Original Article

Left Ventricular Geometry and N-terminal Pro-Brain Natriuretic Peptide in Egyptian Children with Chronic Kidney Disease.

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Abstract

Introduction: Cardiovascular disease is the main cause of death in Chronic Kidney disease (CKD) patients especially for those on dialysis. Left ventricular echocardiography changes are common. N-terminal pro-Brain Natriuretic peptide (NAP) is a sensitive predictor for ventricular stress**.**

Aim of the Study: Our aim is to assess left ventricular Echocardiography abnormalities in CKD patients and their relation to serum NT pro BNP levels.

Methods: The Study included; 51 patients with different stages of CKD (21 patients were (CKD1-4) on predialysis conservative treatment, 30 patients with (CKD 5) on hemodialysis), and 20 healthy control group. Patients were subjected to echocardiography and serum measurement of BNP by enzyme linked immunosorbent assay.

Results: Abnormal left ventricular geometry patterns were seen in 17/21 (81%) CKD pre dialysis patients (concentric hypertrophy in 8 patients, eccentric hypertrophy in 8 patients and concentric remodeling in one patient). Those on dialysis 28/30 (93%) showed abnormal left ventricular geometry patterns (23 had concentric hypertrophy, 4 had eccentric hypertrophy and one patient had concentric remodeling). Mean NT pro BNP level was significantly higher in ESRD on dialysis (182.49 ± 136.57) vs pre dialysis group (29.72 ± 34.77) and control group (1.13 ± 2.97) ($p<0.001$). Total patient sample (51cases) showed significant positive correlations between NT pro BNP level with hypertension, left ventricular mass (LVM), $LVM^{2.7}$, LVM^2, relative wall thickness (RWT) and serum creatinine ($p = 0.0007$, 0.01, 0.0007, 0.0005, 0.0002 respectively),significant negative correlation with ejection fraction ($P = 0.04$).

Conclusion: Measuring plasma concentration of BNP, may be useful for the identification of CKD patients with abnormal left ventricular Geometry.

Recommendations: Routine echocardiography is recommended in early stages of CKD.

Key words: Left ventricular geometry, NT pro BN, Chronic Kidney Disease, End Stage Renal Disease, and Echocardiography.

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Introduction

Cardiovascular disease account for the majority of deaths in adults with ESRD and approximately one fourth of pediatric ESRD deaths. The cardiac abnormalities associated with ESRD include pericardial disease, arrhythmias, abnormalities of left ventricular function, and coronary disease [1].The pathogenesis of cardiovascular damage in chronic renal failure (CRF) patients is far more complex than in the general population, since the risk factors include those identified in the general population and additional risk factors typical of CRF [2].

Left ventricular hypertrophy (LVH) is the most common and identifiable cardiac alteration in ESRD, affecting up to 75% of pediatric dialysis patients [3] and 80% of adults on dialysis [4]. Because of the low incidence of chronic renal insufficiency (CRI) among children, published information on prevalence and severity of abnormalities of left ventricular geometry in children is restricted to relatively small selected groups of patients [5, 6].

Brain Natriuretic Peptide (BNP) belongs to family of; vasopeptide hormones that have major role in regulating BP and volume through direct effects on the kidney and systemic vasculature. There are 4 types; A-type (Atrial), B-type (Brain), C-type and D type [7].The main stimulus for N-Terminal pro- BNP synthesis and secretion is increased left ventricular wall stress. Thus, circulating NT-pro-BNP levels reflect the degree of LV overload. Numerous studies have reported elevated plasma NT-pro- BNP levels in patients with heart failure. It also showed strong correlation with LV filling pressure and increase in proportion to the severity of LV systolic dysfunction and diastolic dysfunction [8]. BNP testing provided the highest test accuracy than any clinical variable in predicting a final diagnosis of heart failure for patients who presented to the emergency department [9].

Methods

Patients This study was performed on 51 patients with CKD (21 patients with CKD stage 1– 4 on conservative treatment) and (30 patients with CKD 5, on regular hemodialysis). Twenty apparently normal children age and six matched were included in the study as a control group, excluded from the study if below one year or older than 18 years old, if suffering from acute renal insult, patients suffering from congenital or rheumatic heart diseases, and patients with other chronic pulmonary disease. A full informed consent was obtained from patient's parents. CKD patients (51 case) were classified into 5 stages according to GFR. According to their treatment option they were grouped as CKD1- 4 on conservative treatment (Pre dialysis Group) and CKD 5 (dialysis Group). Patients were recruited from outpatient CKD clinic and hemodialysis wards of our Children Hospital. Healthy Control Group included patients relatives who are age and sex matched.

N-terminal pro-Brain Natriuretic peptide measurement using enzyme linked immunosorbent assay (ELISA) was done within 3-7 days from sampling. Sample was taken before hemodialysis session to avoid wash out effect of dialysis on BNP plasma level. Kidney function tests, hemoglobin level, calcium, phosphorus, alkaline phosphatase, serum

albumin & serum iron were all measured using standard laboratory methods.

Echocardiography Assessment for both patient groups were done. For dialysis group, at least 24 h time delay from their last hemodialysis session was considered to ensure equilibration between intra and extra vascular hydration and also as echocardiography visibility is worse shortly after dialysis [10]. Single observer for echocardiography staff who do not know BNP laboratory level of the studied patient was strictly respected. Measurements of interventricular septum (IVS), posterior wall (PW), and left ventricular dimension in systole (LVDS) and diastole (LVDD) were performed on two to five cardiac cycles, according to the American Society of Echocardiography recommendations [11,12] using M-mode stop-frames from perfectly oriented short-axis or long- axis para sternal view, whenever this was possible, when short axis was considered suboptimal . LV mass (LVM) was obtained according to a necropsy validated formula LV mass = 0.8 (1.04) ([LVEDD + PWTD+IVSTD] – [LVEDD]) + 0.6 g [13]. For accounting for differences in body size, LV end- diastolic diameter (LVEDD), LVDS, IVS and PW were compared using direct measurements and measurements indexed to $BSA^{0.5}$ and expressed as $LVDD/BSA^{0.5}$, $LVDS/BSA^{0.5}$, $IVS/BSA^{0.5}$ and $PW/BSA^{0.5}$ in cm/m. Body surface area was calculated as (4x body weight + 7) / (body weight +90) which is a simple and accurate means to calculate BSA. LVM was normalized for height in meters raised to the algometric power 2.7, which linearizes the relation between LVM and height, and expressed in $g/m^{2.7}$ (LVMI) [14] and correlates best to lean body mass. LVH was defined as an LVMI greater than the 95th percentile of the healthy control subjects for both boys and girls, [15]. LVM^2 was included in the study for comparison. Relative wall thickness (RWT), a measure of concentricity, was calculated using the following equation septal wall thickness + posterior thickness divided by LV diastolic diameter (RWT = (IVS+PW) / LVDD). The value of 95th percentile of control subject was used as the cut–off to define concentricity.

Accordingly left ventricular geometry patients were categorized as those with normal geometry (normal RWT and normal LVM), Concentric hypertrophy (increased RWT and LVM), Eccentric hypertrophy (normal RWT, increased LVM), and Concentric remodeling (increased RWT and normal LVM). Left ventricular performance was estimated by calculation of fraction shortening (FS) [15].

Statistical Analysis

Results were presented as means ± standard deviation, in addition to range values. Statistical significant differences between groups were calculated using Analysis of Variance of nonbalanced groups (general linear model; GLM) at $p< 0.01$. Cut off values for LV geometry were calculated using univariate procedure. Correlation analysis was done using Pearson correlation coefficient. All statistics were done using SAS v 9.0 (Statistical Analysis System) software.

Results

Patients Demographic and Clinical Data, Laboratory results, Echo findings and its correlation analysis with ANP serum levels are shown in **(Tables 1-9).**

Demographic data of the studied groups show patient frequency distribution: Group (1) with CKD 1-4 stage- pre dialysis group (21 cases) : distributed as 4 (19%) patients in grade I; 6 (28%) patients in grade II; 10 (48%) patients in grade III, and 1 (5%) patient in grade IV . Group (2) with CKD 5 on dialysis (30 cases). Group (3) included (20) healthy age and sex matched children as a control group.The age of the patients in the pre dialysis patients ranged from 2- 12 years old with a mean of 7.24 +/- 3.62 years. In dialysis patients age ranged from 5.42 - 16 with a mean of 11.5 +/- 32.08 years. In pre dialysis group there were 11 males and 10 females while in dialysis group there were 16 males and 14 females. Control group included 20 healthy children with normal serum creatinine, 12 males and 8 females. The age of the children ranged from 2.25-11years with a mean of 7.76 +/- 2.57. Primary causes of CKD in each group are summarized in **(Table 1)**.

Regarding the frequency of most important clinical findings: In the dialysis group; 21patients (70%) had hypertension, 16 (53.3%) had heart failure, 29 (96.7%) had anemia and 16 (53.3%) had stunted growth. In pre dialysis group; 2 patients (9.5%) had hypertension, 2 (9.5%) had heart failure, 21 (100%) had anemia and 12 (57.1%) had stunted growth as shown in **(Table 2).**

Laboratory data of the studied groups are shown in **(Table 3)** Hb, Ca, P, albumin and iron show no statistical significant difference between dialysis & predialysis groups. Only alkaline phosphatase showed significant difference between CKD on conservative treatment versus CKD on dialysis (P< 0.01). Mean BNP level in dialysis patients was significantly higher than that in pre dialysis patients and the control. However no statistically significant differences were found in mean BNP level between pre dialysis patients and the control group when the three groups were compared. However, the mean BNP level in pre dialysis group was significantly higher than in the control group when only the two groups were compared **(Table 4)**.

Table 1 : Primary cause of renal damage in each group

	Pre dialysis (N = 21)	Dialysis (N = 30)
Nephritis	5 (23.8%)	5 (16.7%)
Reno vascular	0	3 (10%)
Obstructive uropathy	2 (9.5%)	4 (13.3%)
Reflux and neurogenic bladder	4 (19%)	3 (10%)
Unknown	3 (13.3%)	13 (43%)
Miscellaneous	7 (33.3%)	2 (6.7%)

Table 2 : Frequency of clinical findings among the studied patients

Clinical findings	Pre dialysis (N = 21)	Dialysis (N =30)
Hypertension	2 (9.5%)	12 (70%)
Heart failure	2 (9.5%)	16 (53.3%)
Respiratory disease	0	2 (6.7%)
Pulmonary hypertension	03 (14.3%)	4 (13.3%)
Bone deformity	0	8 (26.7%)
Bleeding tendency	0	2 (6.7%)
Anemia	21 (100%)	29 (96.7%)
Student growth	12 (57.1%)	16 (53.3%)
Epilepsy	0	5 (16.7%)
Decreased mentality	1 (4.8%)	1 (3.33%)

Table 3 : Laboratory data of studied groups.

		Pre dialysis (N = 21)	Dialysis (N = 30)	P value
Haemoglobin (HB) (g/d)	**Range** **Mean ± SD**	7.1 - 13 10.27 ± 1.67	7.7 - 13.8 10.83 ± 1.56	NS
Calcium (Ca) (mg/Dl)	**Range** **Mean ± SD**	6.9 - 11.6 9.03 ± 1.02	6.2 - 12.6 9.21 ± 1.49	0.62
Phosphorus (P) (mg/dl)	**Range** **Mean ± SD**	2.8 - 7.1 4.88 ± 1.27	2.2 - 8.4 5.49 ± 1.51	0.15
Alkaline Phosphatase (ALP) (IY/ml)	**Range** **Mean ± SD**	293 - 893 553.61 ± 201.17	105 - 881 355.36 ± 223.49	<0.01
Albumin (g/dl)	**Range** **Mean ± SD**	2.3 - 4.3 3.69 ± 0.51	2.4 - 4.3 3.53 ± 0.44	0.24
Iron (Fe) (µg/dl)	**Range** **Mean ± SD**	13 - 117 57.55 ± 32.5	39 - 172 71.8 ± 33.66	0.29

Table 4 : Statistical comparison between mean level of BNP among the 3 studied groups

	BNP (fmol /ml)	
	Range	**Mean ± SD**
Pre dialysis (N = 21)	0 - 111.7	**(C)** 29.72 ± 34.77
Dialysis (N = 30)	11. - 445.2	**(a, b)** 182.49 ± 136.57
Control (N = 20)	0-11.1	1.13 ± 2.97
P value		<0001

a= significant vs control, b= significant vs pre dialysis (3 groups comparison).
c=significant vs control (2groups comparison).

Echocardiography Left ventricular findings:

As shown in **(Table 5)** IVS, IVS/BSA$^{0.5}$ PW, PW/BSA$^{0.5}$, LVDD, were statistically significantly higher in dialysis patients as compared to both pre dialysis (CKD 1-4) and control groups ($p<0.0001$ each), however, there was no statistically significant difference between pre dialysis and control groups in any of these parameters. LVDD/ BSA$^{0.5}$ in dialysis patients was significantly higher than the control group ($p<0.01$) but not significantly different from that in the pre dialysis and control groups. LVDS and LVDS/BSA$^{0.5}$ were not statistically significant between the 3 groups. Comparing means of LVM, LVM$^{2.7}$ and LVM^{2}, RWT between groups, there was statistically significant difference between dialysis and control groups and between dialysis and pre dialysis groups ($P< 0.01$).There was no statistically significant difference between pre dialysis and control groups. FS was not significantly different when compared between the 3 groups **(Table 6)**.

As shown in **(Table 7)** there was abnormal geometry in all grades of CKD: Frequency of each pattern among pre dialytic stages of CKD showed; Normal geometry: one patient with grade I CKD, one patient with grade II CKD, two patients with grade III CKD and no patients with grade IV CKD. Concentric hypertrophy: There was two patients with grade I CKD, two patients with grade II CKD, four patients with grade III CKD and no patients with grade IV CKD. Eccentric hypertrophy: One patient with grade I CKD, three patients with grade II CKD, three patients with grade II CKD and one patient with grade IV CKD. Concentric remodeling: one patient with grade III CKD.

Concentric LV hypertrophy was the most frequent abnormality in dialysis patients affecting 23 patients (77%), while in predialysis, eccentric hypertrophy and concentric hypertrophy were the highest,

they were found in 8 patients representing each 38%. BNP values were higher in patients with left ventricular hypertrophy (concentric and eccentric) than those with normal LV geometry or concentric remodeling **(Table 8).**

When the correlations between BNP level and hypertension, LVM, $LVM^{2.7}$, LVM^{2}, RWT and serum creatinine were tested in predialysis and dialysis patients together (n = 51 cases), significant positive correlations were found (r = 0.46, 0.35, 0.46, 0.47, 0.42, 0.29; p = 0.0007, 0.01, 0.0007, 0.0005, 0.0002, 0.04, respectively) **(Table 9)**. On the other hand when these correlations were tested on pre dialysis and dialysis patients separately, no statistically significant differences were found.

Table 5 : Echocardiographic dimensions in Predialysis (CKD1-4), Dialysis & control groups

		Group I Predialysis	Group II Dialysis	Group III Control	P value
IVS (cm)	**Range** **Mean ±SD**	0.3 - 0.87 0.63 ± 0.13	0.47-1.69 1.01 ± 0.27 **(a, b) sig**	0.46 - 0.66 0.57 ± 0.06	<0.0001
IVS / $BSA^{0.5}$ (cm/m)	**Range** **Mean ±SD**	0.4-1.06 0.73 ± 0.16	0.48 - 1.62 0.4 ± 0.27 **(a, b) sig**	0.46 - 0.77 0.58 ± 0.06	<0.0001
PW(cm)	**Range** **Mean ±SD**	0.25 - 0.8 0.56 ± 0.14	0.4 - 1.3 0.87 ± 0.2 **(a, b) sig**	0.44 - 0.86 0.58 ± 0.07	<0.0001
PW / $BSA^{0.5}$	**Range** **Mean ±SD**	0.33 - 0. 84 0.64 ± 0.13	0.45 - 1.36 0.9 ± 0.22 **(a, b) sig**	0.5 - 0.666 0.59 ± 0.04	<0.0001
LVDD (cm)	**Range** **Mean ±SD**	2.4 - 4.14 3.44 ± 0.53	3.05 - 5.6 4.09 ± 0.66 **(a, b) sig**	2.64 - 3.86 3.44 ± 0.3	<0.0001
LVDD / $BSA^{0.5}$ (cm)	**Range** **Mean ±SD**	2.75 - 5.31 3.98 ± 0.6	2.93 - 5.75 4.22 ± 0.69 **(a)**	2.95 - 4.38 3.51 ± 0.28	<0.0001
LVDS (cm)	**Range** **Mean ±SD**	1.3 - 2.9 2.19 ± 0.52	1.52-3.9 2.56±0.65	1.55 - 243 2.18 ± 0.24	NS
LVDS / $BSA^{0.5}$ (cm/m)	**Range** **Mean ±SD**	1.72 - 3.68 2.5 ± 0.46	1.7 - 3.88 2.64 ± 0.65	1.99 - 2.66 2.23 ± 0.18	NS
RWT	**Range** **Mean ±SD**	0.2 - 0.52 0.35 ± 0.08	0.28 - 0.83 0.47 ± 0.12 **(a, b) sig**	0.26 - 0.38 0.33 ± 0.04	<0.0001

IVS=inter ventricular septum, PW= posterior wall, LVDD= left ventricle dimensions in diastole, LVDS =left ventricle dimensions in systole, RWT= relative wall thickness

a = significant vs control, b = significant vs pre dialysis **(3 groups comparison)**

c = significant vs control **(2 groups comparison).**

Table 6 : Comparison of left ventricular parameters (mean values) in pre dialysis, dialysis and control groups

		Pre dialysis	Dialysis	Control
LVM(G)	**Range** **Mean± SD**	14.41 - 91.58 52.85 ± 20.38	45.18 - 302.27 129.13 ± 58.5 **(a, b)**	24.06 - 6691 48.79 ± 11.6
$LVM^{2.7}(g/m^2)$	**Range** **Mean± SD**	17.03 - 86.94 46.13 ± 18.32	23.2 - 140.96 74.73 ± 32.69 **(a, b)**	22.36 - 44.57 28.03 ± 5.83
LVM^2	**Range** **Mean± SD**	16.31 - 76.31 46.36 ± 13.72	27.58 - 158.28 85.07 ± 34.01 **(a, b)**	26.28 - 45.19 31.97 ± 4.49
RWT	**Range** **Mean± SD**	0.2 - 0.52 0.35 ± 0.08	0.28 - 0.83 0.47 ± 0.12 **(a, b)**	0.26 - 0.38 0.33 ± 0.04
FS (%)	**Range** **Mean ±SD**	26.32 - 61.76 36.89 ± 7.81	22 - 54.68 37.88 ± 7.81 **(NS)**	30.57 - 45.23 36.6 ± 3.32

LVM (G) = left ventricular mass in grams , **$LVM^{2.7}(g/m^2)$ =** left ventricular mass g/surface area.
RWT = relative wall thickness, **FS** = fractional shortening for estimating systolic function.
a = significant vs control, b = significant vs pre dialysis (3 groups comparison)
c =significant vs control (2groups comparison)

Table 7: Left ventricular geometry and BNP level among pre dialysis patients according to their CKD stage.

Grades of CKD	Normal geometry, mean BNP	Concentric / Hypertrophy, mean BNP	Eccentric / Hypertrophy, mean BNP	Concentric /Remodeling, mean BNP
Grade I (N = 4)	1 case (30.4)	2 cases (64.1)	1 case (111.0)	0
Grade II (N = 6)	1 case (2.1)	2 cases (6.0)	3 cases (20.83)	0
Grade III (N = 10)	2 cases (57.0)	4 cases (22.6)	3 cases (13.1)	1 case (4)
Grade IV (N = 1)	0	0	1 case (40.5)	0

Table 8 : The mean value of BNP in dialysis and pre dialysis patients in relation to LV geometry.

	Pre -Dialysis		Dialysis	
LV Geometry pattern	**No (%)**	**Mean BNP (fmol/ml)**	**No of cases (%)**	**Mean BNP (fmol/ml)**
Normal Geometry	4 (19%)	24.53	2 (7%)	29.79
Concentric hypertrophy	8 (38%)	50.56	23 (77%)	80.460
Eccentric Hypertrophy	8 (38%)	35.51	4 (13%)	75.09
Concentric Remodeling	1 (5%)	38.11	1 (3%)	1 (5%)

Table 9 : Correlation between BNP levels and Lt ventricle Mass, LVMI, RWT, FS. in the total patient sample (CKD 1-5) 51cases .

	BNP	
	R	P
Hypertension	0.46	0.0007***
LVM (g)	0.35	0.01
$LVM^{2.7}$ ($g/m^{2.7}$)	0.46	0.0007
LVM^2 (g/m^2)	0.47	0.0005***
RWT	0.42	0.002**
FS (%)	0.05	0.73
Creatinine (mg/dl)	0.23	0.04

LVM (G) = left ventricular mass in grams, $LVM^{2.7}$ (g/m^2) = left ventricular mass g/surface area.
RWT = Relative wall thickness FS = Fraction systole

Discussion

In Egypt, CKD in children represent a community problem with high morbidity and mortality. The profile for those who received kidney transplant in Cairo University Children Hospital (CUCH) through 2009 to 2017 showed dramatic change in their quality of life, especially as Inherited Kidney diseases and uropathies (CAKUT) represented 43%, 26 % of recipients, where early preemptive transplant before progress of CKD morbidities is crucial [16]. Although Hypertension, hypoalbuminemia, proteinuria, anemia, abnormal calcium and phosphorus metabolism are serious morbidities of CKD in children, the cardiovascular risk factors constitute the major cause of mortality in adults [17].

In the present study, Significant Cardiovascular morbidity was evident especially in those on regular hemodialysis where 70% were hypertensive and 53.3% had heart failure. In predialysis (CKD1-4), 9.5% had hypertension and heart failure as well. Anemia was very common among studied patients affecting all the pre dialysis group and 96.7% of dialysis patients. Left ventricular Hypertrophy (LVH) develop early during early stages of (CKD1-4) & report 20% frequency [5, 18]. With CKD progression LV Mass also increase in up to 80% of ESRD patients on Dialysis [6, 19, 20]. With Successful kidney transplant, there is regression of LVH [4].

In the present study, frequency of LVH was high in pre dialysis patients 76% vs 90% in dialysis group. Mitsnefes 2012 reported 17-52% frequency among pre dialysis vs 30-92% on dialysis [21]. In the present study, the means of LVM, $LVM^{2.7}$ and LVM^2 and RWT were significantly higher in dialysis patients than in pre dialysis and control groups, however, there were no statistically significant differences between pre dialysis (CKD1-4) and the control group (Three group comparison). This may be explained by the fact that; although, hypertension, anemia, hyper-phosphatemia, and uremia are present with variable frequencies and degrees in predialysis group, but they look less frequent and properly controlled in such small number randomly selected group; (hypertension in two cases out of twenty one (9.5%), heart failure in 9.5%, pulmonary hypertension 14.3%, bone lesions 0%). Many patients are well controlled with medications (anti hypertensive drugs, phosphate binders, erythropoietin..), diet and fluid control. They are also not exposed to altered hemodynamic state induced by

hemodialysis, therefore their cardiac echocardiography dimensions and Lt Ventricle mass indices are less insulted than dialysis patients when compared to normal control group.

Geometric pattern in the present study showed that concentric left ventricular hypertrophy was the most frequent abnormality in dialysis patients 23/30 (77%), while in pre dialysis group, both eccentric hypertrophy and concentric hypertrophy were the most frequent (38%) for each. Concentric remodeling reported 3% in dialysis group and 5 % in pre dialysis group. Mitsnefes 2006 in his cohort study on CKD patients stage 1-4 (53 cases) found that (48.2%) had normal geometry, eccentric LVH (23.2%), and concentric LVH (12.5%), concentric remodeling in(16.1%) and also concluded that abnormal geometry was found in any stage of CKD irrespective of being early or late [3]. Malikanas 2005 reported a Geometry pattern among stages 1-4 as: normal geometry 48.2%, ecenteric 23 %, concentric 12.5%, remodeling 16% [39] [22]. Matteucci et al (2006) conducted a study on 156 pediatric children CKD stage 1-4 and found that 57.7% had normal geometry, 21% had eccentric LVH, 12.1% had concentric LVH and 10, 2% had concentric remodeling) [23]. Hedvig et al (2010), found that concentric hypertrophy was the most frequent in dialysis patients affecting (35.7%) while in pre dialysis CKD, concentric hypertrophy represent (20%).

Eccentric hypertrophy in the dialysis group represent 28.6%, and there were no patients with eccentric hypertrophy in the pre dialysis group. In both groups there was only one patient with concentric remodeling representing 10% in pre dialysis CKD and 7.1% in dialysis group [24]. Eccentric hypertrophy is mainly caused by volume overload, hypertension and high vascular access blood flow. Other causes for ventricular changes include calcifications of vessel wall and lower aortic compliance leading to faster return of blood across the valve as it is still open described as aortic aging [25].

Uremic cardiomyopathy define cardiac abnormalities in CKD patients due to retention of urea and nitrogenous waste products in the blood. High serum phosphates independently of renal function and high BP predict LVM rise [26]. High parathormone level increase Fibroblast growth factor [27] and high intracellular phosphate promote vascular calcification arterial stiffness and increased LVM even with therapeutic use of phosphate binders & vitamin D [28]. Hemodialysis especially with high ultra-filtration may result in intra or post dialysis hypotension with myocardial hypo perfusion and ischemia, this induce regional wall abnormalities (stunning) due to release of fibroblast growth factor [29]. Dialysis also aggravate left ventricular hypokinesia and dilatation induced by overhydration, hyperdynamic circulation secondary to anemia and high access blood flow volume with further progress to heart failure unless anemia is corrected and access surgery is available. Mortality risk with CVD in CRI patients is higher with left Ventricle systolic dysfunction rather than LVD dilatation [30] and is also high in those with regional abnormal motion RAMA. However progress of LVD secondary to over hydration or hemodialysis will lead to increase of filling pressure and ultimately LV dysfunction.Therefore recommendations for assessment of LVD function by Echo was crucial. E/A, Transmitral flow, Lt

atrial volume, Tricuspid regurge gradient, were recommended for patients starting hemodialysis [31]. LT atrial dilatation & dysfunction in CRI patients on dialysis or over hydration, is another high risk (HR) factor for such patients. With progression of pulmonary hypertension and RV dysfunction mortality risk is at its peak [32].

B-type Natriuretic peptides is a cardiac neurohormone secreted from the ventricles in response to volume expansion and pressure overload [33]. Natriuretic peptides, in general, have a natriuretic and vasodilator effect and suppress the rennin angiotensin aldosterone system. BNP is a 32 amino acid polypeptide containing a 17 amino acid ring structure common to all 17 natriuretic peptides. BNP is synthesized in bursts directly proportional to ventricular expansion and pressure overload. It has been found to be a highly sensitive and specific marker for left ventricular dysfunction [34]. Both symptomatic and asymptomatic LVD is associated with increased circulating concentrations of brain natriuretic peptide (BNP). The N-terminal BNP, has proved to be good marker of both development of CHF and prognosis in patient populations with LVD and superior to other natriuretic peptides as a stronger predictor of LVD and dysfunction [35].Diagnosis of LVH by BNP had 88% sensitivity, +ve predictive value of 92%, while diagnosis of LV dysfunction by BNP had sensitivity of 94% [36]. A significant correlation with creatinine and LVM indexed for height was found in the CRF group [37].

In the present study BNP values were higher with left ventricular eccentric, and with (concentric and eccentric) than those with normal LV geometry or concentric remodeling (Table 8). In either group (predialytic or dialytic), however small number of subgroups comparison can not reflect valid statistical conclusions. Rinat et al 2012 reported that NT-pro BNP levels and their log values were positively correlated with LV mass [38].The present study also observed that Mean BNP level in dialysis patients was significantly higher than that in pre dialysis patients and the control groups (a, b), while no significant differences were found in mean BNP level between pre dialysis patients and the control group when the three groups were compared. When only Pre dialysis and control groups were compared, the mean BNP level was found to be significantly higher in pre dialysis **(Table 4)**. Less incidence and proper medical control of factors triggering ventricular stress and release of BNP in small group number randomly selected (predialysis group) have been already discussed. Similar findings were reported in the study of Hedvig 2010, where mean BNP level in dialysis patients was significantly higher than that in pre dialysis patients and the control group, while no statistically significant differences were found in mean BNP level between pre dialysis patients and the Control group [21]. When correlations between BNP level and hypertension, LVM, $LVM^{2.7}$ LVM^{2}. RWT and serum creatinine were tested in the whole CKD patients (pre dialysis and on dialysis) (n=51), Significant positive correlations were found (r = 0.46, 0.35, 0.46, 0.47, 0.42, 0.29; p = 0.0007, 0.01, 0.0007, 0.0005, 0.0002, 0.04, respectively) **(Table 9)**. On the other hand when these correlations were tested on predialysis and dialysis patients separately, no statistically significant differences were

found, possibly due to the small numbers included in each group. We also found BNA non-significant negative correlation with FS (r = - 0.05, p = O.7). It was reported by [3, 6 and 4] that left ventricle ejection fraction LVEF< 40% correlated with 0.7 ANP level or >95 percentile of normal person without LVD. Areas for diagnosis of CHF equals 0.8 with AF & 0.9 without atrial fibrillation (AF), as AF increase BNA [39]. Hedvig reported that, Brain natriuretic peptide was significantly higher in dialyzed patients in comparison with healthy children (p = 0.012) and with patients at pre dialysis stage (p = 0.039). Significant correlation was found between levels of brain natriuretic peptide and ventricular hypertrophy (p = 0.001). Higher log BNP was seen in children with eccentric hypertrophy than in children with concentric hypertrophy [21].

Difference between adults & children data could be attributed to the fact that reports about this hormone and its correlation with CVD in in children are scarce & is much lacking [40]. Its normal level rises with age & also correlate with obesity. Wahl et al reported its complete removal after each hemodialysis session especially with high flux membranes [41]. Its level reflects convective effects of hemodialysis and not totally related to cardiac function [42]. Children in particular lacks many of the traditional non renal injurious factors to cardiac structure and function which are present in adults. Smoking, diabetes, coronary ischemia, atherosclerosis, etc all these factors contribute to rise in serum ANP and to marked echocardiography changes that are less marked in children with CKD. Adults' variation versus children could explain the fact that mortality in CKD patients due to CVD disease is higher in adults [17]. Charles reported that significant relation between proteinuria and LVM was only evident when using Cardiac Magnetic Resonance Imaging CMRI [43] which is more sensitive in defining LVM, Identifying coarse fibrosis, subclinical and overt ventricular dysfunction. The Pre dialysis patients in the present study also showed non-significant correlation between BNP and GFR. Edward reported structural changes in early CKD when creatinine is frequently near normal and before uremia was present [44]. In our study, 76% of pre dialysis group showed LVH equally presented as concentric or eccentric hypertrophy which might explain the rise in their ANP irrespective of their GFR.

A poor significant negative correlation was seen between BNP with fraction shortening (FS) for estimation of systolic function (R = 0.05 P = 0.7) within total patient sample (51 cases). This could be attributed to the facts that; systolic dysfunction (EF <40%) is uncommon in pre dialysis CKD [19]. There is also limitations to use Ejection fraction (EF) in quantifying LVF as newer imaging techniques. In LVS dysfunction with pulmonary hypertension, the RV function becomes an independent predictor of outcome [45].

Conclusion

Cardiac complications as left ventricular hypertrophy and left ventricular dysfunction are common in children with CKD. It is more profound with the progression of the disease during dialysis. Measuring BNP may be useful for the identification of CKD patients with LVH or LVD.

Recommendations

Routine echo should be done to all patients with CKD even in early stage and whenever NT pro BNP level is increased. Factors of significant impact on echo indices reported in the study should be early corrected eg; good control of hypertension, correction of anemia and efficient dialysis to remove uremic toxins related to uremic myopathy. Early transplantation should be encouraged before cardiac changes are fatal or irreversible.

Limitations

Small sample size and scarce researches on NAP in children.

Implication of Practice

This study highlighted the importance of echocardiography and the measurement of BNP for early diagnosis and management of cardiac complications during the course of CKD in children.

List of abbreviations

Echo	Echocardiography	LVM	Left Ventriclar Mass
ELISA	Enzyme Linked Immunosorbent Assay	LVMI	Left Ventriclar Mass indices
ESRD	End Stage Renal Disease	NT -NAP	N-terminal pro-Brain Natriuretic Peptide
CVD	Cardiovascular Disease	RWT	Relative Wall Thickness
CKD	Chronic Kidney Disease	LVS	Left Ventricular systole
CRI	Chronic Renal Insufficiency	LVD	Left Ventricular diastole
LV	Left Ventricle	LVDS	Left Ventricular diameter in systole
LVH	Left Ventricle Hypertrophy	E/A	Early to late diastolic transmitral flow velocity.

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Statements

Ethics approval and consent to participate
This study protocol and the consents were approved and deemed sufficient by the Ethical Committee of Pediatric nephrology unit, Children Hospital, Cairo University and National Research Centre and informed written consent was obtained in every case from their legal guardians.

Consents for publication
The contents and material of the manuscript have not been previously reported at any length or being considered for publishing elsewhere.

Availability of data and material
"Not applicable"

Conflict of interest
The authors declare no conflict of interest.

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