



Plasma N-terminal pro-brain natriuretic peptide level as a marker of adverse outcome in patients with co-existing diabetes, chronic kidney disease and heart failure

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ABSTRACT

Introduction: N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a novel marker of cardiac disease and heart failure; both are in patients with diabetes and chronic kidney disease.

Objectives: This study aimed to investigate the NT-proBNP and adverse outcome in patients with diabetes complicated by chronic kidney disease (CKD).

Patients and Methods: We measured the serum levels of NT-proBNP. The association of this novel marker with re-hospitalization and mortality rate were prospectively compared among the studied groups.

Results: Among 120 patients, baseline NT-proBNP at the time of admission was significantly elevated in patients with CKD ($P = 0.001$). Levels of NT-proBNP were significantly elevated in patients with diabetes and CKD than those with CKD alone ($P = 0.04$) at the end of follow-up. Higher proBNP levels significantly correlated with decreased glomerular filtration rate (GFR) and higher serum creatinine levels ($P = 0.03$, $P < 0.001$, respectively). In addition, increased mortality was noticed in those patients.

Conclusion: NT-proBNP levels have prognostic implication in the setting of CKD, diabetes mellitus and heart failure. Adverse outcomes are; a higher rate of need for dialysis, re-hospitalization and increased mortality which are correlated with levels of NT-proBNP.

Implication for health policy/practice/research/medical education:

Measuring N-terminal pro-B-type natriuretic peptide (NT-proBNP) level in patients with coexisting chronic kidney disease, diabetes and heart failure may predict the risk of adverse outcomes consisting, the need for dialysis, re-hospitalization and mortality.

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Introduction

Type 2 diabetes (T2DM) and chronic kidney disease (CKD) are increasing in prevalence worldwide (1). Both diseases lead to aggravated cardiovascular morbidity and mortality, which is considered as the most frequent cause of death in patients with diabetes or CKD (2).

B-type natriuretic peptide (BNP) is significantly correlated with all-cause mortality in patients with congestive heart failure or acute coronary syndromes (3). N-terminal pro-B-type natriuretic peptide (NT-proBNP) is the biologically inert, amino terminal pro-peptide counterpart. It has a

longer half-life, and therefore, its levels may be more stable than BNP levels. Its concentration varies according to age, gender, body mass index which is an obvious limitation to its use in the clinical context (4).

Multiple trials have reported that type 2 diabetes and impaired kidney function augment the levels of proBNP, but the optimal cut-off values were not well-known (5,6).

Objectives

This study aims to evaluate the level of NT-proBNP level and its association with echocardiographic findings,

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re-hospitalization and death in the setting of common clinical scenario of coexisting CKD and heart failure.

Patients and Methods

Study population

This study is a prospective observational study that was conducted in the emergency department of two large teaching hospitals during the period from November 2016 to April 2017.

One hundred and twenty adult patients who were diagnosed with heart failure were included in the study. CKD was defined based on an estimated glomerular filtration rate (eGFR) of ≤ 60 mL/min. The Modification of Diet in Renal Disease (MDRD) equation was used to estimate the GFR of the study subjects.

CKD stages

According to the Kidney Disease Improving Global Outcomes (KDIGO) guideline, CKD was classified into 5 stages. All patients were subjected to the following assessments;

A complete medical history and clinical examination including thorough cardiac examination was performed.

NT-proBNP level, serum creatinine, and transthoracic echocardiography were tested at the time of recruitment and after 6 months.

Additionally, serum potassium, C-reactive protein (CRP), serum troponin and HbA1c (for diabetic individuals) were measured in patients at baseline. Re-hospitalization, need for dialysis and mortality were recorded for every patient. The planned follow-up period was 6 months.

Inclusion criteria

Patients with DM or CKD (GFR < 60 mL/min) who have been admitted to the intensive care unit (ICU) at both hospitals from November 2016 to April 2017 with clinical presentation of congestive heart failure were eligible for study entry.

Exclusion criteria

We excluded patients who underwent cardiopulmonary resuscitation, pregnant females, patients on hormonal therapy or contraceptives, and patients with acute coronary syndrome, poor echocardiography image quality, atrial fibrillation, or valvular heart disease.

Echocardiographic study

Transthoracic echocardiography was done to estimate left ventricular ejection fraction (EF) and left cardiac chambers dimensions and volumes.

Determination of NT-proBNP

Anticoagulant-free venous blood samples have been assayed for NT-proBNP using a commercial enzyme-

linked immunosorbent assay (ELISA) kit, employing an anti-serum specific to the amino terminal (Biomedica Gruppe, Germany).

Ethical issues

The research adhered to fundamentals of Declaration of Helsinki. The Ethical and Research Committee of the National Research Centre approved the protocol for this study, approval number NRC-REC-1214. The study has been conducted in Zagazig University hospitals and Cairo University hospitals. All participants agreed to take part in the study and signed a declaration of informed consent.

Statistical analysis

For comparisons between groups, normally distributed data were analysed using independent *t* test. Non-normally distributed were analysed using the Mann-Whitney U test. To compare continuous variables between > 2 groups, we used one-way ANOVA or the Kruskal-Wallis equality-of-populations rank test according to the data distribution. Spearman's correlation analysis was performed to explore variables with a significant correlation with proBNP. A model to predict hospitalization or mortality was created using logistic regression analysis. STATA software version 13.1 was used.

Results

Study population

The baseline characteristics were generally comparable between the studied groups with regard to age and gender (most of the study participants were male). Most patients had left ventricular hypertrophy (LVH) and a comparable EF and CRP level, but all of these results were statistically not significant (Table 1).

When analysing the results, patients were classified into three groups;

- Group 1: patients with diabetes mellitus and no CKD
- Group 2: patients with both diabetes and CKD
- Group 3: patients with CKD, no diabetes

Hypertension (HTN) was more prevalent, and severe heart failure was only encountered in patients with both DM and CKD with heart failure. Diabetic patients with normal kidney function had significantly lower serum potassium and serum uric acid levels than patients with CKD, but serum uric acid potassium and were statistically non-significant between groups 2 and 3 (Table 1).

Baseline NT-proBNP and troponin levels

At the time of ICU admission, baseline NT-proBNP and troponin levels were elevated in patients with CKD as compared to patients with diabetes alone. This finding was statistically significant regarding proBNP ($P=0.0001$). However, when we compared groups 2 and 3 (both had CKD, the mean value of either markers was statistically not significant across both groups) (Table 2).

Table 1. Baseline data of subgroups

	DM with normal kidney function (n=59)	DM with CKD (n=43)	CKD without DM (n=18)	P value
Age, years, mean (SD)	58.98 (10.67)	62.25 (12.64)	60.5 (14.25)	0.2
Male/Female	37/22	27/16	13/5	0.7
Hypertension	53	39	15	0.6
NYHA class, II/III/IV at admission	41/18/0	24/18/1	11/7/0	0.5
LVH at admission	54	35	16	0.3
Serum K, mEq/L, median (IQR)	4 (3.8-4.1)	4.98 (4-5.6)	4.85 (4-5.2)	0.001
CRP, mg/L, median (IQR)	6.8 (3.2-15)	5 (2.3-10)	5.05 (3.1-8)	0.2
Uric acid, mg/dL, median (IQR)	5.68 (4.9-6.32)	7.2 (6.6- 8.1)	7.3 (6.3-9)	0.001
HBA1C %, median (IQR)	7.58 (6.9-8.47)	8 (7-8.9)	5.45 (5.3-5.6)	0.001
GFR, mL/min, median (IQR)	102 (92-114)	42 (23-60)	51.5 (48-56)	0.001
EF% at admission, median (IQR)	45 (35-50)	45 (40-50)	45 (35-53)	0.8
Re-hospitalization	7 (9.8%)	6 (17 %)	2 (11.1%)	0.03
Death	0	2	1	0.2

Table 2. Cardiac biomarkers at time of ICU admission and after 6 months

	DM without CKD (n=59)	DM with CKD (n=43)	CKD without DM (n=18)	P value
Baseline NT-proBNP at ICU admission, pg/mL, Median (IQR)	729 (196-1877)	3078 (1279-4232)	3786 (1845-5216)	0.0001
Troponin at ICU admission, ng/mL, Median (IQR)	0.07 (0.01-0.19)	0.2 (0.01-0.41)	0.20 (0.03-0.46)	0.1
Follow-up pro BNP after 6 months, pg/mL Median (IQR)	878 (300-3400)	729 (254-3719)	355 (128-742)	0.07

NT-proBNP levels after six months of follow-up in the studied groups

CKD patients with diabetes had significantly higher levels of proBNP than patients with CKD alone after six months of follow-up, as shown in Table 2.

Changes in NT-proBNP from recruitment till completion of follow-up period

ProBNP levels were significantly increased from baseline to the end of the follow-up period in DM patients with normal kidney function (group 1; $P \leq 0.001$). However, in patients with CKD (group 2 and group 3), NT-proBNP levels were significantly decreased at the end of follow-up ($P=0.02$ and $P=0.002$, respectively). In group 2 (DM with CKD), six patients required hemodialysis. They had very high initial levels of NT-proBNP, which tended to decrease at the end of follow-up, however this finding was statistically non-significant as shown in Table 3 ($P > 0.05$).

Levels of NT-proBNP and its relation to EF% and left ventricular diastolic dysfunction grade

The levels of NT-proBNP were significantly higher in

patients with a left ventricular EF% less than 50% (HF with reduced ejection fraction; HFREF) than in patients with a left ventricular EF% more than 50% (HF with preserved ejection fraction; HFPEF) at both baseline and after follow-up. In addition, NT-proBNP levels were significantly correlated with the grade of left ventricular diastolic dysfunction (LVDD). ProBNP levels were significantly elevated in patients with severe diastolic dysfunction than in those with milder grades (Table 4).

Factors associated with higher NT-proBNP levels

Higher NT-proBNP levels were affected by gender, older age at enrolment, the presence of HTN, lower GFR, LVDD grade, increasing NYHA (New York Heart Association) stage, and higher serum troponin and creatinine levels (Table 5).

Re-hospitalization

Re-hospitalization was encountered more in group 2 (17%) in comparison to 9.8% and 11.1% in groups 1 and 3, respectively (Table 1). Among several factors included in the study, baseline proBNP predicts re-hospitalization.

Table 3. The change in pro BNP level in all groups during the study

	Baseline proBNP	Follow-up proBNP	P value
DM with normal kidney function (n=59), Median (IQR)	729 (196-1877)	878 (300-3400)	<0.001
DM with CKD (n=43)	3078 (1279-4232)	729 (254-3719)	0.02
CKD with no DM (n=18)	3786 (1845- 5216)	355 (128-742)	0.002
CRF on dialysis (n=6)	5381.5 (3458-6782)	2704.5(214-6100)	0.3

Table 4. NT pro BNP level in relation to EF% and LVDD grades

	EF <50% (n=67)	EF ≥50% (n=53)	P value
Baseline pro BNP, Median (IQR)	1707.5 (653- 4107)	900 (133- 3078)	0.02
Follow-up pro BNP, Median (IQR)	912 (448.5-3656)	300 (101- 961)	<0.001
	Mild LVDD grades 1 and 2, (n=53)	Severe LVDD grades 3 and 4, (n=67)	
Baseline pro BNP, Median (IQR)	850 (176-3267)	2099.5 (729-4200)	0.005
Follow-up pro BNP, Median (IQR)	374 (101-1000)	1071.5 (400-3719)	0.001

Increasing NYHA class, EF, and the follow-up serum creatinine level had a significant ability to predict re-hospitalization (Table 6).

Mortality

Increased mortality was noticed in patients in group 2 (both DM and CKD) followed by group 3 (CKD only), but this result was statistically not significant as seen in Table 1. Baseline NT-proBNP was a determinant of mortality. The stage of NYHA classification and EF% were significant predictors of mortality in our study ($P < 0.05$) (Table 7).

Discussion

Both DM and CKD are increasingly recognized as serious, worldwide public health concerns, since there is a strong correlation of diabetes and CKD with cardiovascular disease (CVD) (6,7). NT-proBNP has been linked to both type 2 DM and renal disease patients, while NT-proBNP was a useful prognostic marker, in addition to BNP and troponin T for short-term follow-up (<3 years) of CKD patients with cardiac disease (8,9).

Among our patients, HTN was more prevalent in diabetic patients who developed CKD (group 2). HTN in patients with diabetes or CKD was found to accelerate vascular complications in this population and to predispose individuals to cardiac diseases (10-12).

Among our patients, baseline NT-proBNP was elevated in patients who have CKD (group 2 and group 3) than

in those without CKD. Left ventricular (LV) functional or structural abnormalities result in elevated levels NT-proBNP in patients with CKD (13). This finding is in agreement with a study by Hickman et al, which demonstrating increased prevalence of heart failure with declining eGFR (14). The rise in NT-proBNP levels is proportional to kidney function deterioration (15). However, cut-off values for elevated NT-proBNP patients with CKD are not completely known (2).

NT-proBNP levels were significantly elevated from baseline to the completion of the follow-up in DM patients with normal kidney function, while in patients with CKD (group 2 and group 3), proBNP levels were significantly decreased after six months of follow-up. However, group 2 still had a significantly higher proBNP level than group 3.

One explanation is possibly along with progression of diabetes, the diabetic group might develop silent ischemia

Table 6. Logistic regression for predictors of hospitalization

	OR (95% CI)	P value
Age	1.98 (0.94-1.02)	0.3
Gender		
Female	0.98 (0.32-3.01)	0.9
Male	1	
DM	1.77 (0.48-6.59)	0.4
HF	6.38 (0.81-50.1)	0.08
Increasing NYHA class	2.49 (1.01-6.16)	0.047
EF%	1.95 (0.91-0.99)	0.02
Baseline NT-proBNP	1.7 (0.99-2.6)	0.04
Serum troponin	0.98 (0.85-1.13)	0.8
Serum creatinine	1.19 (0.97-1.46)	0.09
Follow-up creatinine	1.29 (1.04-1.62)	0.02

Table 5. Association of selected clinical and echocardiographic variables with NT-proBNP

	Rho	P value
Age at enrolment	0.39	<0.001
Female sex	0.20	0.02
Hypertension	0.21	0.01
DM	0.02	0.8
GFR	-0.21	0.03
EF	-0.15	0.07
LVDD grade	0.24	0.004
LV hypertrophy	0.09	0.3
NYHA	0.27	0.001
Serum troponin	0.51	<0.001
Serum creatinine	0.48	<0.001

Table 7. Logistic regression for predictors of mortality

	OR (95% CI)	P value
Age	0.99 (0.91-1.09)	0.9
DM	1.79 (1.1-8.94)	0.8
NYHA	17.90 (1.98-162.14)	0.01
EF %	1.85 (0.75-2.97)	0.01
Baseline NT-proBNP	1.3 (0.99-1.0004)	0.03
GFR	0.97 (0.91-1.03)	0.3
Serum creatinine	1.17 (0.74-1.83)	0.5
F/U NT-proBNP	1.4 (0.99-2.21)	0.04
Re-hospitalization	17.57 (1.49-206.4)	0.02

or some degree of left ventricular diastolic dysfunction. This development could explain the increase in proBNP levels at the end of the follow-up period in comparison to patients in groups 2 and 3 who usually show symptoms earlier and may have started anti-failure treatment at an earlier stage, reflected by the improvement of proBNP levels at the end of the follow-up period. Participants in the CKD groups were also given increasing doses of diuretics compared to patients in group 1. Diuretics decrease the secretion of proBNP peptide from ventricular myocardial wall, through releasing stress off the ventricular walls. In addition, in diabetic patients who develop CKD, hyperglycemia spontaneously improves over time even without hypoglycemic medications by the effect of decreased insulin clearance with GFR reduction. Moreover, according to a literature review, diabetes mellitus was found to contribute independently to high plasma NT-proBNP levels (16).

In diabetes complicated with CKD, which necessitates dialysis, the proBNP levels increase substantially. Furthermore, their proBNP level tended to decrease by the end of the follow-up. Dialysis therapy decreases the levels of NT-proBNP probably due increased clearance and achieving better volume control (17). A large study demonstrated that NT-proBNP levels obtained before dialysis could predict mortality in patients receiving haemodialysis (HD) (18). A higher proBNP level was significantly related to a lower GFR and higher serum creatinine level but not to diabetes in our study. It was also significantly related to female gender, older age at enrolment, the presence of HTN, lower EF percentage, LVDD grade, NYHA stage, and troponin level. Studies have shown an inverse moderate, but significant correlation between eGFR and NT-proBNP concentrations (19).

Numerous studies reported a correlation between NT-proBNP values and cardiac failure severity as assessed by various parameters. These studies also found that age, body mass index (BMI), and eGFR were significant predictors of log NT-proBNP. The log NT-proBNP showed an inverse correlation with EF (15).

Mortality was higher in patients with DM complicated with CKD in our study. Moreover, among several factors included in the study, the baseline proBNP level did not show a strong ability to predict re-hospitalization or mortality. Only increasing NYHA class, percent of EF and follow-up serum creatinine levels were able to significantly predict re-hospitalization.

Additionally, the class of NYHA, percent of EF and re-hospitalization were significantly predictors of mortality in our study ($P < 0.05$).

The combination of percentage reduction in NT-proBNP and the absolute values have been shown to predict outcome in hospitalised patients who have been admitted with decompensated congestive cardiac failure (20). Therefore, NT-proBNP may be a better marker in

predicting death than BNP. This may be due to the longer half-life of NT-proBNP and its status as a more accurate index of LV hypertrophy (21).

The study has some limitations. The small size of this study should be borne in mind, and different numbers of patients were included in each group. Future studies on the current topic with more properly matched groups might be necessary.

Conclusion

This study showed that co-occurrence of CKD with diabetes in patients with heart failure and a high initial proBNP level is associated with a higher risk of worsening heart failure, higher rates of complications such as the need for dialysis, re-hospitalization and higher mortality.

Limitations of the study

This study is limited by the small participants' number. Validation of the findings will require a larger number of recruits.

Authors' contribution

ARS and AS equally contributed to the study design. TA, RA contributed to data collection. RMA and AY were involved in collecting data. RA and TA analyzed data All authors discussed the results and contributed to the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, double publication) have been completely observed by the authors. This article does not contain any studies with animals performed by any of the authors.

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