلال الباراسمبثاوى (معدل ضربات القلب استجابة التنفس العميق، استجابة معدل ضربات القلب لمناروة فالسالف ا ومعدل ضربات القلب الاستجابة الفورية للوقوف) واختبار واحد يعكس الاعتلال السيمبثاوى وهو استجابة ضغط الدم إلى الوقوف.

تم تصنيف نتائج المرضى على أنها (طبيعية) إذا كانت جميع الاختبارات طبيعية و(اعتلال بارسمبثاوى مبكر) إذا كان واحد من الاختبارات الثلاثة من وظيفة الباراسمبثاوى غير طبيعى، و(اعتلال باراسمبثاوى محدد) إذا كان اثنين أو أكثر من الاختبارات الثلاثة من وظيفة الباراسمبثاوى غير طبيعية. و(اعتلال مشترك) إذا كان واحداً أو أكثر من الاختبار الباراسمبثاوى بالاضافة إلى السمبثاوى غير طبيعين. ولأغراض التصنيف، تم تفسير نتائج الاختبارات الحدودية على أنها طبيعية.

\الاستنتاج : الاعتلال القلبى العصبى اللارادى مرتفع بشكل ملحوظ فى المرضى الذين يعانون من أمراض القصور الكلوى المزمن المرحلة (الثالثة – الخامسة وهم ليسوا على غسيل كلوى منتظم) أكثر من الاصحاء.

الخلل الباراسمبثاوى المبكر هو النوع الأكثر شيوعاً فى المرضى الذين يعانون من الاعتلال القلبى العصبى اللارادى.