Clinical Utility of B-type Natriuretic Peptides in Patients with Heart Failure and Renal Dysfunction

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Abstract

Background: **Increased plasma level of B-type Natriuretic peptide (BNP) in chronic kidney disease (CKD) and hemodialysis patients with volume overload and heart failure (HF) is common and decreases during dialysis. BNP and N- terminal pro-hormone B-type Natriuretic peptide (NT-proBNP) are established HF markers, but the concomitant presence of CKD changes their interpretation in a significant manner.** ***Aim:*** **to evaluate the effect of compromised kidney function on the level of BNP in Egyptian patients with CKD and ESRD.** ***Patients and Methods:*** **from June 2011 to June 2012, forty-seven patients (17 CKD patients on regular follow up and 30 ESRD patients on regular hemodialysis) were tested for serum BNP and Echocardiography. Normal range of BNP was calculated from 17 apparently healthy individuals (control group).** ***Results:*** **Plasma BNP was significantly higher in both CKD patients and ESRD patients compared to controls (p<0.001). In CKD group, BNP values did not differ between patients with normal diastolic function and those with impaired diastolic function (p= 0.57). However, in ESRD patients, BNP was significantly higher in patients with impaired diastolic function compared to those with normal diastolic function (p=0.018). A positive correlation was found between diastolic dysfunction and BNP levels in CKD patients (r= 0.45; p=0.013). Our study could not prove that the BNP could provide a certain cutoff value to diagnose ventricular function. BNP value for diagnosis of left ventricle systolic dysfunction was set at > 37 pg/ml (p =0.08). While, BNP value for diagnosis of left ventricle diastolic dysfunction was set at >39.1 pg/ml (p= 0.24).** ***Conclusion:*** **BNP can be considered as a diagnostic and prognostic test for diagnosis of HF in CKD and ESRD patients. High plasma level of BNP may indicate the need for further pharmacological treatment for HF.**

Keywords: B-type natriueritg peptide, CKD, ESRD

Introduction

The increased mortality in patients with chronic kidney disease (CKD) is predominantly due to cardiovascular complications[(1)]. Biomarkers of cardiac overload [B-type Natriuretic peptide (BNP), N-terminal pro-B-type Natriuretic peptide (NT-pro BNP)] as well as inflammatory markers [high-sensitivity C-reactive protein (hsCRP)] have shown a prognostic value for all-cause mortality in patients with CKD[(1)]. Cardiovascular disease is the leading cause of death in patients with ESRD[(2)], the most common manifestation of cardiovascular disease in CKD patients is left ventricular hypertrophy (LVH), predominantly as a result of hypertension and anemia. LVH is a powerful independent predictor of cardiovascular disease in CKD patients, however; identifying

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which patients will suffer cardiovascular events is challenging, and requires early identification and treatment. The ability to detect significant cardiovascular dysfunction at an early stage could facilitate more aggressive and focused treatment of those at increased risk[3]. Currently, LVH and LV dysfunction are considered the strongest predictors of cardiovascular mortality in dialysis patients. The synthesis of cardiac Natriuretic peptides is high in the presence of alterations in the LV mass and function. Brain Natriuretic peptide (BNP) is a Natriuretic hormone initially identified in the brain, but released primarily from the heart, particularly the ventricles. Cleavage of the prohormone, pro-BNP produces biologically active 32 amino acid BNP as well as biologically inert 76 amino acid N-terminal pro-BNP (NT-proBNP)[2].

BNP and NT-proBNP are co-secreted in equimolar amounts from the heart in response to left ventricular overload. Diagnostically they are used as a rule-out tests to exclude HF in patients presenting with shortness of breath. The Natriuretic peptides have been shown to predict survival in patients with congestive HF[4]. Elevated concentrations of BNP and NT-proBNP were reported in both ESRD and non-dialysis CKD patients[5]. Cardiac biomarkers have been used in the risk stratification of death for ESRD patients[6]. Natriuretic peptides such as brain Natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are commonly used in the diagnosis and evaluation of HF. However, their utility in patients with CKD is less clear as renal dysfunction itself can be associated with elevated concentrations of these biomarkers. Given the high prevalence of LVH and left ventricular systolic dysfunction in patients with CKD, diagnosis or exclusion of HF becomes important in this population. Most studies to date indicate that the upward adjustment of diagnostic cutoff points preserves the usefulness of both BNP and NT-proBNP in the CKD patient, with similar clinical performance of each biomarker[7]. The measurement of circulating Natriuretic peptides has an established role in the diagnosis and management of patients with HF. Although there is a high prevalence of cardiovascular diseases (CVD), in patients with CKD and ESRD[8], the utility of Natriuretic peptide measurement is unclear in this population. Early identification of CKD patients at risk of premature cardiovascular events has become a major public health issue given the emergence of even mild renal dysfunction as an independent risk factor for cardiovascular events[9]. Much of this risk can be explained by a combination of accelerated atherosclerosis[4], and greater prevalence of LVH with advancing CKD[10]. Circulating levels of Natriuretic peptides (atrial Natriuretic peptide– ANP, brain Natriuretic peptide– BNP) have been associated with structural and functional cardiac abnormalities in patients at different stages of CKD. Increased circulating natriuretic peptide levels have also been associated with left ventricular dilatation and dysfunction (abnormalities frequently described as uremic cardiomyopathy) and shortened survival of patients with ESRD[11]. However, it is difficult to interpret Natriuretic peptide measurements in renal disease because of the relationship between their circulating levels and renal function (due to renal metabolism and excretion). This is a particular issue with natriuretic peptides, which are partially-cleared by the kidney, as well as by the endopeptidase system. Thus, levels are inversely-related to glomerular filtration rate (GFR). Moreover, the effect of increasing prevalence of LVH with increasing severity of CKD may further compromise the diagnostic utility of natriuretic peptides, particularly as a tool for assessment of left ventricular systolic dysfunction (LVSD)[12].

Patient and Methods

The study was conducted at the Clinical Pathology Department in collaboration with the Nephrology and Cardiology units of the Suez Canal university hospital in the period from June 2011 to June 2012. The study included 47 patients (17 CKD patients on regular follow up and 30 ESRD patients on regular hemodialysis). Seventeen apparently healthy individuals with no history or evidence of CKD or cardiovascular disease served as a normal control group. The serum level of the BNP was estimated by enzyme linked immunosorbant assay technique according to manufacturer's instructions *(BNP ELISA kit, Wuhan EIA-ab Science Co., Ltd, China).* Echocardiography to assess left ventricular function (systolic and diastolic function) was done for CKD and ESRD patients as well as for the control group.

Results

CKD patients were significantly older than ESRD patients (p=0.001), while no sex difference between CKD patients and ESRD patients was observed (Table 1). Normal range of BNP was calculated from the mean values of the normal control group (2.69±0.97 pg/ml). Using ANOVA, BNP was significantly higher in both CKD patients and ESRD patients compared to controls, p<0.001 (Table 2). Echocardiography assessment of left ventricle function revealed no difference between CKD and ESRD patients (Table 3). In CKD group, BNP values did not differ between patients with normal diastolic function and those with impaired diastolic function (p= 0.57). However, in ESRD patients, BNP was significantly higher in patients with impaired diastolic function compared to those with normal diastolic function (p=0.018) (Table 4). Diabetes mellitus as a co-morbid condition was significantly higher in CKD patients (p=0.001), while serum creatinine was significantly higher in ESRD patients (p< 0.001). Other co-morbid parameters did not differ between CKD and ESRD patients (Table 5).

Table 1: Demographic characteristics of patient population

Variables	CKD (n=17)	ESRD (n=30)	P Value
Age (years)			
Mean ± SD	57.9 ± 15	38.6 ± 18	0.001*
Range	23–80	12–75	
Gender no. (%)			
Male	8 (47.1)	18 (60)	0.391
Female	9 (52.9)	12 (40)	

Statistically significant at p < 0.05, CKD= chronic kidney disease; ESRD= end stage renal disease.

Using Spearman's correlation, no correlation was found between diastolic dysfunction and BNP levels in ESRD patients (r= 0.12; p= 0. 635). However, a positive correlation was found between diastolic dysfunction and BNP levels in CKD patients (r= 0.45; p=0.013) (Figures 1, 2). ROC curve analysis was performed to determine the best BNP cutoff value for diagnosis of left ventricle dysfunction (systolic and diastolic). Our study could not prove that the BNP could provide a certain cutoff value to diagnose ventricular function. BNP value for diagnosis of left ventricle systolic dysfunction was set at > 37 pg/ml (sensitivity 87.5%, specificity 61.5%, AUC 0.69, p =0.08) (Table 6, Figure 3). While, BNP value for diagnosis of left ventricle diastolic dysfunction was set at >39.1 pg/ml (sensitivity 56%, specificity 77.4%, AUC 0.62 p= 0.24) (Table 6, Figure 4).

Discussion

The measurement of circulating Natriuretic peptides has an established role in the diagnosis and management of HF. Although there is a high prevalence of cardiovascular

disease in patients with CKD and ESRD, the utility of natriuretic peptide measurement is unclear in this population[8]. The BNP is a neuro-hormone peptide, composed of 32 amino acid residues with a relative molecular mass of 3500000 Da. Increased ventricular volume and pressure in response to myocardial ischemia cause BNP to be synthesized and secreted by ventricular myocytes. A number of studies have shown that BNP plays a key role in the pathogenesis and progression of CVD in patients with ESRD.

Table 2: BNP levels among the study population

	Controls (n=17)	CKD group (n=17)	ESRD group (n=30)	*P*-value
BNP (pg/ml)				< 0.001*
Mean ± SD	2.69 ± 0.97	27.6 ± 7.0*	39.0 ± 6.7* ^	
95% CI	2.23 – 3.14	24.0 – 31.2	36.5 – 41.5	
Median	2.55	28	39.2	
Range	1.4 – 4.7	17 – 41	26.9 – 50.1	

ANOVA test; Statistically significant at p < 0.05, *=Statistically Significant compared to control group, ^= Statistically Significant compared to CKD group, CI= confidence interval

Table 3: Echocardiography assessment of left ventricle function in both groups

LV parameters	CKD group (*n*=17)	ESRD group (*n*=30)	*P*-value
Ejection fraction (%)			0.23
Mean ± SD	60.3 ± 7.8	56.8 ± 10.6	
Range (53-77)	40 – 77	25 – 74	
ESD			0.36
Mean ± SD	41.3 ± 9.5	38.8 ± 8.9	
Range (22-40)	23 – 56	26 – 56	
EDD			0.01
Mean ± SD	43.6 ± 6.7	49.4 ± 7.5	
Range (38-57)	34 – 55	34 – 66	
Fractional shortening			0.26
Mean ± SD	36.7 ± 9.7	33.5 ± 8.9	
Range (27-46)	28 – 63	13 – 59	
PW thickness			0.94
Mean ± SD	9.76 ± 1.25	9.8 ± 2.0	
Range (7-11)	8 – 12	6 – 14	
Diastolic function No. (%)			0.53[a]
Normal	10 (58.8)	21 (70.0)	
Grade I	5 (29.4)	5 (16.6)	
Grade II	2 (11.8)	2 (6.7)	
Grade III	0	2 (6.7)	

Statistically significant at p < 0.05; a=Fisher's exact test; ESD=End systolic diameter, EDD= End diastolic diameter, PW thickness= Posterior wall thickness.

Previous studies have demonstrated that elevated concentrations of BNP in patients undergoing dialysis were closely related to LVMI and cardiac dysfunction[11]. Others have found an association between BNP levels and atherosclerosis in hemodialysis patients[12]. Additionally, BNP was suggested to affect the degree of left ventricular hypertrophy in patients with ESRD, indicating that it may play a role in initiating the processes that cause abnormal cardiac structure and function[13,14]. Despite these previous findings the role of BNP in the pathogenesis and progression of CVD in patients with CKD not requiring dialysis remains poorly studied.

Table 4: BNP & diastolic function in both groups

	Diastolic function		*P*-value
	Normal	Impaired	
CKD patients, no. (%)	10 (58.8%)	7 (41.2%)	0.57
BNP (pg/ml)	26.8 ± 6.5	28.8 ± 8.03	
ESRD patients, no. (%)	21 (70.0%)	9 (30.0%)	0.018*
BNP (pg/ml)	37.1 ± 5.8	43.3 ± 7.0	

Statistically significant at $p < 0.05$

Our results showed that BNP was significantly higher in both CKD patients and ESRD patients compared to controls, Also, it was significantly higher in ESRD patients compared to CKD patients. Several investigators indicated that elevated BNP and NT pro-BNP concentrations can result from renal failure[15-17]. Our results agreed with previous studies which confirmed that concentrations were higher in patients with progressively more advanced CKD stage III[18]. Li Xin et al [19] also found that the BNP was higher in CKD patients than in the control group and its level increased progressively in parallel with the decline in GFR. BNP levels were significantly higher in the early, middle and late phase CKD groups than in the control groups[19]. In agreement with our study, Spanaus and coworkers[20] showed that BNP and Nt-ProBNP were significantly higher among patients with progressive kidney disease and concluded that both BNP and NT-pro BNP plasma concentrations indicate increased risk for accelerated progression of CKD to ESRD. In our study, left ventricle diastolic function was not affected by kidney function, this may be due to small sample size and the concomitant ventricular dilation due to volume overload.

Table 5: The co-morbidities between two groups

	CKD group (*n*=17)	ESRD group (*n*=30)	*P*-value
Diabetes Mellitus, no. (%)	9 (52.9)	2 (6.7)	0.001[a]
Arterial Hypertension, no. (%)	14 (82.4)	18 (60)	0.11
Hemoglobin (g/dl)	9.52 ± 1.95	9.71 ± 1.74	0.73
Hematocrit (%)	29.31 ± 6.73	29.95 ± 5.72	0.73
Serum Calcium (mg/dl)	8.71 ± 1.33	8.56 ± 1.16	0.69
Serum Creatinine (mg/dl)	4.57 ± 2.23	9.02 ± 2.24	< 0.001

Data are presented as Mean ± SD; [a] =Mann-Whitney test; statistically significant at $p < 0.05$

In CKD group, BNP values did not differ between patients with normal diastolic function and those with impaired diastolic function, however, in ESRD patients, BNP was significantly higher in patients with impaired diastolic function compared to those with normal diastolic function. Accordingly, Lang et al[21] found substantially raised levels of BNP and ANP in patients with isolated diastolic dysfunction in the absence of systolic failure or of significant LV hypertrophy. This indicates that the BNP can be better used for diagnosis of diastolic dysfunction. A positive correlation was found between diastolic dysfunction and BNP levels in CKD patients, however, we could not prove that the BNP can provide a certain cutoff value to diagnose ventricular function. According to our study, the best cutoff value of BNP for diagnosis of left ventricle systolic dysfunction was > 37 pg /ml however, a lower BNP cutoff value (>17.9 pg/ml) was reported by others[2]. The inconsistency between our results and theirs may be due to the difference in the studied population. The best cutoff value of BNP for diagnosis of left ventricle diastolic dysfunction was > 39.1 pg /ml, accordingly Karaca et al [22] showed that BNP was significantly higher in patients with proven diastolic dysfunction at a cutoff value of 37.0 pg/ml.

Table 6: Cut off values of BNP for diagnosis of Left ventricular dysfunction (N=47)

	Left Ventricular Dysfunction			
	Systolic [g] (BNP > 37.0)		Diastolic [h] (BNP > 39.1)	
	Estimate	95% CI	Estimate	95% CI
Sensitivity	87.5	37.3 – 99.7	56.2	29.9 – 80.2
Specificity	61.5	44.6 – 76.6	77.4	58.9 – 90.4
Positive predictive value	31.8	13.5 – 55.5	56.2	29.9 – 80.2
Negative predictive value	96.0	79.6 – 99.9	77.4	58.5 – 90.6

[g]=Based on EF (<53%) Echocardiograms were read by a sonographer or cardiologist experienced in echocardiography and blinded to clinical information. LVEF was estimated based on the visual assessment of LV contractile performance and wall motion in multiple 2-dimensional views. Subjects were classified as having a normal LV systolic function (EF >53%), mild systolic dysfunction (EF 40% to 53%), or moderate-to-severe systolic dysfunction (EF <40%). [h]=Based on diastolic function; Under normal conditions, most of the blood will fill the ventricle during early diastole (passive filling). Diastolic dysfunction ranges from grade 1 to grade 3.

Previous studies have confirmed the importance of BNP as a marker of HF in Kidney disease patients. A cohort study on 3916 patients with HF suggested that BNP and NT-pro BNP were independent markers correlating strongly with the outcomes of CHF including: mortality, morbidity and hospitalization[23]. In another study on 213 subjects, it was demonstrated that as renal function declined, BNP levels increased, especially among the subset of patients with ventricular hypertrophy[24]. Similarly, another group of researchers found that among 389 patients with and without decompensated HF, those with GFR greater >60 ml/min/1.73m^2 had lower BNP levels than patients whose GFR was <60 L/min/ 1.73m^2[25]. When assessing BNP levels in dialysis patients, it was noted its levels were predictive of the presence of LVD, cardiac events and survival in the presence of end stage renal disease, concluding that BNP levels may provide information regarding the overall status of renal function[26] A more comprehensive study was conducted, in which patients

Were recruited to cover a variety range of renal function, including patients on hemodialysis, and patients with functional renal allograft. Patients were evaluated by echocardiography for cardiac hypertrophy, dilatation, systolic and/or diastolic dysfunction[27]. The study concluded that GFR superseded ventricular function as the most important determinant of serum BNP levels. It was also reported that hypo-albuminemia, anemia, use of beta blockers and age were significant confounders of serum BNP levels as has also been reported in earlier studies[28, 29]

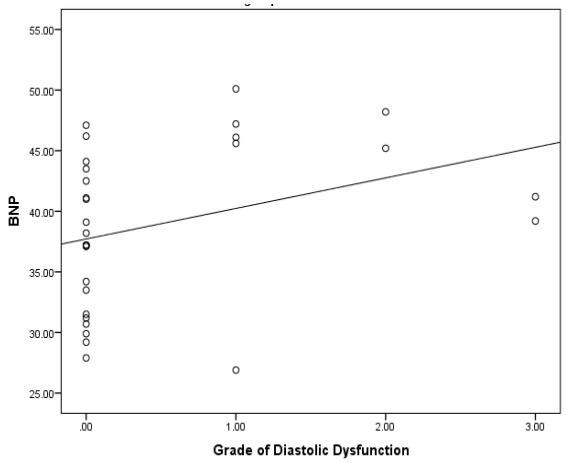

Figure 1: Spearman's rank correlation between BNP levels and diastolic dysfunction in ESRD group (r= 0.12; p= 0.635).

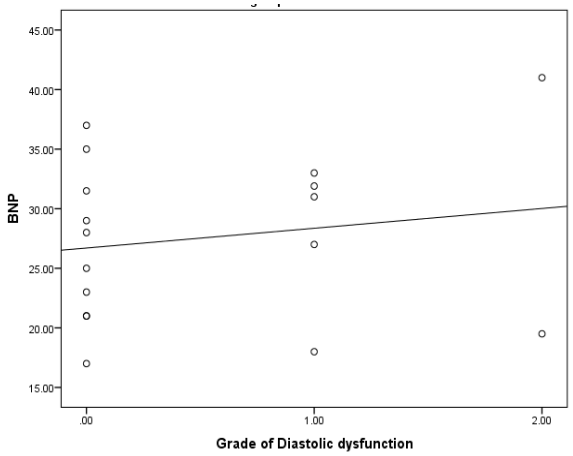

Figure 2: Spearman's rank correlation between BNP levels and diastolic dysfunction in CKD group (r= 0.45; p= 0.013).

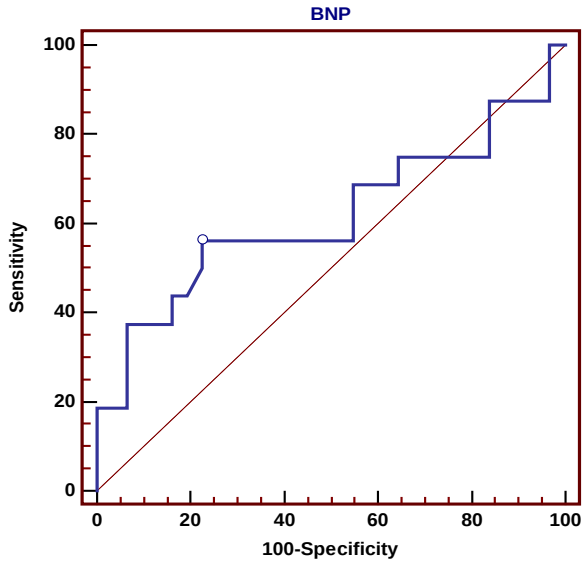

Figure 3: ROC curve of BNP's cutoff values for diagnosis of Systolic dysfunction; Area under the curve "AUC" =0.69 (p = 0.08).

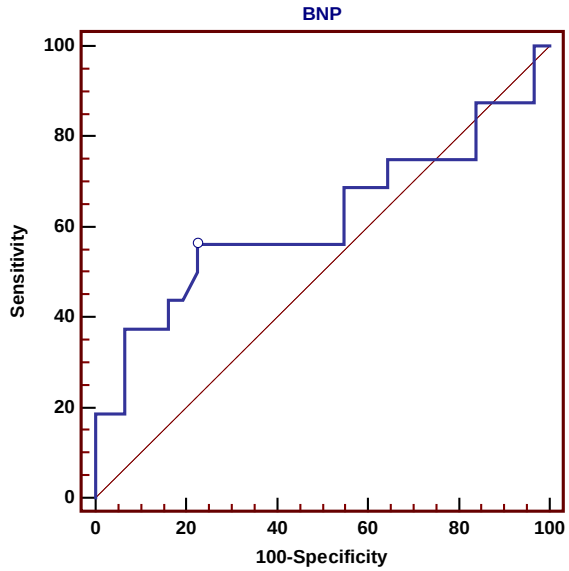

Figure 4: ROC curve of BNP's cutoff values for diagnosis of diastolic dysfunction; Area under the curve "AUC" = 0.62 (p = 0.244).

Conclusion

BNP can be considered as a diagnostic and prognostic test for diagnosing HF in CKD and ESRD patients, especially those with diastolic dysfunction, and in diagnosing impaired left ventricular function in HD

patients. Further studies are needed to confirm the outcome on larger cohorts and to validate cutoff values of-BNP in CKD with HF.

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