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Significance of Combined Use of Natriuretic Peptides and Neutrophil Gelatinase-associated Lipocalin for Diagnosis of Renal Failure and Type 2 Diabetes Mellitus

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Abstract

Background Both natriuretic peptides, NPs (BNP and CNP), and neutrophil gelatinase-associated lipocalin (NGAL) were reported to rise in chronic kidney disease (CKD) and type2 diabetes mellitus (T2DM). Their role in detecting and follow up of these two diseases has been well elucidated.

Objective To evaluate the use of a combination of NPs and NGAL in detecting renal insufficiency (per se) or early diabetic nephropathy.

Method The study included 40 patients with CKD (mean age 50.63±9.25 years), 41 patients with T2DM (mean age 53.66±8.32 years) and 38 apparently healthy normal subjects (mean age 52.42±8.81 years) as controls. Natriuretic peptides, and NGAL were measured by enzyme linked immunosorbent assay (ELISA), and glycated hemoglobin (HbA1c) by fully automated boronate affinity assay. Renal function tests, glucose, and electrolytes were estimated by routine laboratory methods.

Result There was an increase in NGAL, N-terminal pro-C-type natriuretic peptide (NT-proCNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) in both groups of patients. The HbA1c was high in the T2DM group only. Receiver operating characteristic (ROC) curve revealed good sensitivity and specificity when using NGAL and NT-proBNP to discriminate between CKD and T2DM or between CKD and controls, or T2DM and controls.

Conclusion Combined use of NGAL and NT-proBNP in T2DM may be a better diagnostic marker for an early deterioration in renal function of diabetes mellitus than the HbA1c level alone.

Keywords Natriuretic peptides, neutrophil gelatinase-associated lipocalin, glycated hemoglobin, renal failure, diabetes mellitus

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List of abbreviations: CKD = Chronic kidney disease, CNP = C-type natriuretic peptide, HbA1c = Glycated hemoglobin, NGAL = Neutrophil gelatinase-associated lipocalin, NP = Natriuretic peptides, NPCR = Natriuretic peptides clearing receptors, NT-proBNP = N-terminal pro-B-type natriuretic peptide, NT-proCNP = N-terminal pro-C-type natriuretic peptide, T2DM = Type 2 diabetes mellitus

Introduction

Diabetes mellitus (DM) has been considered the most common metabolic disorder in the world and one of the

leading causes of death [1]. Type 2 diabetes mellitus (T2DM) was found to associate, independently, increased risk of hospitalization for heart failure (HF), HF-related complications, and death of cardiovascular disease [2,3].

Recent articles stress the role of natriuretic peptides (NPs) in DM and related disorders [4]. An inverse relationship was found between BNP, or N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and body mass index (BMI). [5] The expression of NPs clearing receptors (NPRC) in adipose tissue of obese subjects was found to be upregulated by insulin [6]. Other data suggested a role for NPs in blood glucose control and insulin sensitivity by increasing glucose uptake in human adipocytes [7]. Furthermore, NPs were believed to be markers for early diagnosis, risk assessment, and intervention requirement in diabetes and its complications, and may, thus, improve diabetes care [8].

The presence of diabetes is a cause of increased risk of developing heart failure, and about 75% of patients with unexplained idiopathic dilated cardiomyopathy were found to be diabetics [9]. The diabetic ischemic heart injury which is, partly, caused by mitochondrial dysfunction is affected by many variables as renin-angiotensin, cardiac autonomic neuropathy, free radicals and calcium homeostasis [10], Furthermore, the role of NPs in heart failure and other CVD has been thoroughly studied [11,12].

Renal diseases are among the consequences of T2DM, which were, also, reported to show increased levels of NPs [13,14]. The N-terminal pro-C-type natriuretic peptide (NT-proCNP) could be protective to the renal system by acting as anti-inflammatory, antifibrotic, and vasodilator agent [15]. The baseline of BNP was considered by some authors to be an independent predictor of the annual rate of decline in estimated glomerular filtration(eGFR), and recommended monitoring of BNP as a factor that can play an important role in management of diabetic nephropathy [16].

The neutrophil gelatinase-associated lipocalin (NGAL) is a routinely used as a marker of acute kidney injury, [17] and has been reported to associate a rise in NPs. It was also found to correlate with the glycated hemoglobin (HbA1c), the marker for metabolic control in diabetes mellitus [18].

The aim of the present study was to test the importance of combined use of plasma NPs and NGAL, in the diagnosis and follow up of CKD and T2DM.

Methods

A total of 119 participants with age range between 33 years to 72 years were distributed among 3 groups: Forty patients with CKD (approved by clinical examination and laboratory outcome) comprising of 26 males and 14 females. The duration of the disease ranged from 1.5-3 years. None of them had been on dialysis. Forty-one with T2DM by clinical and laboratory diagnosis, consisting of 23 males and 18 females. Duration of the disease ranges from 4 months to 1.5 years. Thirty-eight apparently healthy people served as controls (17 males and 21 females.

Demographic characteristics including age and sex, weight and height were recorded for all participants.

Five milliliters of venous blood samples were collected from each patient and control subject, after an overnight fast, for measurement of NT-proBNP, NT-proCNP, NGAL and HbA1c by enzyme linked immunosorbent assay (ELISA) technique, All Kits were purchased from Sun long Biotech, China. Other tests involving urea, creatinine and electrolytes (Na^+, K^+, and Ca^{2+}) were done on all patients and controls by common routine laboratory tests.

Statistical Analysis

Statistical analyses were performed by using statistical package for social sciences (SPSS) software version 25.0 (SPSS, Chicago). Continuous data were presented as mean± standard deviation (SD), and analyzed with analysis of variance (ANOVA) with least

significant difference (LSD) as post hoc analysis. Categorical variables were expressed as number and percentage and analyzed with Chi-square test. Pearson's correlation was used to examine the correlation between NGAL, NT-proCNP, and NT-proBNP with other variables. Receiver operating characteristic curve (ROC) was used to evaluate the efficiency of NGAL, TN-pro CNP and TN-pro BNP in the context of discrimination between RF, T2DM and healthy controls. A p value less than 0.05 was considered to indicate a statistically significant difference.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by the Institutional Review Board, College of Medicine, Al-Nahrain University (document number 150 on April, 14. 2021).

Results

Demographic characteristics of the study population

The mean age±SD did not differ significantly among the three study groups. Despite the higher number of females in the controls there was no statistically significant difference among the groups. Body weight and BMI were significantly higher in the T2DM and control groups than those of the CKD (Table 1).

Table 1. Demographic characteristics of the study population

Variables		CKD (n=40)	T2DM (n=41)	Controls (n=38)	p value
Age (years)	Mean±SD Range	50.63±9.25 33-70	53.66±8.32 38-72	52.42±8.81 38-69	0.172
Sex	Male, N (%) Female, N (%)	26 (65%) 14 (35%)	23 (56.1%) 18 (34.9%)	17 (44.74%) 21 (55.26%)	0.061
Weight (kg)	Mean±SD Rang	78.68±9.05[a] 59-97	83.95±6.63[b] 60-97	87.21±9.08[b] 65-102	<0.001
Height (cm)	Mean ±SD Range	168.9±5.64[a] 159-179	166.73±4.17[b] 159-175	165.26±4.31[b] 155-172	0.005
BMI (kg/m^2)	Mean ±SD Range	27.55±2.6[a] 21.2-32.37	30.22±2.46[b] 21.77-35.63	32.0±3.75[c] 23.0-38.29	<0.001

For each variable, different small letters of the means indicate significant difference between each two groups by post hoc LSD

Renal function tests

Patients in the CKD group, per se, had higher levels of urea and creatinine than other groups; with highly significant differences. On the other hand, there was a significant difference between T2DM patients and the control group in serum urea and creatinine.

Although the values of all included electrolytes (Na^+, K^+, and Ca^{2+}) were within normal limits in different groups, variations in the serum level between different groups did occur. Patients in T2DM group had lower serum levels of K^+ and Na^+ than other groups with significant differences (Table 2).

Table 2: Renal function tests in the study groups

Variables		CKD (n=40)	T2DM (n=41)	Controls (n=38)	p value
Urea (mg/dl)	Mean±SD Range	126.2±19.4[a] 95-178	50.76±7.0[b] 37-61	33.79±6.28[c] 22-48	<0.001
Creatinine (mg/dl)	Mean ±SD Rang	5.71±1.5[a] 2.8-9.0	1.39±0.27[b] 0.9-2.0	0.84±0.15[c] 0.6-1.2	<0.001
K^+ (mEq/l)	Mean ±SD Range	5.26±0.17[a] 5.02-5.66	4.73±0.5[b] 3.69-5.72	4.32±0.36[c] 3.7-5.0	<0.001
Na^+ (mEq/l)	Mean ±SD Range	141.3±5.81[a] 132-155	139.12±3.74[b] 133-148	140.3±2.95[ab] 136-147	<0.001
Ca^{2+} (mg/dl)	Mean ±SD Range	8.59±0.34[a] 7.93-9.33	8.7±0.46[a] 8.09-9.42	9.47±0.35[c] 7.93-10.0	<0.001

For each variable, different small letters of the means indicate significant difference between each two groups by post hoc LSD

Serum levels of NGAL NP and HbA1c in the study population

The mean serum level of NGAL in patients with CKD, T2DM, and controls showed highly significant differences, the highest was in the CKD group. There were, also, significant differences in the levels of CNP and BNP among the three groups. Both NPs were higher in the CKD group than the others. The glycated hemoglobin, HbA1c, and serum glucose were higher in patients with T2DM patients than other groups with highly significant differences (Table 3).

Table 3. Serum Levels of NGAL natriuretic peptides, and HbA1c

Variables		CKD (n=40)	T2DM (n=41)	Controls (n=38)	p value
NGAL (ng/ml)	Mean±SD Range	110.4±42.3[a] 36-195	102.2±22.1[a] 38-184	37.7±18.4[b] 14-77	<0.001
TN-pro CNP (pg/ml)	Mean ±SD Rang	6.53±1.74[a] 2.6-9.0	4.25±1.5[b] 1.0-8.0	2.24±0.82[c] 0.09-6.3	<0.001
TN-pro BNP (pg/ml)	Mean ±SD Range	667.1±163[a] 257-978	302.3±32.6[b] 234-422	102.3±46.5[c] 21.0-343	<0.001
HbA1c (%)	Mean ±SD Range	5.62±0.54[a] 4.8-6.9	9.77±1.21[b] 7.8-12.0	5.34±0.46[a] 4.5-6.3	<0.001
Glucose (mg/dl)	Mean ±SD Range	103.0±10.5[a] 86-125	340.0±50.0[b] 280-400	96.0±9.0[a] 85-113	<0.001

For each variable, different small letters of the means indicate significant difference between each two groups by post hoc LSD

Diagnostic value of NGAL, TN-pro CNB and TN-pro BNP using ROC

Discrimination between CKD and T2DM

The area under curve (AUC) for NT-proCNP was 0.825, 95%CI = 0.729-0.92, p = 0.022. The sensitivity and specificity of the test at a cut off value of NT-pro-CNP = 5.3 pg/ml were 80% and 78%, respectively.

The AUC for NT-proBNP was 0.869, 95%CI = 0.780-0.957, p <0.001. The sensitivity and specificity of the test at a cut off value of NT-proBNP = 341 pg/ml were 80% and 95%, respectively, whereas NGAL shows much lower sensitivity and specificity (Figure 1).

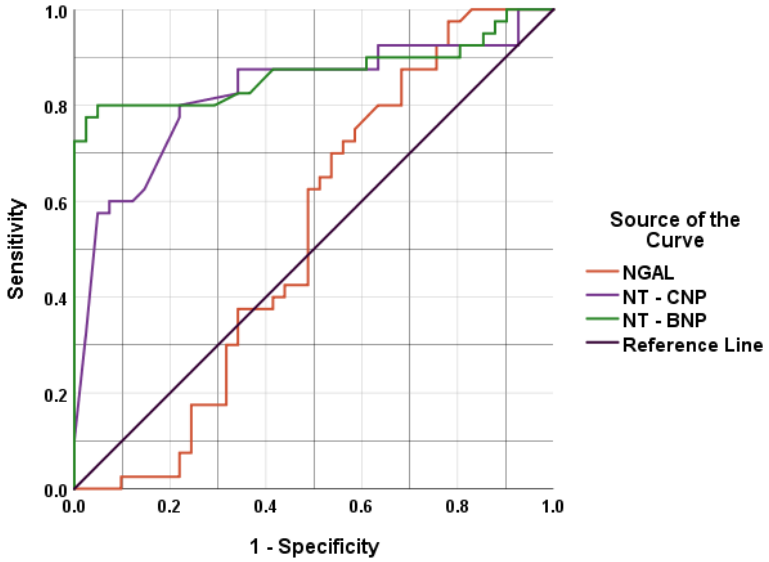

Figure 1. Receiver operating characteristic curve of NGAL, NT-pro-CNP, NT-pro-BNP in the context of discrimination between CKD and T2DM

Discrimination between CKD and controls

For NGAL, the AUC was 0.962, 95%CI = 0.922-1.0, p <0.001. The sensitivity and specificity of the test at a cut off value of NGAL= 78.5 ng/ml was 90% and 100%, respectively.

The AUC for NT pro-CNP was 0.922, 95%CI =0.867-0.977, p <0.001. The sensitivity and specificity of the test at a cut off value of NT-proCNP= 4.95 pg/ml were 82% and 90%, respectively.

The AUC for NT-proBNP was 0.985, 95%CI = 0.966-1.0, p <0.001. The sensitivity and specificity of the test at a cut off value of NT pro-BNP = 449 pg/ml were 98% and 92%, respectively (Figure 2).

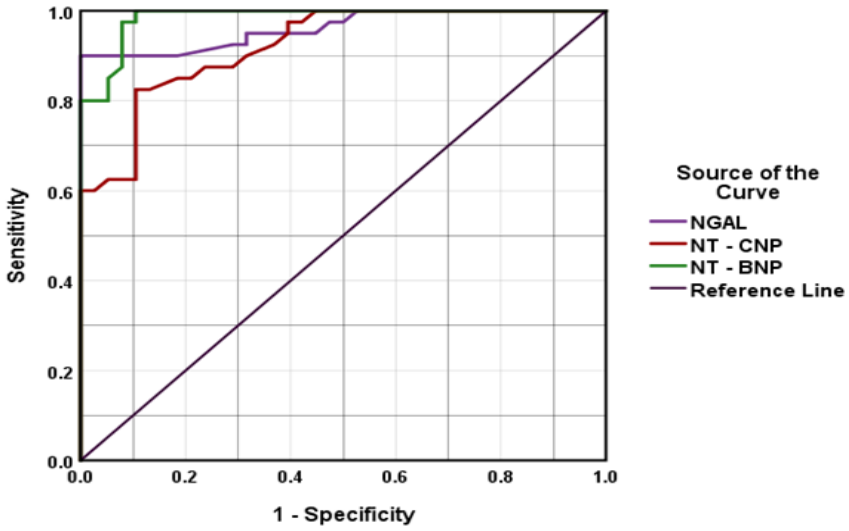

Figure 2. Receiver operating characteristic curve of NGAL, NT-proCNP, NT-proBNP in the context of discrimination between CKD and controls

Discrimination between T2DM and controls

The AUC for NGAL was 0.977, 95%CI = 0.95-1.0, p <0.001. The sensitivity and specificity of the test at a cut off value of NGAL= 58.5 ng/ml were 95% and 82%, respectively.

The AUC for NT-proCNP was 0.766, 0.95%CI = 0.656-0.876, p <0.001. The sensitivity and specificity of the test at cut off value of NT-proCNP= 3.9 pg/ml were 63% and 76%, respectively.

The AUC for NT-proBNP was 0.930, 95%CI = 0.858-1.0, p <0.001. The sensitivity and specificity of the test at cut off value of NT-proBNP = 256 pg/ml were 90% and 89%, respectively (Figure 3).

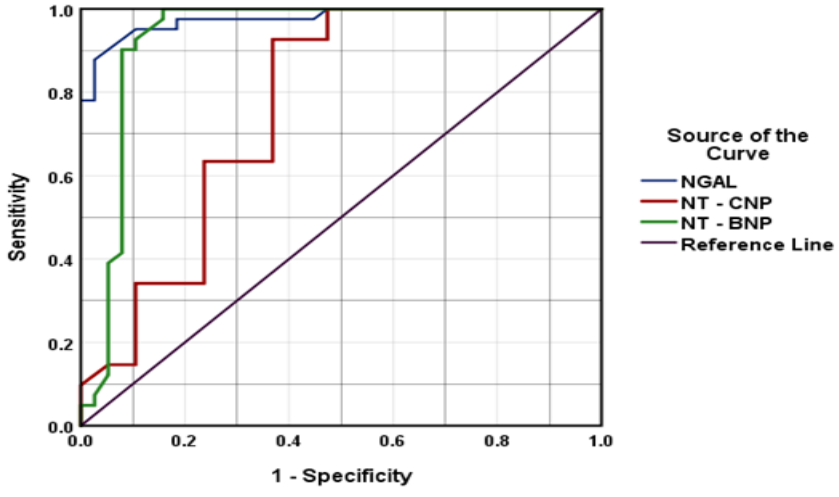

Figure 3. Receiver operating characteristic curve of NGAL, NT-proCNP, NT-proBNP in the context of discrimination between T2DM and controls

Pearson's correlation of NGAL, NT-proCNP, and NT-proBNP with other variables

In patients with CKD

Creatinine demonstrated a positive significant correlation with each of NGAL (r = 0.412, p = 0.008) and NT-BNP (r = 0.313, p = 0.049) as shown in figure (4).

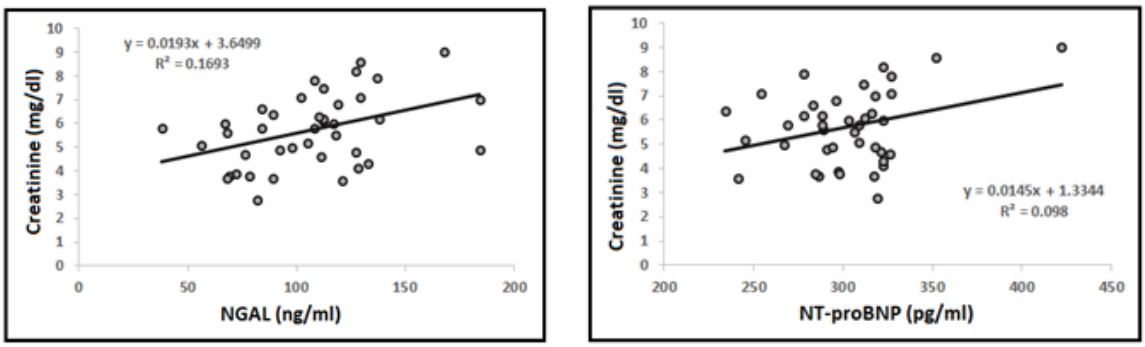

Figure 4. Scatter plots and regression lines between NGLA, NT-pro-BNP and Creatinine in patients with CKD

In patients with T2DM

The only significant correlation in this group was between HbA1c and each of NGAL (r= 0.394, p = 0.011) and NT-proCNP (r = 0.347, p = 0.026) as shown in figure (5).

In control group

There were no significant correlations between the included parameters.

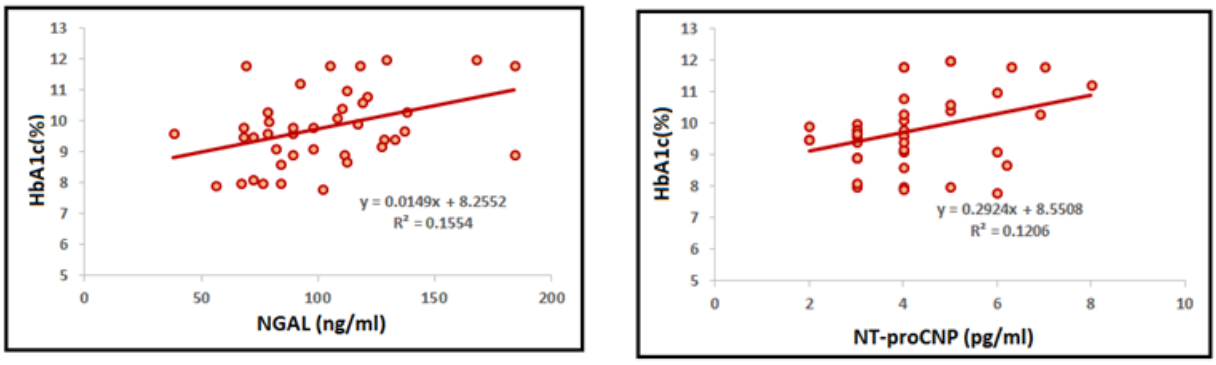

Figure 5. Scatter plots and regression lines between each of NGAL and NT-pro-CNP and HbA1c in patients with T2DM

Discussion

The concentrations of NPs in CKD and T2DM were reported to be high in many previous and recent reports [4,19], and have, strongly, been considered as markers for death risk rate in T2DM [20]. The present results showed a marked increase in both NPs (BNP and CNP) in both groups of patients. However, the rise was more in the CKD group, while T2DM patients still had a significantly higher levels than their controls.

The rise in NGAL in both groups (CKD and T2DM) has, also, been reported and confirmed by many recent reports [21,22]. This reflects a graded progression of cardio-renal and vascular stress.

Elevated NPs in T2DM, even in the absence of overt renal failure, indicate early subclinical myocardial strain, endothelial dysfunction, and neurohormonal activation related to chronic hyperglycemia and metabolic disturbances. The more pronounced rise in CKD likely reflects the combined effects of increased peptide production due to chronic volume and pressure overload, along with reduced renal clearance. Together, this pattern suggests that T2DM initiates natriuretic peptide activation, which is further amplified as renal function deteriorates in CKD.

Th ROC curve analysis gave good sensitivity and specificity for the NGAL and NT-proBNP to discriminate between CKD and T2DM, and, also, between each of CKD or T2DM and their control group. The NGAL was reported to be a good marker for evaluation of renal function in patients with renal dysfunction and for detection of diabetic nephropathy in patients with T2DM [22]. In the present results, the significant rise in the NGAL in the diabetic patients, as compared to the controls, could suggest changes in renal function in those patients, with a significant correlation between NGAL and HbA1c. Different trends of correlation between NGAL and HbA1c emerged from different reports: some had reported a positive [18,22], while others found a negative correlation [21]. Furthermore, NGAL was suggested to be a marker for normo-albuminuria renal insufficiency of diabetes mellitus [23,24] and in non-albumin uric children with type 1 diabetes mellitus, [25] and gestational diabetes, which is probably due to placental over secretion [26]. Changes in serum electrolytes in both CKD and T2DM are expected and are due to many reasons. [27-29]

In conclusion, NGAL and the NPs were significantly increased in patient groups versus controls, with NT-proBNP and NT-proCNP being highest in CKD and intermediate in T2DM, whereas NGAL was similarly raised in both CKD and T2DM relative to controls. ROC analysis demonstrated that all three markers, particularly NGAL and NT-proBNP, have excellent diagnostic accuracy in discriminating CKD and T2DM from healthy individuals, while NT-proBNP and NT-proCNP, but not NGAL, provide good discrimination between CKD and T2DM. The positive correlations of creatinine with NGAL and NT-proBNP in CKD, and of HbA1c with NGAL and NT-proCNP in T2DM, further support their pathophysiological relevance, indicating that higher marker levels parallel worsening renal dysfunction and poorer long-term glycemic control.

From the present results we could suggest the use of a combination of NGAL and NPs in early stages of T2DM to detect the possible existence of early renal changes, and further follow up during treatment, which may give better results than the HbA1c alone.

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Author contribution

Dr. Al-Shamma: Conceptualization. Dr. Malik: Methodology. Kurshead: Data collecation. Dr. Al-Mayah: Writing the original draft. Dr. Al-Shamma, Dr. Al-Mayah and Kurshead: Writing-review and editing.

Conflict of interest

The authors declare that they have no conflict of interest.

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