Is N-terminal pro-brain natriuretic peptide a reliable marker for body fluid status in children with chronic kidney disease?

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Abstract

Introduction: Brain natriuretic peptides, released in response to left ventricular stress, have a strong prognostic value in dialysis patients. However, their role in detecting abnormalities of fluid status is under debate; the relationship between volume status and brain natriuretic peptide s (BNPs) differs among various studies. The aim of our study was to evaluate the clinical utility of N-terminal proBNP in the assessment of fluid status and cardiovascular risk in this setting.

Material and methods: The study included 65 children: 10 pre-dialysis, 13 hemodialysis, 12 peritoneal dialysis patients and 30 healthy controls. Volume status was determined by multifrequency bioimpedance and NT-proBNP, as well as echocardiography to estimate the left ventricle structure and function.

Results: The median log NT-proBNP values of hemodialysis and peritoneal dialysis patients were 3.66 (2.05–4.90) and 3.57 (2.51–4.13) pg/ml, respectively, and significantly higher compared with the control group ($p < 0.001$, $p < 0.001$). On simple correlation, NT-proBNP was correlated with markers of volume overload and cardiac dysfunction. On multivariate regression analysis, only left ventricle mass index ($\beta = 0.402$, $p = 0.003$) and left atrium diameter ($\beta = 0.263$, $p = 0.018$) were independently associated with NT-proBNP (adjusted R^2 of the model: 0.707, $p < 0.001$).

Conclusions: Our research suggested that NT-proBNP, which was correlated with LV systolic and diastolic dysfunction and fluid overload as assessed by bioimpedance, can be used to evaluate cardiovascular states in a chronic kidney disease (CKD) population. From the early stages of CKD, periodic monitoring of NT-proBNP levels may be essential for early detection of patients with high risk of cardiovascular events, and for taking preventive intervention as soon as possible.

Key words: chronic kidney disease, pediatrics, bioimpedance analysis, volume status, N-terminal pro-brain natriuretic peptide.

Introduction

Cardiovascular disease (CVD) is prevalent in patients with chronic kidney disease (CKD) and remains the major cause of mortality [1, 2].

Although there are many potential cardiovascular risk factors that play an important role in the development of CVD, including both traditional and uraemia-related risk factors, many recent studies have focused on novel risk factors such as malnutrition, inflammation, and overhydration in the CKD population [1, 3–5]. Overhydration as well as accumulation of uremic toxins may influence the development of hypertension, left ventricular hypertrophy (LVH), and LV dysfunction and eventually leads to the development of congestive heart failure in patients with CKD [6]. This suggests that accurately measuring the volume state will profoundly impact on dialysis patients' blood pressure, cardiac health, and clinical outcome [1, 7, 8].

Several objective methods have been proposed to support the correct estimation of volume status in dialysis patients, because interpretation of clinical indicators is subjective and lacks precision in diagnosing excess intravascular volume [9]. The most commonly used methods include ultrasound of the inferior vena cava, radionuclide dilution techniques, assessment of extracellular water (ECW) by bioimpedance analysis (BIA) and brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) as biochemical markers [10–21]. Among them, the brain natriuretic peptides (BNPs), BNP and NT-proBNP, released in response to left ventricular stress, have been repeatedly reported to be predictive of increased cardiovascular mortality. However, their role in detecting abnormalities of fluid status is under debate; the relationship between volume status and BNPs differs among various studies [22–25]. The prevalence of volume overload during the earlier stages of CKD is unclear and its significance has not been explained. Only a limited number of studies have been conducted in CKD patients not yet on dialysis [26–28].

In this study, we aimed to assess the relationship of NT-proBNP with fluid status measured by BIA and with cardiovascular changes in children undergoing hemodialysis (HD), peritoneal dialysis (PD), and in children with CKD with no need of renal replacement.

Material and methods

This single-center cross-sectional study involved 35 CKD pediatric patients (13 patients on HD, 12 patients on PD and 10 patients with stage 3B-4 CKD) and 30 age- and sex-matched healthy individuals as controls. Patients with CKD who underwent HD or PD for at least 6 for months and patients with stage 3B-4 CKD who were followed up in the nephrology outpatient clinic with a glomerular filtration rate (GFR) of 15-44 ml/min/1.73 m^2 were included in the study. The HD patients underwent 3.5–4 h lasting dialysis 3 times per week. Ten patients in the PD group underwent automated peritoneal dialysis (APD) using a standard calcium dialysate and 2 patients received continuous ambulatory peritoneal dialysis (CAPD). Exclusion criteria were infections (as judged by the attending pediatric nephrologist), the presence of congenital or acquired heart disease, contraindications for BCM (an implanted electronic medical device) or connection to an external electronic medical device (pacemaker), any kind of metal implants or amputations; overnight enteral nutrition. Also those who did not sign the informed consent form were excluded from the study.

Baseline demographic data were collected. Age (years), weight (kg), height (cm), body mass index (BMI) (kg/m^2), body surface area (BSA), CKD etiologies and types and duration (month) of renal replacement therapies of children were recorded. Paleness, tachypnea, tachycardia, and presence of edema in the physical examination was recorded. The systolic and diastolic blood pressure of HD patients were measured before dialysis and during routine outpatient examinations in PD patients in a sitting position with a cuff appropriate for their arm using an electronic oscillometric device. Blood sampling, and echocardiographic and BIA calculations were performed before dialysis in the HD patients, when the abdomen was empty in PD patients, during routine follow-up in the predialysis group and early in the morning in the control group. Plasma levels of NT-proBNP were measured before and after each HD session.

Ethics

The study is compliant with ethical standards. Ethics board approval of Ondokuz Mayıs University Faculty of Medicine was granted (24.11.2011, Decree no: 2011/443) and the study was supported by Ondokuz Mayıs University Scientific Research Projects Commission (Project code PYO. TIP.1901.12.019). The study was initiated after the study content was clearly explained to the parents of all children (patients and controls), and informed consent was provided.

BIA evaluation

We applied the Body Composition Monitor (BCM, Fresenius Medical Care) using multi-frequency bioimpedance spectroscopy (BIS) in order to assess the hydration status. The children were laid on a non-conductive surface, and metal jewelry was removed. Skin cleansing was performed before the procedure and two electrodes were then fixed on the dorsal surfaces of one foot and hand on the same side, vertical to the extremity axis, as described in the operator's manual. Contact of the upper extremities and body and lower

extremities with one another was avoided during the procedure. The device connection was enabled with these electrodes. Calculations were completed in 1 to 4 min after the data of sex, height (cm), body weight (kg), and blood pressure (systolic and diastolic as mm Hg) of each child were recorded. Body composition analysis was performed using the Fluid Management Tool version 3.2.11. The calculations were repeated by re-replacement of electrodes when the required data quality could not be provided. Accordingly, the parameters (overhydration (OH), relative fluid load (OH/ECW %), total body water (TBW) (l), ECW (l), intracellular water (ICW) (l), the ratio of ECW to ICW (E/I)) were recorded.

NT-proBNP evaluation

The blood samples were transferred to red-topped vacuum blood collection tubes and clotting was allowed to occur. Complete blood samples were centrifuged at +4°C for 5 min for 4000 cycles/min on Jouan C4i (France) centrifugation apparatus for degradation of serum after blood clotting. The obtained sera were transferred to Eppendorf tubes and preserved in a –20°C freezer. Kits and serum samples were heated to +25°C room temperature before initiation of the study. Serum NT-proBNP levels were determined using VIDAS PC apparatus (bioMérieux, France) and NT-proBNP commercial kits with enzyme-linked fluorescent assay (ELFA) in the research laboratories of Ondokuz Mayıs University Faculty of Medicine. The results were specified as pg/ml. The analytic calculation reference range of NT-proBNP kit was 20–25 000 pg/ml. The study was performed in accordance with the manufacturer's instructions.

Echocardiographic evaluation

M mode and 2 dimensional calculations were performed using 3.5 and 5.5 MHz probes appropriate to the children's age in a lying position after rest (10–30 min) using a Toshiba Aplio SSA-770 Cardiac Imaging system echocardiography device. Left atrium diameter (LAD), left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), left ventricular ejection fraction (EF) (%), left ventricular shortening fraction SF (%), left ventricular mass index (LVMI), and left ventricular mass (LVM)/height$^{2.7}$ were calculated using the Devereux formula (LVM = 1.04 × ((PWT + IVST + LVDd)^3 – (LVDd)^3) – 13.6)). Calculations higher than 39.36 g/m$^{2.7}$ in boys, and 36.88 g/m$^{2.7}$ in girls were considered as left ventricular hypertrophy. Mitral valve early diastolic flow rate to late atrial filling velocity ratio (E/A) was recorded on Doppler examination for evaluation of diastolic dysfunction.

Statistical analysis

Analyses were done using IBM SPSS Statistics 22.0 (SPSS IBM Corp, Armonk, New York, USA). Compatibility of variables was investigated using visual (histogram and probability diagrams) and analytic (Shapiro-Wilk) tests. The characteristics of patient and control groups were determined using descriptive statistics. Parameters compatible with a normal distribution were defined as mean ± standard deviations (SD), and parameters that did not fit a normal distribution were defined as median and distribution (lower-upper limit). The nonparametric variable of NT-proBNP was log transformed for analysis. We used the parametric variant analysis ANOVA for comparison of more than two groups, and the nonparametric variant analysis Kruskal-Wallis test for parameters that did not show a normal distribution. In HD patients, the paired t-test was used to assess measurements of log NT-proBNP obtained before and after HD. The correlation coefficients and statistical significance between intergroup variables were calculated using Pearson's correlation test or Spearman's test. The effect of independent variables on dependent variables was evaluated using regression analysis. The *p*-values smaller than 0.05 were considered as statistically significant.

Results

Baseline characteristics of the study population

Table I summarizes the baseline characteristics of the total study population as well as patient subgroups. The main frequent cause of CKD was congenital kidney abnormalities (54.3%), followed by nephronophthisis (20%). There was no statistically significant difference considering age, sex, body weight, and BSA between the HD, PD, predialysis patients and controls; a significant difference was detected between the systolic and diastolic blood pressure levels ($p < 0.001$, $p < 0.001$ respectively). Accordingly, systolic blood pressure of the HD and PD groups was significantly higher compared with the control group ($p = 0.002$, $p = 0.002$, respectively); and the diastolic blood pressures of PD, HD and predialysis groups were significantly higher compared with the control group (PD control $p = 0.002$; HD control $p = 0.04$; predialysis control $p = 0.015$).

The highest NT-proBNP levels were detected in the HD group, and a significant increase was detected in HD and PD groups compared with the controls (HD control $p < 0.001$; PD control $p < 0.001$) (Figure 1). Although the log NT-proBNP level of the predialysis group was found to be increased compared with the control group, the difference was not statistically significant ($p = 0.08$).

Table I. Baseline clinical characteristics and results of NT-proBNP, BIA and echocardiographic data of the study cohort

Variables	HD group (n = 13)	PD group (n = 12)	Predialysis group (n = 10)	Control group (n = 30)	P-value
Age [years]	11.92 ±3.13	11.42 ±3.18	10.50 ±2.27	10.11 ±3.74	0.366
Boys/girls	7/6	4/8	7/3	14/16	0.372
Dialysis vintage [months]	11 (7–60)	33.50 (6–79)	–	–	0.068
Weight [kg]	35.44 ±12.71	31.95 ±12.48	40.65 ±13.84	35.83 ±16.48	0.595
BSA [m^2]	1.17 ±0.32	1.09 ±0.29	1.23 ±0.31	1.13 ±0.35	0.772
Urine output [ml/day]	300 (10–1000)	150 (50–2500)	1530 (1200–4400)	–	< 0.00[de]
Systolic blood pressure [mm Hg]	123.6 ±16.9	124.1 ±19.2	117.2 ±12.2	106 ±10.5	< 0.001[ab]
Diastolic blood pressure [mm Hg]	80 (60–100)	77.5 (60–100)	80 (60–87)	60 (46–82)	< 0.001[abc]
NT-proBNP [pg/ml]:					
NT-proBNP	4576 (112–80324)	3783 (323–13540)	230 (20–47604)	26 (20–151)	< 0.001[ab]
Log NT-proBNP	3.66 (2.05–4.90) Pre-HD: 3.63 ±0.84 Post-HD: 3.64 ±0.92	3.57 (2.51–4.13)	2.35 (1.3–4.68)	1.41 (1.2–2.18)	< 0.001[ab]
BIA parameters:					
OH [l]	1.77 ±1.72	1.04 ±1.30	0.34 ±0.95	–0.02 ±0.48	< 0.001[abd]
Rel OH (%)	15.1 ±14.59	7.69 ±13.04	0.19 ±12.06	–0.52 ±5.17	< 0.001[ad]
TBW [l]	21.47 ±8.36	17.38 ±8.31	21.59 ±8.87	19.52 ±7.93	0.532
ECW [l]	10.04 ±3.88	8.04 ±3.98	9.46 ±3.89	8.50 ±3.51	0.447
ECW/ICW	0.89 ±0.18	0.85 ±0.12	0.78 ±0.58	0.76 ±0.04	0.002[ad]
ECW/TBW	0.46 ±0.05	0.45 ±0.03	0.43 ±0.02	0.43 ±0.01	0.003[a]
Echocardiographic examination (systolic-diastolic functions):					
LAD [mm]	32.98 ±5.53	30.95 ±5.28	30.53 ±2.87	25.78 ±3.51	< 0.001[abc]
LVEDD [mm]	46.57 ±8.74	42.73 ±7.21	43.48 ±7.99	40.6 ±5.09	0.084
LVESD [mm]	31.01 ±9.81	27.27 ±6.51	27.67 ±7.09	25.96 ±3.13	0.131
LVMI [$g/m^{2,7}$]	95.29 ±24.59	85.21 ±22.32	63.03 ±15.53	31.62 ±9.64	< 0.001[abcde]
LVEF (%)	65.90 (31.1–77.9)	70.10 (45.2–77.5)	67.65 (46.6–76.9)	66.70 (56.5–73.9)	0.739
LVSF (%)	36.80 (14.9–45.8)	39.60 (22.6–44.7)	37.5 (23.7–45.2)	36.60 (28.7–42.3)	0.720
E/A	1.64 ±0.35	1.54 ±0.65	1.81 ±0.70	2.01 ±0.41	0.005[ab]

Data are presented as means ± standard deviations (x ± SD) or as median with range. P < 0.05 was considered significant. NT-proBNP – N-terminal proB-type natriuretic peptide, OH – absolute fluid overload (AFO), Rel OH – relative fluid overload (RFO) is defined as the AFO to ECW ratio, ECW – extracellular water, ICW – intracellular water, TBW – total body water, LAD – left atrial dimension, LVEDD – left ventricular end-diastolic diameter, LVESD – left ventricular end-systolic diameter, LVMI – left ventricular mass index, LVEF – left ventricular ejection fraction, LVSF – left ventricular shortening fraction, E/A – mitral E wave to A wave ratio. [a]Significant difference between HD and control group. [b]Significant difference between PD and control group. [c]Significant difference between predialysis and control group. [d]Significant difference between HD and predialysis group. [e]Significant difference between PD and predialysis group.

The measurements of log NT-proBNP levels before and after HD are shown in Figure 2. Our results show that there were no significant changes in log NT-proBNPs after HD ($p = 0.76$).

Table I shows the parameters obtained using BIS. HD patients had a significantly higher hydration status by BIS. The OH value was significantly higher in the HD group compared with the PD and control groups; the Rel OH value was significantly higher in the HD group compared with the predialysis and control group, and the E/I and ECW/TBW ratios were significantly higher in the HD group compared with the control group. A statistically significant difference was detected between the groups considering the LAD, LVMI and E/A ratio ($p < 0.001$, $p < 0.001$, $p = 0.005$, respectively). LAD and LVMI were higher in the HD, PD, and predialysis groups compared with the control group. A significant decrease was detected in the E/A ratio in the HD and PD group compared with the control group (HD control $p = 0.039$; PD control $p = 0.01$) (Table I).

Correlations between NT-proBNP and other baseline variables

NT-proBNP was found to be positively correlated with diastolic blood pressure ($r = 0.460$, $p < 0.001$), OH ($r = 0.483$, $p < 0.001$), Rel OH ($r = 0.448$, $p < 0.001$), E/I ($r = 0.410$, $p = 0.001$), and ECW/TBW ($r = 0.391$, $p = 0.001$).

Whereas a positive correlation was detected between NT-proBNP and LAD and LVMI ($r = 0.571$, $p < 0.001$, $r = 0.793$, $p < 0.001$, respectively), a negative correlation was detected between NT-proBNP and E/A ($p < 0.001$, $r = –0.474$) (Figure 3).

Multivariate regression analysis included NT-proBNP as the dependent variable and diastolic blood pressure, BIA parameters and systolic–diastolic cardiac functions that were previously identified in univariate analyses as independent variables. As shown in Table II, LVMI and LAD were independently associated with NT-proBNP (adjusted R^2 of the model: 0.707, $p < 0.001$).

Discussion

In the current study, we found higher baseline plasma concentrations of NT-proBNP in a cohort of pediatric chronic dialyzed patients. We show concentrations of NT-proBNP to be correlated with LV systolic and diastolic dysfunction and fluid overload as assessed by bioimpedance. After adjustment for known clinical variables, NT-proBNP concentration was found to have an independent effect on both LAD and LVMI. We investigated, in addition, the acute effect of a HD session on plasma NT-proBNP and observed no significant change.

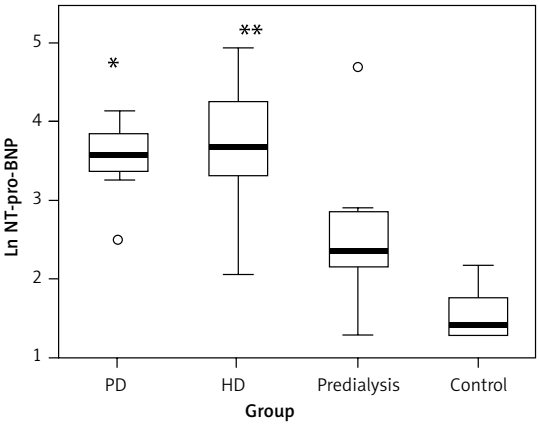

Figure 1. Ln NT-pro-BNP levels of groups. Ln NT-pro-BNP level = log N-terminal pro-brain natriuretic peptide

**p < 0.001 (p-value between PD vs. control groups), **p < 0.001 (p-value between HD vs. control groups).*

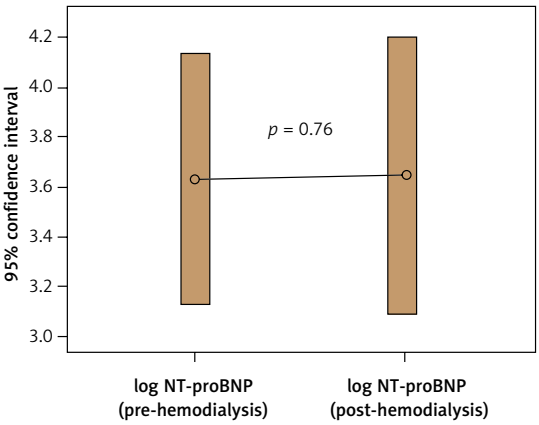

Figure 2. Comparison of the log NT-proBNP levels in pre- and post-hemodialysis patients

Natriuretic peptides are involved in the regulation of blood pressure and body fluid homeostasis. They are mainly synthesized by cardiac myocytes against increased wall stress and separated as BNP and NT-proBNP after secretion as prohormones. Many studies have demonstrated that the normal reference range of BNP and NT-proBNP levels may vary regarding age, sex, the kit used for the calculation and measurement method because there is no standardized calculation method for determining serum levels of natriuretic peptides [29–31]. We decided to measure NT-proBNP, as it is a larger peptide with a longer half-life, and so less likely to be affected by dialysis. In addition, BNP is less stable than NT-proBNP in vitro, especially if analysis is delayed.

Recent studies have revealed the strong association between natriuretic peptides and left ventricular hypertrophy and systolic dysfunction [32–36]. As such there has been debate in the published literature as to whether measurement of NT-proBNP can add value in aiding clinical judg-

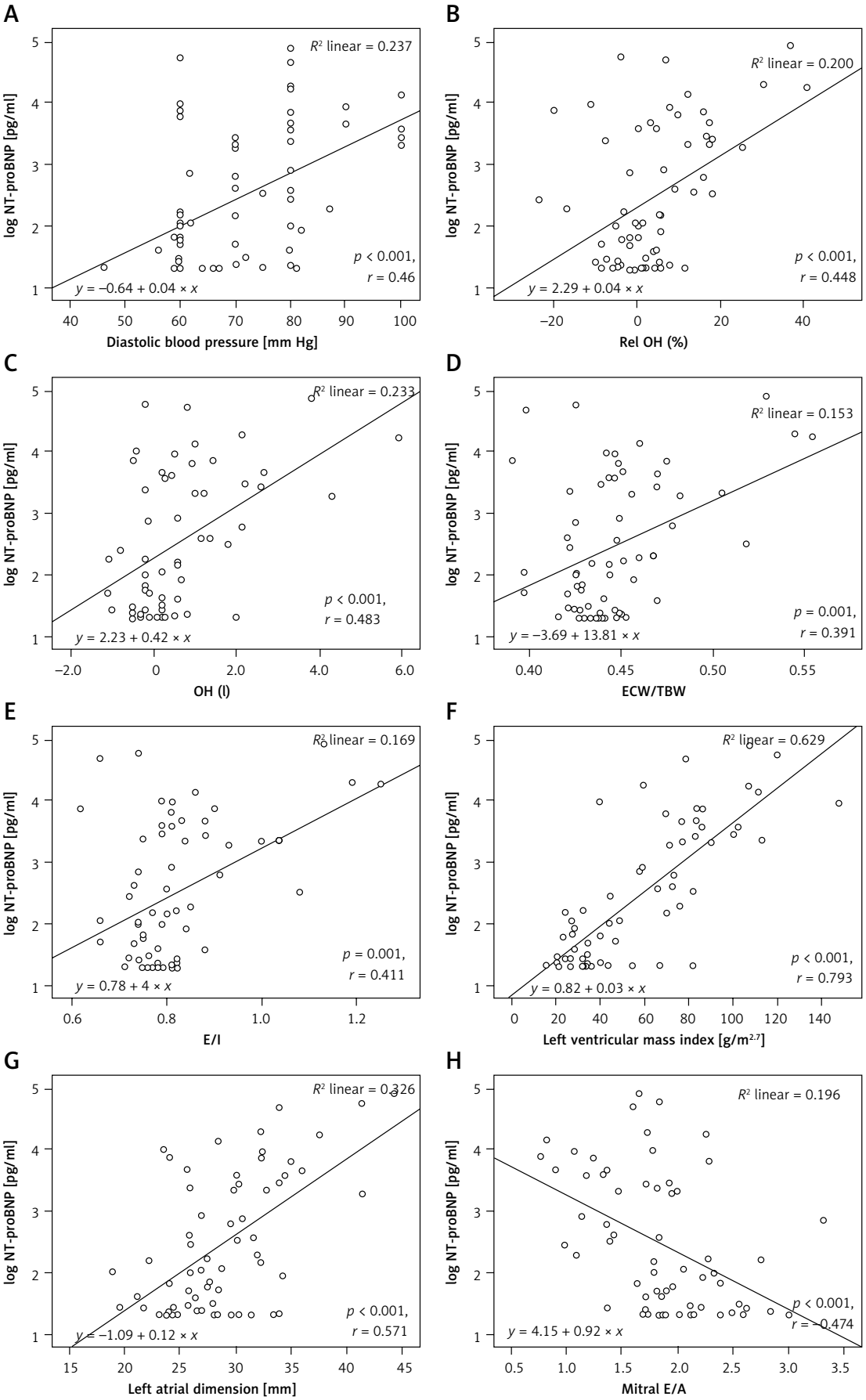

Figure 3. Correlation of log NT-pro-BNP level with diastolic blood pressure (**A**), Rel OH (**B**), OH (**C**), ECW/TBW (**D**), E/I (**E**), LVMI (**F**), LAD (**G**), mitral E/A (**H**)

Table II. Stepwise regression analysis using log NT-proBNP level as a dependent variable

Variable	β	Standard error	*P*-value
LVMI [g/m^2]	0.402	0.005	0.003
LAD [mm]	0.263	0.024	0.018

Selected variables: diastolic blood pressure, OH, Rel OH, ECW/ICW, ECW/TBW, mitral E/A, LAD, LVMI.

ment of volume status [24, 37] or left ventricular dysfunction [38, 39]. On the other hand, some reports of NT-proBNP measurements have shown no association with left ventricular mass index or volume load [19, 25, 29]. Kumar *et al.* [40] measured NT-proBNP in 366 stable outpatients undergoing hemodialysis with a corresponding pre- and post-dialysis multifrequency bioimpedance assessment of extracellular water and they reported that serial NT-proBNP values may aid clinical assessments of volume status in patients undergoing dialysis. Ouali *et al.* [41] identified a significant correlation between BNP concentrations and left ventricle functions in patients with CKD undergoing hemodialysis.

Our study showed that NT-proBNP levels were higher in HD and PD patients compared to the control group. NT-proBNP level is considered to be more directly influenced by kidney function [20, 21]. Though NT-proBNP increases progressively along with the diminishing glomerular filtration rate, the increase is proportionally higher for HD and PD groups. Although NT-proBNP levels were increased in the predialysis group compared with the control group, no statistically significant difference was found ($p = 0.08$). This statistical insignificance might be due to the limited number of predialysis patients in our study. Also we observed no significant change in plasma NT-proBNP values after a single HD session; this may be a reflection of the fact that patients tend to have shorter dialysis sessions, and as such may fail to achieve normovolemia.

Multifrequency bioimpedance measurement has been suggested as a reliable noninvasive technology for estimating body water compartments in adults [13–15]. Also, its application in pediatric dialysis has been advocated [16]. Some authors consider multifrequency bioimpedance technology as a promising approach in body water compartment estimation [13, 17, 25]. In recent years, data obtained by its application in dialyzed children and adolescents and in pediatric nephrotic syndrome have been reported [16, 42]. Using multifrequency bioimpedance, we identified that OH, ECW/ICW, and ECW/TBW were increased in the HD and PD groups compared with the control group. However, no significant difference was seen in TBW or ECW levels among all the groups. In a recent study, Milani *et al.* [18] studied 16 young patients undergoing dialysis and assessed TBW and ECW volumes using multifrequency bioimpedance and deuterium-bromide dilution as reference tests. They concluded that multifrequency bioimpedance measurements could not precisely estimate TBW and ECW in children receiving dialysis.

The results of the present study revealed that LAD and LVMI were significantly higher in HD, PD and predialysis patients compared with the control group whereas E/A ratio was significantly lower in the HD-PD group compared with the controls. There was no significant difference between the groups considering EF and SF levels, which are indicators of left ventricular systolic functions [43, 44]. In our study we found that diastolic functions are affected much earlier than suggested by several previous studies [43, 45]. We found a positive correlation between levels of NT-proBNP and OH, Rel OH, ECW/ICW, LAD, and LVMI and an inverse correlation with E/A ratio. These results are in accordance with the experience in recent reports [38–41]. However, other studies failed to detect a positive association between fluid removed and change of NT-proBNP in patients receiving dialysis [19, 25, 29] suggesting that this mechanism needs to be further elucidated. We identified that high levels of NT-proBNP ($p < 0.001$) were a significant independent risk factor for the increase of LVMI.

It is important to interpret our findings within the context of the study limitations. This study is limited by a relatively small cohort size and a lack of long-term, longitudinal follow-up. For the purpose of our study, no additional follow-up or gold standard measure of fluid overload, namely deuterium dioxide dilution, was used due to ethical concerns about repeated blood sampling in children. It is also important to note that our data represent a single center report. Finally, our findings represent associations, and further studies are needed to evaluate whether implementing NT-proBNP would improve outcomes. Despite these limitations, this pediatric study shows the correlation between NT-proBNP and volume status, as well as LAD and LVMI.

In conclusion, assessment of NT-proBNP appears as a promising diagnostic and prognostic tool in dialysis and predialysis patients. We believe that the use of NT-proBNP from the early stages of CKD is a simple and applicable method for close follow-up and prognosis. When NT-proB-

NP values are significantly elevated, a suggested approach might be to assess the volume status exactly using both clinical and additional evaluation methods. In case of persistent and significant elevations despite adequate management of overhydration, patient referral for further cardiac evaluation should be considered. However, studies are needed to establish whether this approach results in improved outcome of dialysis patients. Moreover, reference values for dialysis patients should be validated in future studies.

Conflict of interest

The authors declare no conflict of interest.

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