The Prognostic value of N-Terminal-ProBrain Natriuretic Peptide in the Diagnosis and to Detect the Progression of Left Ventricular Mass and Function in Patients with Chronic Kidney Disease

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Abstract: Introduction: Mild renal dysfunction is an important cardiovascular risk factor predispose to coronary heart disease. In recent years natriuretic peptides have become promising candidates in the early detection of cardiovascular disease (CVD) such as heart failure. In end stage renal disease (ESRD) patients, the clinical benefit of N-terminal probrain natriuretic peptide (NT-proBNP) measurements has not been well established. **Aim of the study:** Is to evaluate the role of serum NT-proBNP levels in diagnoses and to detect the progression of left ventricular dysfunction and left ventricular mass in a sizable cohort of stable patients on chronic HD without clinical signs of progressive heart failure. **Patients and methods:** This study was conducted on 100 persons, 55 were known as ESRD patients on regular conventional hemodialysis (HD) [Dialysis group] and 25 patients with chronic kidney disease(CKD) not on HD [CKD group] in addition to 20 healthy volunteers [control group]. All participants were thoroughly interrogated and examined clinically and were subjected to plasma NT-proBNP level and transthoracic echocardiography at baseline and after six months. **Results:** Mean NT-proBNP showed significantly higher mean in dialysis group (252.88 ±125.193 fmol/ml) compared to the CKD group(168.266 ±134.881 fmol/ml[*P*=0.007], and the control group(9.075±6.707fmol/ml)[*P*<0.001].There was a significant strong inverse correlation between NT-proBNP and ejection fraction(EF) (*P*<0.001). There was also a strong positive correlation between NT-proBNP and change of EF over six months (Δ EF) (*P*<0.001). Also there was a significant strong positive correlation between NT-proBNP and left ventricular mass (LVM) & LVM index(LVMI) and change of LVM & LVMI over six months (Δ LVM) (*P*<0.001). **Conclusion:** The study recommended that plasma NT-proBNP assessment is an easy non invasive test and should be monitored in HD patients owing to its close relation to LVM, systolic dysfunction and cardiovascular morbidity and mortality in this population. Rising NT-proBNP levels may reflect worsening ventricular stress and may help earlier diagnostic and therapeutic strategies.

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Keywards: NT-proBNP**,** CKD, LVM & LVMI.

1- Introduction

In recent years, increasing evidence has been provided that even mild renal dysfunction is a powerful cardiovascular risk factor that induces typical cardiovascular alterations and thus predisposes to coronary heart disease as well as to non coronary cardiovascular problems. Numerous heterogeneous abnormalities have been described in patients with early renal dysfunction [e.g., microalbuminuria, reduced estimated glomerular filtration rate (GFR)]. One final common pathway seems to be endothelial cell dysfunction. In patients with early renal dysfunction, a long list of classical and non classical cardiovascular risk factors have been identified(1,2).

HD techniques have improved remarkably in recent decades, however outcomes remain poor. CVD are the most common cause of death and dialysis related strategies have not been successful in reducing mortality rates (3,4).The linked phenomena of left ventricular hypertrophy and cardiac fibrosis have been well described as a frequent component of CKD and ESRD for many decades. However, in recent years there has been a growing appreciation of the impact of these cardiac abnormalities on morbidity and mortality in CKD and ESRD, including congestive heart failure and arrhythmias. In addition, the fundamental physiologic and pathologic mechanisms that underlie these disease states have come under increasing uncertainty, and new insights have been obtained that not only increase the underlying complexity of the disorders but also open up new avenues for their prevention and treatment (4).

Circulating biomarkers play a major role in the early detection of CVD such as heart failure. In recent years natriuretic peptides have become promising candidates in this respect. BNP, which is

homologous to atrial natriuretic peptide, is present in the brain and the heart. The circulating concentration of BNP is less than 20% of the atrial natriuretic peptide level in healthy people, but equals or exceeds that of atrial natriuretic peptide in patients with congestive heart failure(5).

BNP starts as a precursor protein. This is modified within the cell into a prohormone, proBNP, which is secreted from the left ventricle in response to myocardial wall stress. In the circulation, proBNP is cleaved into a biologically active C-terminal fragment—BNP—and a biologically inactive N-terminal fragment (NT-proBNP)[5].NT-proBNPis primarily cleared by the kidney. BNP is cleared by receptor-mediated binding and removed by neutral endopeptidase, as well as by the kidney.

The circulating half life of brain natriuretic peptide(BNP) is 23 minutes, whereas the inactive fragment NT-proBNP has a much longer half life about 60-120 minutes, which is of relevance for its use as a diagnostic tool (6). The clinical benefit of using these markers to screen for cardiovascular risk has been well documented in the general population (7). Patients with ESRD have one of the highest cardiovascular risk scores. In this population the clinical benefit of NT-proBNP measurements has not been well established (8).

Aim of the study:

Our aim was to evaluate the impact of serum NT-proBNP level to diagnose and to detect the progression of left ventricular dysfunction and LVM in a sizable cohort of stable patients on chronic HD without clinical signs of progressive heart failure.

2- Patients & methods

This study was conducted on one hundred persons, fifty five of whom were known as ESRD patients on regular conventional HD (Dialysis group) in Theodor Bilharz Research Institute (TBRI), Cairo, Egypt, and twenty five patients with CKD not on HD (CKD group), in addition to twenty of healthy volunteers (control group). All patients were clinically stable and gave informed consent. The study was approved by the ethics committee of Theodor Bilharz research institute.

Patients with clinical signs of heart failure, atrial fibrillation, uncontrolled hypertension, diabetes mellitus, severely anemic patients with Hb<10g/dl, and patients with malignancy or active inflammation were excluded from the study.

All participants were thoroughly interrogated and examined clinically and were subjected to complete blood count(CBC), kidney function tests (blood urea & serum creatinine).and serum electrolytes(Na, K, Ca& Phosphorus), lipid profile(Total cholesterol, triglycerides, HDL & LDL).

Assessment of N-T pro BNP:

- Enzyme immunoassay for quantitative determination of NT-proBNP
- Biomedica Slovakia S.R.O, cat No. SK-1204, principles of NT-proBNP

Sample preparation:

- Freshly collected fasting blood samples obtained before a midweek hemodialysis session were centrifuged within one hour; serum samples were stored at -70 C. Samples were well mixed before assaying. Samples were fasting to avoid lipemic samples.
- Dilute concentrate 1:10 (e.g 100 ml WASHBUF + 900 ml distilled water). Crystals in the buffer concentrate will dissolve at room temperature. The diluted WASHBUF is stable at 2-8^{0}C. Use only diluted WASHBUF (washbuffer) for the assay.

Principles for the assay:

This kit is a sandwich enzyme immunoassay for the determination of NT-proBNP in human EDTA plasma or serum.

- In a first step, sample and conjugate (sheep anti human NT-proBNP-HRPO) are pipetted into the wells of the microtiter strips, which are precoated with polyclonal sheep anti NT-proBNP antibody. NT-proBNP present in the sample binds to the precoated antibody in the well and forms a sandwich with the detection antibody. In the washing step all non-specific unbound material is removed.
- In a second step, the substrate (TMB Tetramethylbenzidine) is pipetted into the wells. The enzyme catalysedcolour change of the substrate is directly proportional to the amount of NT-proBNP present in the sample. This colour change is detectable with a standard microtiterplate ELISA reader.

Assay protocol:

- All reagents and samples must be at room temperature (18-26°C) before use in the assay.
- Mark position for BLANK/STD/SAMPLE/CTRL (Blank/Standard/Sample/Control) on the protocol sheet.
- Take microtiter strips out of the alu bag, take a minimum of one well as Blank. Store unused strips with desiccant at 2-8° C in the alu bag. Strips are stable until expiry date stated on the label.
- Add 50 µl STD/SAMPLE/CTRL (Standards/Sample/Control) in duplicate into respective well, except blank.
- Add 200 µl CONJ (Conjugate) into each well, except blank, swirl gently.
- Cover tightly and incubate 3 hours at room temperature (18-26°C).

- Aspirate and wash wells 5x with 300µl diluted WASHBUF (Wash buffer), remove remaining WASHBUF by hitting plate against paper towel after the last wash.
- Add 200 µl SUB (Substrate) into each well.
- Incubate for 30 min at room temperature (18-26°C) in the dark.
- Add 50 µl STOP (Stop solution) into each well.
- Measure absorbance immediately at 450nm with reference 620 nm, if available

Calculation of results:

- Subtract the blank extinction from all other values
- Construct a Standard curve from the STD values, using a half logarithmic graph paper or a commercial available software
- Read the sample concentration from the constructed STD curve
- The assay has been evaluated using a 4 PL algorithm method. Other curve fitting methods needs an evaluation by the user.
- It is recommended to re-assay samples with NT-proBNP concentrations extending 640 fmol/ml. Dilution factors must be taken into consideration for calculation of the samples

Assay characteristics:

Normal range: Median: 4.8 fmol/ml (n = 66)

Standard range: 0 to 640 fmol/ml

Sample volume: 50 µl human serum or EDTA plasma

Detection Limit: (0 fmol/ml + 3 SD) 3 fmol/ml

Incubation time: 3 hours / 30 min

Precision

Intra-Assay(n=16)		
Mean(fmol/ml)	13	146
SD(fmol/ml)	10	7.3
CV%	8	5

Intra-Assay(n=10)		
Mean(fmol/ml)	17	163
SD(fmol/ml)	1.78	8.1
CV%	10	7

Transthoracic echocardiography

Transthoracic echocardiography were done to all subjects patients and control group at baseline and a follow up after six months for the estimation of EF, fractional shortening(FS), end systolic and diastolic dimensions, left ventricular posterior wall thickness (LVPWT), Interventricular septum thickness(IST), LVM, LVMI and diastolic dysfunction.

Statistical methods:

Descriptive statistics were expressed as mean ± SD. Comparison between the mean values of three groups was performed using one way analysis of variance (ANOVA). Spearman rank correlation coefficient was used to determine significant correlations among different parameters. Differences were considered significant when $p< 0.05$, and highly significant if $p< 0.001$. Statistical analysis was performed the aid of the SPSS computer program (version 16 windows).

3- Results

The demographic features of the studied groups are shown in table 1.Mean patient age and sex in dialysis group, in CKD group and in control Group[Table 1].

Body weight and body mass index(BMI) of Dialysis group, CKD group and Control group[Table 1].

Mean duration on dialysis in the dialysis group was (6.27 ± 4.51) years; range 1-20 years [Table 1].

Laboratory Data:

Mean serum creatinine level, mean blood urea level and mean eGFR, serum sodium, potassium, calcium and phosphorus, serum total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL) and triglyceride level in dialysis group, CKD group and control group are shown in [Table 2].

NT-proBNP Level:

Mean NT-proBNP level in dialysis patients group was 252.88 [±125.193] fmol/ml; range 30 – 650 fmol/ml [Table 3, Figure 1].

Mean NT-proBNP level in CKD patients group was 168.266 [±134.881] fmol/ml; range 30 – 632 fmol/ml [Table 3, Figure 1].

Mean NT-proBNP level in control group was 9.075 [±6.707] fmol/ml; range 3.0 – 30 fmol/ml [Table 3, Figure 1].

NT-proBNP showed significantly higher mean in dialysis group compared to the CKD group (P=0.007), and the control group (P<0.001). [Table.3]

Echocardiography :

Mean EF, mean delta EF (ΔEF), mean FS, mean delta FS(ΔFS), mean end-diastolic dimention (EDD), mean delta EDD (ΔEDD), mean end-systolic dimention (ESD), mean delta ESD(ΔESD), mean posterior wall thickness (PWT), mean delta PWT (ΔPWT), mean IVS, mean delta IVS (ΔIVS), mean LVM, mean delta LVM (ΔLVM), mean LVMI, mean delta LVMI (ΔLVMI) in dialysis group, CKD group and control group are shown in (Table.4) & significant different between studied groups[Figures 2, 3, 4, 5, 6].

Diastolic dysfunction:Fivty five percent of dialysis group had diastolic dysfunction.46.7% of

CKD group had diastolic dysfunction.None of the control group had diastolic dysfunction.

Diastolic dysfunction x6months:Sixty percent of dialysis group had diastolic dysfunction.46.7% of CKD group had diastolic dysfunction.None of the control group had diastolic dysfunction.

Patient Group – Significant Correlations

Correlations between the patients' NT-proBNP level and each of serum creatinine, eGFR, lipid profile parameters and echocardiographic findings in patients with chronic renal disease (dialysis group and CKD group)

There was a significant strong inverse correlation between NT-proBNP and eGFR (*P*<0.001) and a significant strong correlation between NT-proBNP and serum creatinine level (*P*<0.001) [Table5].

NT-proBNP level and echocardiographic findings[Table 6]

- There was a significant strong inverse correlation between NT-proBNP and EF (P<0.001)[Fig.7]
- There was strong positive correlation between NT-proBNP and change of EF over six months (Δ EF) (*P*<0.001).
- There was a significant strong inverse correlation between NT-proBNP and FS (*P*<0.001).
- There was a significant strong positive correlation between NT-proBNP and LVM (*P*<0.001)[Fig.8].
- There was strong positive correlation between NT-proBNP and change of LVM over six months (Δ LVM) (*P*=<0.001).
- There was a significant strong positive correlation between NT-proBNP and LVMI (P<0.001). Using analysis of variance correlation remained positive after accounting for BMI[Fig.9]
- There was strong positive correlation between NT-proBNP and change of LVMI over six months (Δ LVMI) (*P*<0.001).

Table 1: Demographic features of the studied groups.

Variable	Dialysis group(n=55)	CKD group(n=25)	Control group(n=20)	*P* value Sig.
Age(yrs)	56.07±11.871(range 23-75)	55.8±11.636(range 25-72)	51.55 ±13.426(range 25-70)	0.07 NS
Gender Male/Female	26(43.3%)/34(56.7%)	19(36.7%)/11(63.3%)	9(45%)/11(55%)	NS
Weight(kg)	71.1667 ± 14.54	78.3 ± 9.59	79.35 ±13.87	NS
BMI(*Kg/m²*)	25.58 ± 5.0	27.27 ± 2.86	27.6 ± 4.19	0.4S NS
DOD(yrs)	6.27 ± 4.5			

Values are the mean ± SD , (n) = number tested , (%) = percent,
BMI=Body mass index, *Sig.*=significance,*DOD*=Duration of dialysis,NS=non sig.

Table (2): Biochemical Laboratory data of the studied groups.

Variable	Dialysis group(n=55)	CKD group(n=25)	Control group(n=20)	*P* value Sig.
S.Creatinine*(mg/dl)*	8.315 ± 2.843	4.083±2.035	0.795 ±0.153	< 0.001 HS
Urea*(mg/dl)*	114.05 ± 34.542	114.0 ± 48.51	24.05 ±3.316	< 0.001 HS
eGFR	5.0 ± 0	19.1 ± 16.742	93.6 ± 25.87	< 0.001 HS
S. Calcium*(mg/dl)*	8.07 ± 1.14	7.876 ± 1.051	9.13 ± 0.675	< 0.001 HS
S. P *(mg/dl)*	5.02 ±1.807	4.71 ± 1.53	3.515 ± 0.64	0.002 S
T.Chlesterol*(mg/dl)*	171.466 ± 49.15	172.467 ±47.843	186.1 ±20.396	0.439 NS
Triglyceride*(mg/dl)*	156.6 ± 65.21	139.167 ± 64.643	101.8 ± 19.635	0.002 S
HDL*(mg/dl)*	35.05 ± 6.057	37.6 ± 4.438	43.15±3.167	< 0.001 HS
LDL*(mg/dl)*	107.246 ± 44.373	105.266 ±42.297	120.55 ±23.105	0.378 NS

eGFR=estimated glomerular filtration rate,HDL=high density lipoprotein,LDL=low density lipoprotein,HS=high significant,NS=non significant

Table (3): Mean NT-proBNP level in the studied groups.

Variable	Dialysis group(n=55)	CKD group(n=25)	Control group(n=20)	*P* value
NT-proBNP*(fmol/ml)*	252.88 ± 125.193	168.266 ±134.881	9.075 ±6.707	*P**<0.007 *P***< 0.001

*P**=dialysis group compared witn CKD group,p**=dialysis group compared with control group.

Table (4): Echocardiography data of the studied groups.

Variable	Dialysis Group (n= 55)	CKD Group (n= 25)	Control Group (n= 20)	*P (value)* Sig.
EF (%)	63.833 ± 9.23	62.4 ±9.22	68.95±3.17	0.013 NS
ΔEF (%)	-5.703 ± 12.8	-0.491 ± 12.75	-0.194 ±3.52	0.72 NS
FS (%)	35.117 ± 6.549	34.1 ± 6.588	38.7 ±3.45	0.3 NS
ΔFS (%)	-7.21 ± 16.96	-0.915 ±18.48	-2.08 ±4.42	0.179 NS
EDD*(mm)*	53.22 ± 8.28	52.37 ± 8.42	48.13 ±6.63	0.52NS
ΔEDD*(mm)*	2.96 ± 10.02	2.53 ±9.61	-1.55±7.6	0.186NS
ESD*(mm)*	34.85 ± 8.29	34.29 ± 8.5	32.37 ±5.58	0.483NS
ΔESD*(mm)*	4.06 ± 18.06	4.57 ± 16.28	0.313 ±8.75	0.616NS
PWT*(mm)*	11.11 ± 2.22	11.06 ± 2.13	8.7 ±1.06	<0.001HS
ΔPWT*(mm)*	2.84 ± 12.9	2.38 ± 12.56	0.091 ±3.9	0.121NS
IVS*(mm)*	11.24 ± 2.43	11.71 ± 2.7	8.68 ±0.97	<0.001HS
ΔIVS*(mm)*	5.325 ± 15.32	0.35 ± 13.48	-0.77 ±4.17	0.663NS
LVM gm	241.27 ± 80.43	234.33 ± 61.88	142.35 ±42.43	<0.001HS
ΔLVM	7.19 ± 23.84	-0.44 ± 21.55	-0.188 ±5.97	0.216NS
LVMI	138.87 ±55.73	127.3 ± 36.21	74.8 ±16.4	<0.001HS
ΔLVMI	7.725 ± 23.75	-0.082 ± 21.44	-0.43 ±5.88	0.16NS

Table (5): Correlations between the patients' NT-proBNP level and each of serum creatinine, eGFR, hemoglobin and each of lipid profile parameters.

NT-proBNP level	*P* value
1.serum creatinine	<0.001HS
2. eGFR	<0.001HS
3. Hemoglobin	<0.001HS
4.Total cholesterol	0.197NS
5.Triglycerides	0.011S
6.HDL	<0.001HS
7.LDL	0.401NS

eGFR=estimated glomerular filtration rate,HDL=high density lipoprotein,LDL=low density lipoprotein,HS=high significant,NS=non significant

Table (6): Correlations between NT-proBNP leveland echocardiographic findings:

NT-proBNP	*P* value
1. Ejection fraction	<0.001 HS
2. Delta ejection fraction	<0.001HS
3. Fractional shortening	<0.001 HS
4. Left ventricular mass	<0.001 HS
5. Delta left ventricular mass	<0.001HS
6. Left ventricular mass index	<0.001 HS
7. Delta left ventricular mass index	<0.001HS

HS=high significant

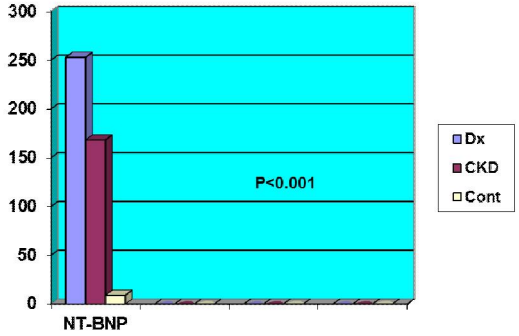


Figure (1): NT-pro BNP between Studied Groups

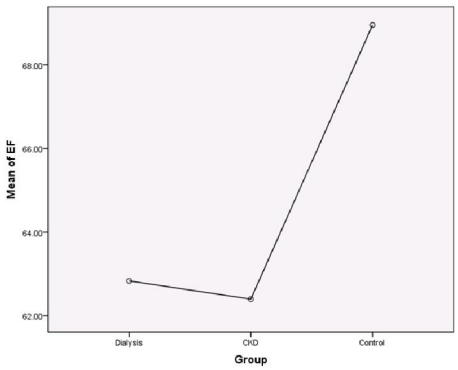
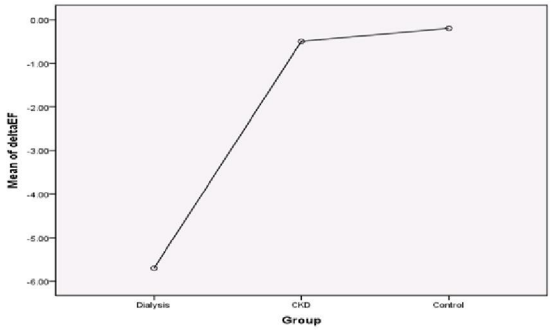
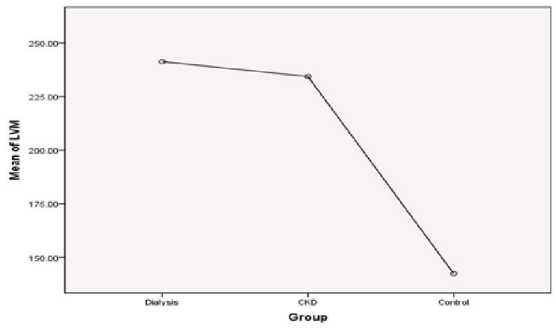
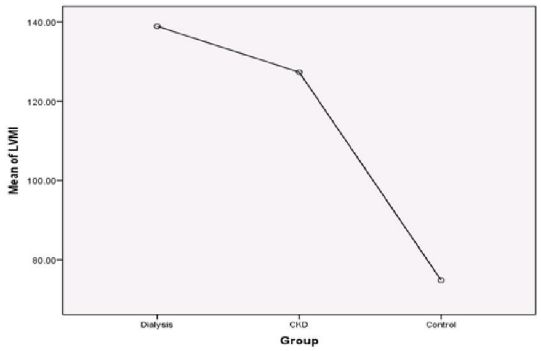
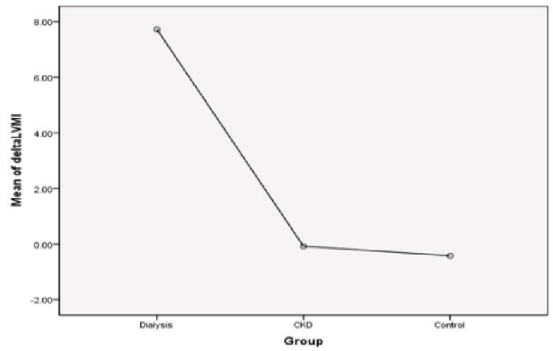


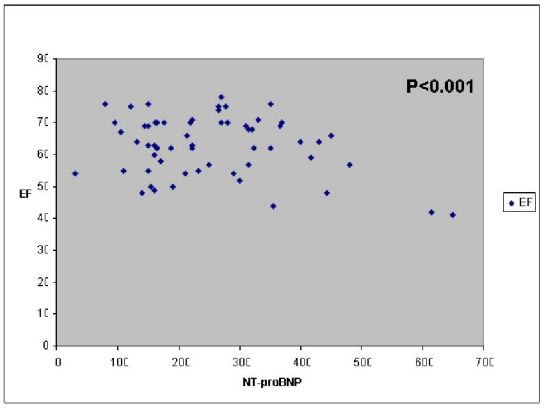
Figure (2): Mean EF between studied groups

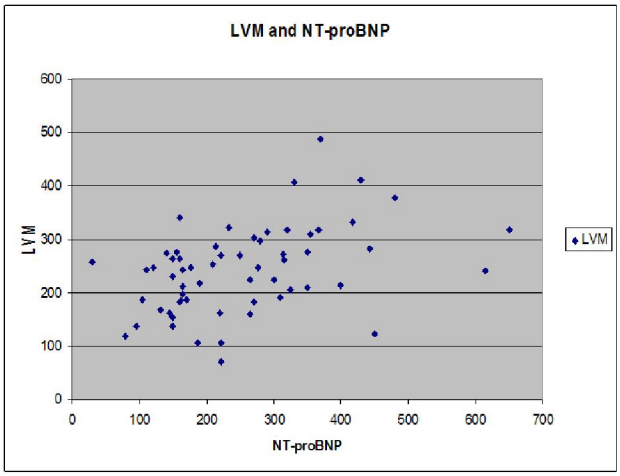












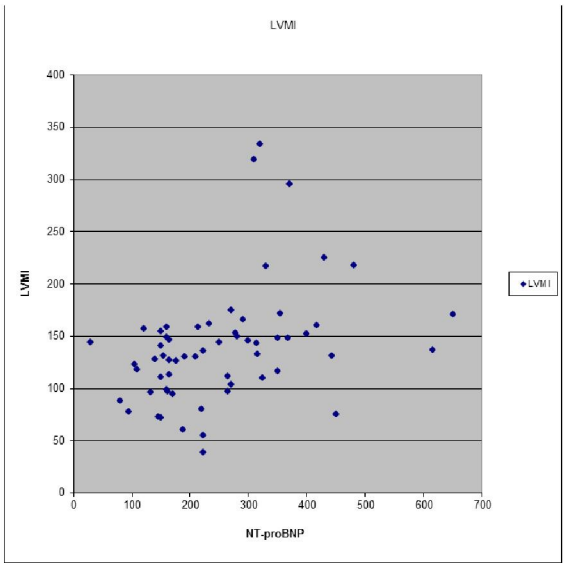


Figure (9): Correlation between NT-proBNP leveland left ventricular mass mass index

4. Discussion:

It is now well established that CKD is associated with markedly increased risk of cardiovascular disease, and the majority of deaths in patients with ESRD are from cardiovascular causes. Left ventricular hypertrophy and left ventricular systolic function are highly prevalent in patients with ESRD and are associated with poor cardiovascular outcomes. Given that cardiac biomarker levels may reflect left ventricular structure and function and predict outcomes, there has been escalating interest in the measurement of such biomarkers in asymptomatic patients with ESRD to stratify cardiovascular risk (9).

In patients with end-stage renal disease, the risk of cardiovascular disease and death is significantly higher than that in the general population, and BNP has been found to be a valuable prognostic indicator of cardiac disease(10).

In our study mean NT-proBNP levels were significantly higher in the dialysis group compared to the CKD and control groups. Also in the same context NT-proBNP levels showed significant inverse correlation with eGFR. This is in agreement with the study by Rosner and Roberts and their colleagues (11,12)., that showed increased NT-proBNP and BNP in ESRD population. These results are also in agreement with the Satyan and his colleagues (9), study that showed significant increase in NT-proBNP in the dialysis population.

One important study(13) was conducted in almost 3,000 patients from the Dallas Heart Study who were between the ages of 30 and 65 years—a relatively young, mostly healthy population. The authors found that natriuretic peptide levels did not vary as long as the estimated glomerular filtration rate was within the normal range. However, when the estimated glomerular filtration rate dropped below a threshold of 90 mL/min/1.73 m^2, the concentrations of both NT-proBNP and BNP increased exponentially. NT-proBNP levels rose more than BNP levels, as NT-proBNP is primarily cleared by the kidney.

More recent studies found that the high levels of NT-proBNP in patients with chronic kidney disease do not simply reflect the reduced clearance of this peptide; they also reflect compromised ventricular function (14,15).This relationship was supported by studies of the fractional renal excretion of NT-proBNP and BNP in several populations with and without renal impairment .Interestingly, fractional excretion of both peptides remained equivalent across a wide spectrum of renal function. Seemingly, cardiac disease drove the increase in values rather than the degree of renal impairment (5) .

Multiple studies showed that high levels of natriuretic peptides are associated with a higher risk of death in patients with acute coronary syndrome, independent of traditional cardiovascular risk factors such as electrocardiographic changes and levels of other biomarkers. However, these data were derived from patients with mild renal impairment(14).

Mean EF in the dialysis patient group in the current study was 63.833% ,60% of the patients had diastolic dysfunction and mean LVM and LVMI were significantly higher in the dialysis group and CKD group compared to the control groups. This is consistent with many other studies(9,16-19)**.**

The present study showed significant strong inverse correlation between NT-proBNP and EF (P<0.001). Also using multivariate regression analysis this relationship remained positive after accounting for other NT-proBNP correlations as systolic blood pressure, Hb, and eGFR. Satyan and his colleagues (9)., in their study on HD patients observed a strong significant inverse correlation between NT-proBNP and EF. Similar results were observed by Anwaruddin and his colleagues (20), were they found in their study on renal function, congestive heart failure and NT-proBNP that increased NT-pro BNP concentrations were strongly associated with left ventricular dysfunction.

The present study showed strong positive correlation between NT-proBNP and delta change in EF over 6 months follow up. None of the studies that observed the role of NT-proBNP in dialysis patients reported on follow up echocardiographic data.

The present study showed strong positive correlation between NT-proBNP and LVM and LVMI. This is in agreement with Madsen and his colleagues (21), who showed in their study on NT-proBNP and prediction of mortality in HD patients that NT-proBNP is strongly correlated to left ventricular hypertrophy.In further agreement Satyan and his colleagues (9), in their study comparing cardiac tropnin and NT-proBNP as predictors of cardiovascular outcomes, revealed that NT-proBNP was strongly related to LVMI.

NT-pro-BNP had a strong predictive value for all-cause and cardiovascular mortality, mortality was higher for those with higher levels of NT-pro-BNP(15,22).NT-pro-BNP level strongly correlates with left ventricular systolic dysfunction in asymptomatic HD patients. Because NT-pro-BNP level consistently correlated with poor left ventricular systolic function(LVSF), it is possible that this biomarker may predict outcomes better than cardiac troponinT level (23).

Apple et al (22) compared the prognostic value of NT-proBNP with that of cardiac troponin T in hemodialysis patients who had no symptoms and found that NT-proBNP was more strongly associated

with left ventricular systolic dysfunction and subsequent cardiovascular death.

The present study also showed strong positive correlation between NT-proBNP and delta change in LVMI over 6 months follow up. None of the studies that observed the role of NT-proBNP in dialysis patients reported on follow up echocardiographic data.

Conclusion

Based on the results of the current study it can be concluded that:

- It is important for patients with ESRD to perform regular echocardiographic assessment of cardiac functions owing to the increased incidence of cardiovascular morbidity especially left ventricular dysfunction and overt heart failure in these patient.

- Plasma NT-proBNP level is markedly elevated in the patients with ESRD on regular hemodialysis especially those with left ventricular dysfunction or hypertrophy.

- Plasma NT-proBNP assessment is an easy non invasive test and should be monitored in hemodialysis patients owing to its close relation to left ventricular mass, systolic dysfunction and cardiovascular morbidity and mortality in these patients.

- Our results may help in planning preventive strategies for heart failure in HD patients.

- Longitudinal (prospective cohort) studies over a longer period of time are needed to follow progress of cardiac function and NT-proBNP levels in response to different therapeutic strategies for treatment of heart failure in hemodialysis patients.

The authors declared that there is no conflict of interest

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