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NT-proBNP as a Predictor of Chronic Kidney Disease Progression

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Abstract

Background: N-terminal pro–B-type natriuretic peptide (NT-proBNP) is a cardiac biomarker with emerging relevance in chronic kidney disease (CKD). While elevated NT-proBNP levels are commonly attributed to cardiac dysfunction, recent evidence suggests they may also reflect renal pathology and predict CKD progression. This single-center study aimed to evaluate the predictive role of NT-proBNP in CKD progression independent of structural heart disease.

Methods: We enrolled 24 patients with stage 3–5 CKD, all with normal cardiac function confirmed by echocardiography (normal ejection fraction and left ventricular indices). Baseline NT-proBNP and comprehensive metabolic parameters (renal function, lipids, glycemic markers, inflammatory markers, nutritional indicators) were measured and repeated at 24 weeks. Changes in NT-proBNP were correlated with changes in renal function (creatinine clearance) and other variables. Statistical significance was set at $p<0.05$. We also considered advanced analyses (ROC curve and multivariate regression) to further assess NT-proBNP's prognostic performance.

Results: NT-proBNP levels rose significantly over 24 weeks ($p<0.001$) as renal function declined (creatinine clearance decreased, $p<0.001$). There was an inverse correlation between the change in NT-proBNP and the change in creatinine clearance ($r = –0.437$, $p<0.05$), even after excluding patients with heart failure or other cardiac abnormalities. Baseline NT-proBNP correlated negatively with serum albumin and total protein ($r = –0.525$ and $–0.414$, respectively), and these correlations persisted at follow-up ($r = –0.577$ and $–0.483$; $p<0.01$). Subgroup analysis showed the NT-proBNP–renal function relationship was more pronounced in diabetic CKD patients ($r = –0.638$, $p<0.05$) than in non-diabetics. NT-proBNP changes were not significantly associated with body mass index, blood pressure, lipid profile, or HbA1c. High-sensitivity C-reactive protein (hs-CRP) levels increased during follow-up; however, the change in hs-CRP did not correlate with the change in NT-proBNP.

Conclusion: NT-proBNP levels increased in tandem with CKD progression, suggesting NT-proBNP is a promising marker for monitoring renal deterioration independent of heart function. Its strong association with nutritional status (albumin/protein levels) implies a multifactorial biomarker role. Larger prospective studies and advanced statistical analyses (e.g., threshold determination via ROC, multivariate models) are warranted to validate NT-proBNP's prognostic value and to integrate it into clinical decision-making for CKD..

Keywords: N-Terminal pro-B-Type Natriuretic Peptide, Kidney Diseases, Chronic, Disease Progression, Biomarkers, utrition; Inflammation, Prognosis

INTRODUCTION

Chronic kidney disease (CKD) is a progressive disorder characterized by a gradual decline in renal function and is a significant global health challenge (1). Its prevalence is rising worldwide, driven by severe complications and substantial healthcare costs (1,2). Major clinical consequences include progression to end-stage renal disease (ESRD), CKD-related complications, and a heightened risk of cardiovascular disease (CVD) regardless of etiology (3). Early detection and intervention are essential to slow disease progression and prevent adverse outcomes, underscoring the need for improved biomarkers and timely diagnostic strategies.

CKD patients face a markedly higher risk of cardiovascular death than the general population, and indeed many succumb to cardiac events before reaching ESRD (3,4). Reduced kidney function itself is a major risk factor for cardiovascular complications (3-5). Left ventricular hypertrophy (LVH), often stemming from long-standing hypertension and anemia, is common in advanced CKD and strongly predicts mortality. Even subtle cardiac alterations can emerge early in CKD, highlighting the intertwined nature of cardiac and renal health (3-5).

Natriuretic peptides play a key role in cardiovascular assessment and fluid homeostasis (6,7). B-type natriuretic peptide (BNP) and its N-terminal fragment NT-proBNP are well-established biomarkers for diagnosing and managing heart failure, and guidelines recommend their measurement in that context (7). Unlike BNP, which is cleared by enzymes and has a short half-life, NT-proBNP is primarily eliminated by the kidneys via glomerular filtration (8). Consequently, NT-proBNP levels are more closely related to glomerular filtration rate (GFR) than BNP levels (8,9). As GFR declines, NT-proBNP tends to accumulate due to reduced renal clearance, even in the absence of overt heart failure. This dependency on renal excretion means CKD can elevate NT-proBNP levels per se, which historically led clinicians to discount elevated NT-proBNP in CKD patients without heart failure. However, several studies show that in patients without heart failure, higher NT-proBNP is still strongly prognostic for adverse outcomes, including cardiovascular events and kidney function decline (10,11). Elevated NT-proBNP may reflect chronic neurohormonal activation and venous congestion that contribute to CKD progression, rather than just reduced clearance (12).

Beyond cardiovascular implications, natriuretic peptides have been linked to renal outcomes. Early observations in the 2000s indicated that BNP/NT-proBNP levels rise as CKD advances and might predict progression to ESRD (13,14). Spanaus et al. reported that higher baseline BNP predicted faster CKD progression in non-diabetic CKD patients (13). Carr et al. similarly demonstrated prognostic value for N-terminal BNP in predialysis CKD: in a cohort of 83 CKD stage 4 patients without heart failure, elevated NT-proBNP was associated with a markedly increased risk of mortality or cardiovascular events, and higher baseline levels trended with progression to ESRD (15).

Although kidney dysfunction clearly influences NT-proBNP concentrations, the relationship between NT-proBNP and CKD progression has not been fully elucidated. Many prior investigations did not rigorously exclude cardiac disease, leaving open the question of whether elevated NT-proBNP was simply a marker of subclinical heart failure in CKD patients. To address this gap, the present study focused on CKD patients with normal cardiac structure and function, verified by echocardiography, thereby isolating the renal contributions to NT-proBNP levels. By excluding confounding cardiac abnormalities, we aimed to objectively evaluate NT-proBNP's role in renal function decline. The primary aim was to determine whether NT-proBNP correlates with CKD progression toward ESRD, independent of cardiac dysfunction.

METHODS

Study Design and Participants

This single-center prospective study was conducted at the Nephrology Clinic of Ankara Education and Research Hospital. A total of 24 patients with CKD stage 3–5 (pre-dialysis) were enrolled. All participants had a history of hypertension, and 13 had diabetes mellitus. Key inclusion criteria were age ≥18 years, CKD stage 3–5 (estimated GFR <60 mL/min/1.73 m²) not yet on renal replacement therapy, and the absence of symptomatic heart disease. To ensure cardiac health, each patient underwent a comprehensive echocardiographic evaluation; only those with normal left ventricular ejection fraction (LVEF), normal left ventricular mass index (LVMI), and normal right ventricular size/function were included. This stringent inclusion criterion was intended to eliminate confounding by overt structural heart disease.

Exclusion Criteria

We excluded patients with any condition that could independently influence NT-proBNP or renal outcomes aside from CKD. Specifically, exclusion criteria were: (1) acute or chronic infections, (2) chronic liver disease or active malignancy, (3) uncontrolled volume overload (edema unresponsive to diuretics), (4) any history of solid organ transplantation or current immunosuppressive therapy, (5) known heart failure or prior diagnosis of cardiomyopathy, (6) known coronary artery disease or prior myocardial infarction, and (7) pregnancy. Patients under evaluation for any of these conditions were also excluded. All participants provided written informed consent. The study protocol was approved by the local Ethics Committee (Ankara Education and Research Hospital, Approval No. 0291-2153) prior to commencement.

Data Collection and Measurements

Baseline demographics (age, sex) and clinical data (comorbidities such as diabetes, blood pressure, medications) were recorded. A physical examination was performed including measurements of height and weight to calculate body mass index (BMI = kg/m²). Blood pressure was measured with a standard sphygmomanometer after a 15-minute rest. Fasting venous blood samples were obtained in the morning (after an overnight 12-hour fast) at baseline and at the 24-week follow-up. The following laboratory

parameters were measured at both time points using standard automated techniques: serum NT-proBNP, urea, electrolytes, fasting glucose, glycated hemoglobin (HbA1c), lipid profile [total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C)], albumin, total protein, transferrin, ferritin, high-sensitivity C-reactive protein (hs-CRP), hemoglobin, and hematocrit. Proteinuria was assessed by spot urine protein or 24-hour protein excretion, as available. Renal function was assessed using the Cockcroft–Gault formula to estimate creatinine clearance (mL/min). The term 'creatinine clearance' is used consistently throughout the study to reflect this calculation method. All laboratory analyses were performed in the hospital's central lab using standardized methods. NT-proBNP levels were measured in pg/mL using an electrochemiluminescence immunoassay (Elecsys, Roche Diagnostics). For interpretability, NT-proBNP values were analyzed on a continuous scale and also categorically in some analyses (e.g., by median or clinically relevant cut-offs).

Follow-up

Participants were followed for 24 weeks (~6 months). At the end of follow-up, clinical data and the same laboratory measurements were repeated. The primary outcome was the change in renal function over 24 weeks, assessed by change in creatinine clearance (or creatinine clearence). We also noted whether any patient progressed to a more advanced CKD stage or required dialysis during this short follow-up. Secondary outcomes included changes in NT-proBNP and their associations with changes in other parameters (e.g., fluid/nutritional markers and metabolic measures).

STATISTICAL ANALYSIS

Continuous variables are presented as mean ± standard deviation or median [interquartile range] as appropriate to their distribution. Categorical variables are summarized as counts and percentages. We used the Shapiro-Wilk test to assess normality of continuous data. Changes in biochemical parameters from baseline to 24 weeks were evaluated using paired t-tests for normally distributed variables or Wilcoxon signed-rank tests for non-normal data. Correlations between changes in NT-proBNP and changes in other variables (e.g., creatinine clearance, albumin, etc.) were analyzed using Spearman's rank correlation coefficients (since NT-proBNP and some clinical variables showed skewed distributions). For baseline cross-sectional correlations, Pearson or Spearman correlation was applied as appropriate. A two-tailed p-value <0.05 was considered statistically significant for all analyses.

Given the limited sample size, formal multivariable modeling was not initially performed in the original analysis. However, to enhance analytical robustness, we developed exploratory strategies for advanced statistical analysis. We planned a receiver operating characteristic (ROC) curve analysis to assess the discriminatory ability of baseline NT-proBNP for predicting renal function decline. Specifically, we considered defining "CKD progression" as a ≥20% decline in creatinine clearance at 24 weeks and then evaluating the area under the ROC curve (AUC) for baseline NT-proBNP to predict this outcome. Additionally, we contemplated a multivariate regression model (logistic or linear regression, depending on outcome distribution) to adjust for potential confounders (age, sex, baseline GFR, diabetes status, blood pressure, etc.) and test whether NT-proBNP is an independent predictor of kidney function decline. All statistical analyses were performed using IBM SPSS Statistics (Version 22.0, Armonk, NY).

RESULTS

The study cohort included 24 patients with chronic kidney disease (CKD) stages 3–5 (15 women [62.5%] and 9 men [37.5%]). Thirteen patients (54%) had diabetes

Table 1. Demographic and clinical characteristics of patients

Parameter	Total (n=24)	Patients with DM (n=13)	Patients without DM (n=11)
Gender, Female/male	15 (62.5%) / 9 (37.5%)	7 (46.7%) / 6 (66.7%)	8 (53.3%) / 3 (33.3%)
Age (years)	50.6 ± 14.3	–	–
BMI (kg/m²)	26.5 ± 4	–	–
Systolic BP (mmHg)	129.7 ± 18	–	–
Diastolic BP (mmHg)	81.8 ± 11.3	–	–
Diabetes Mellitus	13 (54.2%)	–	–
Stage 3 CKD	6 (25%)	–	–
Stage 4 CKD	16 (66.7%)	–	–
Stage 5 CKD	2 (8.3%)	–	–
Ejection Fraction (%)	62 ± 5.1	–	–
LVMI	80.8 ± 23.2	–	–

BMI: Body Mass Index; BP: Blood Pressure; CKD: Chronic Kidney Disease; LVMI: Left Ventricular Mass Index; DM: Diabetes Mellitus.

Table 2. Biochemical parameters of all patients at baseline and 24 weeks

Parameter	Baseline	24th Week	p value
Creatinine (mg/dL)	3.1 ± 0.9	3.7 ± 1.0	0.001
Creatinine clearance (mL/min)	24.9 ± 9.06	21.6 ± 7.3	0.001
NT-proBNP (pg/mL)	75.5 ± 66.4	131.8 ± 121.3	0.001
Glucose (mg/dL)	116.5 ± 40.3	115.5 ±76.8	>0.05
Urea (mg/dL)	102.7 ± 31	120.4 ± 25.3	<0.01
Uric acid (mg/dL)	6.5 ± 1.6	5.7 ± 1.0	>0.05
Total protein (g/dL)	7 ± 0.9	7 ± 0.7	>0.05
Albumin (g/dL)	3.8 ± 0.5	3.9 ± 0.5	>0.05
Total cholesterol (mg/dL)	198.7 ± 54.3	183.6 ± 55	>0.05
Triglyceride (mg/dL)	154.8 ± 75.6	157.7 ± 101	>0.05
HDL-cholesterol (mg/dL)	46.8 ± 14.0	49.5 ± 16.3	>0.05
LDL- cholesterol (mg/dL)	116.8 ± 49.1	105.6 ± 44.3	>0.05
Magnesium (mmol/L)	0.8 ± 0.1	0.8 ± 0.1	>0.05
Transferrin (g/L)	1.9 ± 0.3	2.1 ± 0.3	>0.05
Hemoglobin (g/dL)	11.4 ±1.7	11.0 ± 1.2	<0.05
Hematocrit (%)	32.4 ± 4.8	32.1 ± 3.6	>0.05
Ferritin (ng/mL)	155.2 ± 134.4	128.5 ± 112.2	<0.05
HbA1c (%)	7.0 ± 2.0	6.6 ± 2.4	<0.05
24-hour urine protein (g/day)	3.3 ± 2.8	2.6 ± 3.3	<0.05
hs-CRP (mg/L)	1.8 ± 2.3	2.4 ± 2.1	<0.05

HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; hs-CRP: High-sensitivity C-reactive protein.

mellitus (DM), and all had a history of hypertension. The gender and diabetes distribution are presented in **Table 1**, showing that 7 of 13 patients with DM (46.7%) were female, while 6 (66.7%) were male; among non-diabetics, 8 (53.3%) were female and 3 (33.3%) were male.

At baseline, the mean age was 50.6 ± 14.3 years, BMI was 26.5 ± 4 kg/m², and mean systolic and diastolic blood pressures were 129.7 ± 18 mmHg and 81.8 ± 11.3 mmHg, respectively. Most patients were in stage 4 CKD (66.7%), with smaller proportions in stage 3 (25%) and stage 5 (8.3%). Echocardiographic evaluation confirmed normal cardiac function in all participants, with a mean left ventricular ejection fraction (LVEF) of 62 ± 5.1% and left ventricular mass index (LVMI) of 80.8 ± 23.2 g/m². Detailed demographic and clinical data are summarized in **Table 1.**

Changes in Renal Function and NT-proBNP

Over the 24-week follow-up period, there was a statistically significant deterioration in renal function accompanied by an increase in NT-proBNP levels. Serum creatinine rose from 3.1 ± 0.9 mg/dL to 3.7 ± 1.0 mg/dL ($p < 0.001$), while creatinine clearance declined from 24.9 ± 9.1 mL/min to 21.6 ± 7.3 mL/min ($p < 0.001$). In parallel, NT-proBNP increased from 75.5 ± 66.4 ng/mL at baseline to 131.8 ± 121.3 ng/mL ($p < 0.001$), as shown in **Table 2.**

No patients developed clinical or echocardiographic evidence of heart failure during follow-up, confirming that the observed NT-proBNP elevation was not attributable to new cardiac dysfunction. Other parameters showing statistically significant changes over 24 weeks included urea ($p < 0.01$), hemoglobin ($p < 0.05$), ferritin ($p < 0.05$), HbA1c ($p < 0.05$), 24-hour urine protein ($p < 0.05$), and hs-CRP ($p < 0.05$), indicating mild progression of uremic and inflammatory status. Lipid profile and serum albumin remained stable, with no significant differences between baseline and week 24 values (**Table 2**).

Subgroup Analysis by Diabetic Status

In subgroup analyses, patients with diabetes exhibited a more pronounced renal decline and NT-proBNP increase. In the diabetic group, creatinine clearance dropped from 30.3 ± 8.0 mL/min to 25.3 ± 6.8 mL/min ($p < 0.005$), whereas the non-diabetic group showed a smaller, non-significant change (18.6 ± 5.3 → 17.2 ± 5.4 mL/min, $p > 0.05$). Similarly, NT-proBNP rose significantly among diabetics (76.4 ± 70.8 → 127.9 ± 90.1 ng/mL, $p < 0.01$), while the increase among non-diabetics did not reach significance (74.5 ± 64.1 → 136.5 ± 155.2 ng/mL, $p = 0.06$) (**Table 3 and 4**).

Other biochemical variables (glucose, lipid profile, albumin, and magnesium) remained statistically unchanged in both subgroups ($p > 0.05$), suggesting that NT-proBNP variation was predominantly related to renal function changes rather than metabolic differences between diabetic and non-diabetic CKD.

Correlation Analyses

Correlation analyses further clarified the relationship between NT-proBNP and renal parameters. As shown in **Table 6**, the change in NT-proBNP (ΔNT-proBNP) was positively correlated with ΔCreatinine ($r = 0.585$, $p < 0.005$) and negatively correlated with ΔCreatinine

Table 3. Biochemical parameters of patients with diabetes mellitus at baseline and 24 weeks

Parameter	Baseline	24th Week	p value
Creatinine (mg/dL)	2.7 ± 0.7	3.3 ± 1.0	<0.005
Creatinine clearance (mL/min)	30.3 ± 8.0	25.3 ± 6.8	<0.005
NT-proBNP (pg/mL)	76.4 ± 70.8	127.9 ± 90.1	<0.01
Glucose (mg/dL)	136.6 ± 45.0	138.5 ± 99.9	>0.05
Urea (mg/dL)	96.3 ± 29.2	115.1 ± 28.8	<0.05
Uric acid (mg/dL)	6.6 ± 1.46	6.0 ± 1.0	>0.05
Total protein (g/dL)	7.1 ± 0.8	7.1 ± 0.5	>0.05
Albumin (g/dL)	3.7 ±0.5	3.9 ± 0.3	>0.05
Total cholesterol (mg/dL)	202.3 ± 60.3	180.0 ± 47.1	>0.05
Triglyceride (mg/dL)	171.4 ± 81.6	183.5 ± 122.9	>0.05
HDL-cholesterol (mg/dL)	46.6 ± 16.5	47.9 ± 19.8	>0.05
LDL cholesterol (mg/dL)	113.8 ± 57.3	100.1 ± 34.8	>0.05
Magnesium (mmol/L)	0.8 ± 0.08	0.8 ± 0.1	>0.05
Transferrin (g/L)	2.0 ± 0.2	2.2 ± 0.45	>0.05
Hemoglobin (g/dL)	11.4 ± 1.6	11.0 ± 1.4	>0.05
Hematocrit (%)	32.6 ± 4.7	32.0 ± 4.3	>0.05
Ferritin (ng/mL)	138.7 ± 112.8	128.5 ± 122.7	>0.05
HbA1c (%)	8.3 ± 1.8	7.6 ± 2.7	>0.05
24-hour urine protein (g/day)	3.4 ± 2.3	3.1 ± 4	>0.05
hs-CRP (mg/L)	1.8 ± 2.3	2.7 ± 2.5	>0.05

HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; hs-CRP: High-sensitivity C-reactive protein.

clearance ($r = –0.437$, $p < 0.05$), confirming that greater renal decline was accompanied by larger NT-proBNP elevations.

No significant associations were found between ΔNT-proBNP and changes in glucose, lipid fractions, HbA1c, hs-CRP, proteinuria, blood pressure, or BMI (all $p > 0.05$). These findings indicate that the biomarker's variation was largely independent of metabolic or inflammatory parameters (**Table 5**).

When patients were analyzed by diabetes status, these correlations were markedly stronger in the diabetic subgroup. In diabetics, ΔNT-proBNP correlated positively with ΔCreatinine ($r = 0.664$, $p < 0.05$) and negatively with ΔCreatinine clearance ($r = –0.638$, $p < 0.05$), whereas non-diabetic patients exhibited weaker and non-significant associations ($r = 0.319$ and $r = –0.165$, respectively; $p > 0.05$) (**Table 6**). Neither Δhs-CRP nor Δ24-hour urine protein showed significant correlation with NT-proBNP in either subgroup, though a mild positive trend between Δhs-CRP and ΔNT-proBNP was noted in non-diabetics ($r = 0.506$, $p > 0.05$).

Table 4. Biochemical parameters of patients without diabetes mellitus at baseline and 24 weeks

Parameter	Baseline	24th Week	p value
Creatinine (mg/dL)	3.7 ± 0.97	4.3 ± 1	<0.005
Creatinine clearance (mL/min)	18.6 ± 5.3	17.2 ± 5.4	>0.05
NT-proBNP (pg/mL)	74.5 ± 64.1	136.5 ± 155.2	=0.06
Glucose (mg/dL)	92.6 ± 12.4	88.2 ± 8.9	>0.05
Urea (mg/dL)	110.4 ± 32.6	126.7 ± 20.0	<0.05
Uric acid (mg/dL)	6.3 ± 1.9	5.4 ± 1.1	>0.05
Total protein (g/dL)	7.0 ± 1.0	7.0 ± 0.8	>0.05
Albumin (g/dL)	3.8 ± 0.6	3.8 ± 0.6	>0.05
Total cholesterol (mg/dL)	194.4 ± 48.8	187.9 ± 65.2	>0.05
Triglyceride (mg/dL)	135.2 ± 66.1	127.1 ± 59.0	>0.05
HDL-cholesterol (mg/dL)	47.0 ± 11.1	51.3 ± 11.6	<0.05
LDL-cholesterol (mg/dL)	120.3 ± 39.6	111.0 ± 53.3	>0.05
Magnesium (mmol/L)	0.8 ± 0.1	0.9 ± 0.1	<0.05
Transferrin (g/L)	1.7 ± 0.4	2.0 ± 0	>0.05
Hemoglobin (g/dL)	11.3 ± 2.06	10.9 ± 0.9	>0.05
Hematocrit (%)	32.1 ± 5.1	32.3 ± 2.5	>0.05
Ferritin (ng/mL)	174.7 ± 159.7	128.6 ± 104.2	>0.05
HbA1c (%)	5.4 ± 0.3	5.2 ± 0.3	<0.05
24-hour urine protein (g/day)	3.1 ± 3.4	2.0 ± 2.3	>0.05
hs-CRP (mg/L)	1.7 ± 2.5	2.0 ± 1.5	>0.05

Table 5. Correlation between changes in NT-proBNP and other parameters (general population)

Parameter	p-value	Correlation coefficient (r)
Δ Creatinine	< 0.005	0.585
Δ Creatinine clearance	< 0.05	-0.437
Δ Glucose	> 0.05	0.251
Δ Total protein	> 0.05	-0.110
Δ Albumin	> 0.05	0.236
Δ Total cholesterol	> 0.05	-0.137
Δ Triglyceride	> 0.05	0.080
Δ LDL-cholesterol	> 0.05	-0.099
Δ HbA1c	> 0.05	0.250
Δ 24-hour urine protein	> 0.05	-0.127
Δ hs-CRP	> 0.05	0.003
Δ Systolic BP	> 0.05	0.103
Δ Diastolic BP	> 0.05	-0.051
Δ BMI	> 0.05	-0.078

Table 6. Correlation between changes in NT-proBNP and other parameters in diabetic and non-diabetic patients

Parameter	Diabetic (p-value and r)	Non-diabetic (p-value and r)
Δ Creatinine	**< 0.05 / 0.664**	**> 0.05 / 0.319**
Δ Creatinine clearance	**< 0.05 / -0.638**	**> 0.05 / -0.165**
Δ 24-hour urine protein	**> 0.05**	**> 0.05**
Δ hs-CRP	**> 0.05**	**> 0.05**

Table 7. Correlation Between NT-proBNP and Nutritional Parameters at Baseline and 24 Weeks

Parameter	Baseline r and p value	24th Week r and p value
Albumin (g/dL)	–0.525 / < 0.001	–0.577 / <0.005
Total Protein (g/dL)	–0.414 / <0.05	–0.483 / <0.005
Transferrin (g/L)	–0.298 / >0.05	–0.214 / >0.05

As shown in **Table 7**, NT-proBNP demonstrated significant inverse correlations with nutritional parameters, including serum albumin ($r = –0.53$, $p < 0.01$) and total protein ($r = –0.41$, $p < 0.05$) at baseline, and these relationships strengthened at 24 weeks (albumin $r = –0.58$, $p < 0.005$; total protein $r = –0.48$, $p < 0.05$).

DISCUSSION

In this study of CKD patients without confounding cardiac dysfunction, we found that NT-proBNP increased significantly as renal function declined, supporting its role as a marker of CKD progression. BNP and NT-proBNP are classically secreted by the cardiac ventricles in response to wall stress, promoting natriuresis, diuresis, and vasodilation. They are established cardiac biomarkers, and elevated levels have been linked to mortality even in individuals without overt heart failure. Our findings expand on this concept by demonstrating NT-proBNP's prognostic signal in the renal arena. The observed inverse relationship between NT-proBNP and creatinine clearance is consistent with earlier studies and highlights that NT-proBNP can reflect kidney dysfunction severity. Importantly, because we excluded patients with any significant cardiac impairment, we believe that the NT-proBNP elevations largely reflect non-cardiac factors.

Previous work by Spanaus et al. and Carr et al. suggested that higher natriuretic peptide levels predict faster CKD progression in predialysis patients (13,15). Our results align with these and more recent observations. Ascher et al. analyzed longitudinal data from the SPRINT trial and reported that participants with ≥25% increases in NT-proBNP over one year had significantly faster subsequent creatinine clearence decline and higher odds of a ≥30% drop in GFR, compared to those with stable NT-proBNP; notably, this was true even after accounting for baseline kidney function, and was most pronounced in those with CKD at baseline (16). Likewise, Sasaki et al. showed in a 10-year community cohort that individuals in the highest NT-proBNP quartile (≥300 pg/mL) had a nearly doubled risk of developing CKD and a more rapid annual GFR loss relative to those in the lowest quartile (14). In that study, adding NT-proBNP to traditional risk factor models improved prediction of incident CKD, underscoring NT-proBNP's independent value. These large-scale data corroborate our single-center findings and strengthen the evidence that NT-proBNP is not merely a bystander in CKD but a potential predictive biomarker.

Unlike many prior investigations that assessed cardiac status only via history or rudimentary exams, we rigorously excluded patients with any echocardiographic abnormalities. This approach reinforces that the NT-proBNP increases observed in our patients were attributable to renal deterioration rather than occult heart failure. In other words, even with well-preserved cardiac function, CKD progression led to rising NT-proBNP, indicating the biomarker's utility beyond heart failure contexts. Our study design therefore offers a clearer interpretation of NT-proBNP as a renal risk indicator, supporting its cardiac-independent predictive power.

Our analysis also provides insight into mechanistic links between NT-proBNP, nutrition, and fluid status in CKD. We found strong inverse correlations between NT-proBNP and serum albumin, total protein, and transferrin. Malnutrition and hypoalbuminemia are common in CKD due to decreased intake, inflammation, and protein loss, and they are closely tied to worse outcomes (17,18). Satyan et al. previously reported that NT-proBNP was not associated with albumin in asymptomatic hemodialysis patients (suggesting volume status as a bigger driver in that setting), but our pre-dialysis cohort did show such an association (19). The discrepancy may stem from differences in patient populations or sample size. Our findings suggest that poor nutritional status (low albumin/protein) accompanies higher NT-proBNP, potentially because malnutrition often coexists with fluid overload in CKD (the malnutrition-inflammation

complex). Hypoalbuminemia can lead to reduced plasma oncotic pressure and edema, which in turn increases cardiac wall stress and NT-proBNP release. Indeed, other studies have observed NT-proBNP to be inversely related to nutritional markers and positively related to inflammation in CKD. In a recent study, NT-proBNP was inversely associated with serum albumin and prealbumin (and BMI) and directly associated with CRP; furthermore, NT-proBNP levels were significantly higher in patients meeting criteria for protein-energy wasting (19). Our data are in line with this pattern (NT-proBNP ↔ low albumin, high CRP trend), although our CRP correlation did not reach significance. The interplay between NT-proBNP and the malnutrition-inflammation-atherosclerosis (MIA) syndrome is a topic of interest. It appears NT-proBNP may serve as an integrative marker reflecting not only cardiac stress but also volume status and nutritional/inflammatory status in CKD. Clinicians should recognize that an elevated NT-proBNP in a CKD patient without heart failure might be a surrogate for volume overload or poor nutrition rather than a "false-positive" cardiac alarm.

We also examined other factors that could influence NT-proBNP. Obesity can lower circulating natriuretic peptide levels due to increased clearance by adipose tissue receptors and decreased secretion (20). In our cohort, BMI was mostly in the normal range and we did not observe a NT-proBNP–BMI relationship, likely due to limited variability and the small sample. Prior research has noted an inverse NP–BMI relationship in the general population (natriuretic peptide levels tend to be lower in individuals with higher BMI), so in broader CKD cohorts one might need to account for obesity when interpreting NT-proBNP levels (20,21). Similarly, sex differences (higher NT-proBNP in females) have been reported in healthy adults, attributed to hormonal factors, but in our CKD patients these differences were not apparent, possibly overshadowed by CKD severity and volume status (22,23). Inflammation has been postulated to elevate NT-proBNP by cytokine-mediated myocardial strain or direct effects on myocytes (24,25). While we did not find a direct correlation in our data, inflammation likely still plays a role in the complex milieu of CKD that influences NT-proBNP. As noted, NT-proBNP correlates with CRP and other inflammatory markers in some CKD studies.

From a prognostic standpoint, NT-proBNP appears to have substantial value in CKD. It has been associated not only with progression to ESRD but also with cardiovascular outcomes and mortality in CKD populations. Previous studies reported that NT-proBNP was a significant predictor of both all-cause mortality and need for dialysis on follow-up (26,27). Gromadzinski et al. reported an optimal NT-proBNP cutoff of ~385 pg/mL for predicting the composite outcome of death or dialysis (sensitivity 70.8%, specificity 72.7%) (28). Moreover, NT-proBNP remained an independent predictor in multivariate analysis, with an adjusted odds ratio ~4.7 for mortality or RRT at that cutoff. These data suggest that even moderately elevated NT-proBNP levels (on the order of a few hundred pg/mL, well below the usual heart failure threshold) carry prognostic weight in CKD (28). In another study of advanced CKD (stages 4–5), baseline NT-proBNP >1345 ng/L predicted initiation of dialysis within 5 years, and baseline BNP >140 ng/L predicted 1-year dialysis risk, reinforcing that natriuretic peptides can stratify the timing of progression to ESRD (29). Our study was not powered to assess long-term outcomes like mortality or dialysis initiation, but the consistent association of NT-proBNP with short-term GFR decline hints at its broader prognostic significance, aligning with these findings.

Despite its strengths, our study has several limitations that should be considered when interpreting the findings. The most important limitations are the small sample size (n = 24) and the short follow-up period (6 months), which limit the statistical power and generalizability of the results. The relatively small cohort may have reduced the ability to detect weaker associations or to perform robust multivariate analyses. Additionally, the short observational window prevented the assessment of long-term renal outcomes such as initiation of dialysis, doubling of serum creatinine, or mortality.

Another limitation is that renal function was evaluated using creatinine clearance calculated by the Cockcroft–Gault formula, which, although practical and reproducible, may slightly differ from MDRD or CKD-EPI–based eGFR estimations. However, this method was consistently applied across all analyses. Furthermore, NT-proBNP measurements were performed at only two time points (baseline and week 24), which might not fully capture short-term fluctuations related to hydration or metabolic status. Finally, while we rigorously excluded patients with structural or functional heart disease to isolate renal effects, this design may limit extrapolation of the findings to CKD populations with concurrent cardiac comorbidities.

In conclusion, our findings indicate that NT-proBNP may serve as a promising biomarker for predicting renal outcomes, independent of heart failure. Its association with renal function decline, as well as volume and nutritional status, highlights its potential clinical relevance. Further large, multicenter prospective studies are needed to validate these findings and define standardized thresholds for clinical application in CKD management.

CONCLUSION

NT-proBNP may serve as a valuable adjunct marker

for tracking the progression of chronic kidney disease, even in the absence of overt cardiac dysfunction. In our single-center study, rising NT-proBNP levels paralleled declines in renal clearance over 6 months and were associated with indicators of malnutrition and volume status. These findings suggest that NT-proBNP captures key aspects of CKD progression risk that are not reflected by traditional measures alone. If confirmed in larger and longer-term studies, NT-proBNP could be integrated into clinical risk assessment to identify patients at higher risk of renal function loss and to tailor interventions accordingly. Until such data are available, NT-proBNP should be interpreted cautiously yet constructively in CKD: rather than dismissing an elevated NT-proBNP as a false alarm in a CKD patient without heart failure, clinicians should recognize it as a possible red flag for worsening renal and cardiovascular health. Ultimately, additional large-scale, long-term prospective studies with appropriate control groups are needed to validate NT-proBNP's prognostic utility and to determine whether interventions guided by this biomarker can improve clinical outcomes in CKD.

DECLARATIONS

Ethics Committee Approval: The study was approved by the Ankara Education and Research Hospital Ethics Committee (Approval No. 0291-2153) and conducted in accordance with the Declaration of Helsinki.

Data Availability: Datasets are available from the corresponding author upon reasonable request.

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