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Elevated Pro-Brain Natriuretic Peptide, Troponin T and Malnutrition Inflammatory Score in Chronic Hemodialysis Patients with Overt Cardiovascular Disease

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Key Words
Pro-brain natriuretic peptide · Troponin T · Inflammation · Malnutrition · Malnutrition inflammatory score · Hemodialysis · Cardiovascular disease · End-stage renal disease

Abstract
Background: We assessed the relationship between pro-brain natriuretic peptide (pro-BNP), troponin T (TropT) and nutritional status. ***Methods:*** A total of 48 chronic hemodialysis patients were grouped according to the presence [group A (GA); n = 24] or not [group B (GB)] of cardiovascular disease. ***Results:*** Compared to GB subjects, GA subjects were older, had been on hemodialysis for a longer period and had higher prevalences of vascular grafts, hypertension and elevated C-reactive protein (CRP) [GA vs. GB: 1.1 (range 0.1–32.9) vs. 0.4 (0–28.1) mg/dl; p = 0.028], malnutrition inflammatory score (MIS) (GA vs. GB: 7.50 vs. 4.00; p = 0.001), pro-BNP [GA vs. GB: 6,760 (601–103,200) vs. 686 (75–83,700) pg/ml; p < 0.001] and TropT [GA vs. GB: 0.3650 (0.011–0.199) vs. 0.010 (0.0–0.290) ng/ml; p = 0.002]. Pro-BNP correlated with TropT (rho 0.539; p < 0.001), MIS (rho 0.502; p < 0.0001), homocysteine (rho 0.321; p = 0.13) and CRP (rho 0.511; p < 0.0001). Pro-BNP levels were lower in GB patients as the body mass index increased; the opposite occurred in GA. ***Conclusions:*** Patients with cardiovascular disease had elevated pro-BNP and TropT levels. In patients without cardiovascular disease, malnutrition and inflammation were associated with vascular prostheses, while pro-BNP was lower in obese patients.

Introduction

Although chronic hemodialysis has been employed for the treatment of end-stage renal disease for the last 40 years, the mortality rate remains unacceptably high. Cardiovascular disease causes more than 50% of deaths in this population [1–5]. However, the prevalence of malnutrition is also elevated in hemodialysis patients, varying between 23 and 73% according to different studies and contributing to the morbidity and mortality of this population [6–12]. Moreover, the low protein intake and a low body weight are strong predictors of mortality [9, 13, 14]. Albumin is currently being used to assess the nutritional

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Table 1. Causes of renal failure

Cause of renal failure	GB	GA	OR (95% CI)	p (χ^2)
Diabetes mellitus				
n	3	5	1.84	0.35[a]
% of CRF cases	37.5	62.5	(0.32–11.51)	
Glomerulonephritis				
n	8	3	0.29	0.169
% of CRF cases	72.7	27.3	(0.05–1.48)	(1.89)
Nephroangiosclerosis				
n	6	12	3	0.136
% of CRF cases	33.3	66.7	(0.76–12.31)	(2.22)
Interstitial nephritis				
n	1	0	0	0.5[a]
% of CRF cases	100	0	(0–17.9)	
Obstructive uropathy				
n	1	0	0	0.5[a]
% of CRF cases	100	0	(0–17.9)	
Polycystic kidney disease				
n	5	4	0.76	0.5[a]
% of CRF cases	55.6	44.4	(0.14–3.99)	

CRF = Chronic renal failure; OR = odds ratio; CI = confidence interval.

[a] Calculated by Fisher's test.

status of dialyzed patients and is also considered a strong predictor of mortality [11, 15]. However, although it reflects visceral protein reserves, its synthesis, catabolism and distribution are also affected by nonnutritional factors, such as hydration state, capillary permeability, renal and dialysis losses, inflammation and comorbidities [16]. Therefore, integral nutritional scores are preferred to assess malnutrition. In our institution, the malnutrition inflammatory score (MIS) is employed [17].

The *combination* of malnutrition and inflammation produces the most deleterious effects on clinical outcome. Inflammation stimulates muscular proteolysis and catabolism and inhibits repairing mechanisms, leading to sarcopenia, muscle mass loss and consequently low serum creatinine levels [18–21]. Inflammation is also associated with an increase in atherogenesis. Elevated C-reactive protein (CRP) concentrations are associated with cardiovascular disease and predict a higher mortality rate in hemodialysis patients [22, 23]. Finally, the cardiovascular disease risk increases as a consequence of a milieu of inflammation and malnutrition, and cardiac biomarkers are increased due to cardiac parietal stress, vascular remodeling, chronic myocardial ischemia and endothelial dysfunction [24].

We studied different inflammatory, nutritional and cardiovascular biomarkers in patients on chronic hemodialysis, with a particular focus on pro-brain natriuretic peptide (BNP), troponin T (TropT), homocysteine, MIS and body mass index (BMI) subgroups and their associations with cardiovascular disease in this population.

Methods

Design

This was a cohort, transversal, prospective, observational, comparative study of 48 chronic hemodialysis patients.

Patients

The Institutional Review Board of the Hospital Británico de Buenos Aires was notified about the collection of data for the present study. Informed consent was obtained from each patient enrolled. Forty-eight chronic hemodialysis patients who had had more than 3 months of treatment were included. Patients under the age of 18 or over 85, or with a history of neoplasia, drug abuse, active vasculitis, hepatopathy, untreated hypothyroidism or BMI >40 were excluded. No patients were positive for HIV, HVB or HCV. No failed transplant patients were included. Mean age was 59.21 ± 17.35 years (range 26–85), and the average time on hemodialysis was 63 ± 16.98 months (range 5–78).

The causes of chronic renal failure in these patients are listed in table 1. Six of the 8 diabetic subjects were on insulin therapy.

Patients were divided into two groups according to the presence of cardiovascular disease. Group A (GA) included subjects with cardiovascular disease (n = 24), while group B (GB) subjects had no cardiovascular disease (n = 24). Cardiovascular disease was defined as the presence of cardiac ischemic disease and/or peripheral vascular disease and/or cerebrovascular disease, based on clinical findings, imaging and laboratory results. Of the GA patients, 10 had a previous history of acute myocardial infarcts, 5 had chronic cardiac ischemic disease, 4 had heart failure, 3 had cardiac arrhythmias treated with definitive pacemakers and 2 had a previous history of cerebrovascular disease.

Most of the patients were on angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, aspirin and other drugs commonly used in stage 5 chronic renal disease, such as calcium salts, potassium chelators, erythropoietin, intravenous L-carnitine, intravenous iron, statins, omeprazole, folic acid, vitamins and benzodiazepines.

The variables taken into account were age, time on hemodialysis, cause of renal disease, gender, types of vascular access, hypertension, CRP, hematocrit, creatinine, cholesterol, albumin, MIS, homocysteine, folic acid and vitamin B12 levels, pro-BNP, TropT and mean intradialytic ultrafiltration rate. In subgroup analyses, BMI was also considered. Nutritional assessment was performed using the MIS [25, 26], which was updated in our center every 3 months, while the anthropometric measurements were obtained at the end of a dialysis session at the end of the respective trimester. Hematocrit and serum concentrations of creatinine,

cholesterol and albumin were measured by routine procedures. High-sensitivity CRP was calculated by immunoturbidimetry (Vitros 5.1®, Johnson and Johnson, N.J., USA). Homocysteine was measured by fluorescence polarization immunoassay, and folic acid and vitamin B12 by radioimmunoassay. For pro-BNP, a chemoluminiscence method was used (Vitros ECi®, Johnson and Johnson; normal values: <125 pg/ml for subjects <75 years, <450 pg/ml for subjects older than 75 years). TropT was measured by electrochemoluminiscence (Cobas e411, Roche Diagnostics, Indianapolis, Ind., USA; normal value: <0.01 ng/ml). Blood was drawn while subjects were fasting prior to the hemodialysis session. All biochemical measurements were performed at the Central Laboratory of the Hospital Británico.

Hemodialysis

Thrice weekly hemodialysis sessions were performed using biocompatible membranes (Polyflux 10L®, Gambro, Sweden) and a bicarbonate bath, with a mean blood flow of 450 ± 50 ml/min and dialysate flow of 500 ml/min. The mean duration of each session was 4.0 ± 0.5 h. The ultrafiltration rate employed in this study was that registered when the blood samples were collected.

Arteriovenous Accesses

Arteriovenous access was a fistula in 29 patients (60.4%), polytetrafluoroethylene (PTFE) grafts (Gore-tex® vascular graft, W.L. Gore and Associates Inc., USA) in 12 patients (25%) and tunneled catheters (Tesio®, Medcomp, Pa., USA, or Quinton® Permcath™, Covidien AG, Mansfield, Mass., USA) in 7 patients (table 2). The use of a catheter instead of a PTFE graft was due to poor quality of arterial or venous vessels in the upper limbs as assessed by Doppler ultrasound (GA: 2 patients; GB: 3 patients) or secondary failures of PTFE grafts (GB: 2 patients).

Hypertension

Patients with blood pressure >140/90 mm Hg were considered to be hypertensive (n = 27, 56.3%) and were treated pharmacologically.

Statistics

Results are expressed as the median (range), unless indicated otherwise. Fisher's exact test or the χ^2 test were employed for categoric variables. For continuous variables, the Mann-Whitney test was used, and for intervariable correlations, Spearman's rank and rho coefficients were calculated. p values <0.05 were considered significant.

Results

The patients had a mean age of 64 ± 15 years, mean time on hemodialysis of 63 ± 19 months, mean Kt/V of 1.2 ± 0.2, overall MIS of 6.37 ± 3.79 and mean BMI of 26.87 ± 3.92. In GA versus GB subjects, median age was 69.5 (42–84) versus 63.5 (26–85) years (p = 0.05), time on hemodialysis was 29.0 (5–78) versus 15.5 (5–65) months (p = 0.041) and Kt/V was 1.23 ± 0.1 versus 1.21 ± 0.1. Residual renal function was not different between the two groups. The different causes of chronic renal failure in the study subjects are detailed in table 1. Four patients from GA and 2 from GB had no residual renal function. With respect to gender, no significant differences were found between the two groups. The overall distribution of the most prevalent type of vascular access, i.e. arteriovenous fistula (AVF) versus PTFE graft, is depicted in table 2. The analysis of possible associations with cardiovascular risk showed that in GA, there was a significantly higher number of patients with PTFE grafts ($p < 0.014$). In addition, hypertension was more common in GA (hypertensive subjects in GA vs. GB: 18 vs. 9; χ^2 p = 6.857, p = 0.009). Medications prescribed were not different between the groups. Relationships between variables are shown in table 3. Correlations are described in table 4.

Stratified subanalyses were performed and are shown in tables 5 and 6. In table 7, rates of AVF were compared to vascular prostheses, namely PTFE plus tunneled catheters (GA: 12 vs. 12; GB: 17 vs. 7), and significant differences were found with respect to malnutrition scores and inflammatory state in patients with prostheses compared to those with AVFs in both groups, and pro-BNP levels were higher, albeit not significantly so, in subjects with native fistulae in GA.

Table 2. Types of access: intergroup comparisons

Type of access	GB	GA	Total
AVF			
n	17	12	29
%	58.6	41.4	100
PTFE			
n	2	10	12
%	16.7	83.3	100
Catheter			
n	5	2	7
%	71.4	28.6	100
Total			
n	24	24	48
%	50	50	100

$\chi^2 = 6.008$; AVF versus PTFE: p = 0.014.

Discussion

In the present study, we found that chronic hemodialysis patients with cardiovascular disease had elevated levels of pro-BNP and TropT compared to patients with-

Table 3. Relationships between the different variables

Variable	Group	95% Confidence interval		Median	Standard deviation	p (U)
		lower limit	upper limit			
CRP, mg/dl	GB	–0.56	4.26	0.40	5.71	0.028
	GA	0.30	5.99	1.10	6.74	(182)
Hct, %	GB	28.79	32.96	31.0	4.95	0.893
	GA	29.02	33.73	31.0	5.59	(281.5)
Creatinine, mg/dl	GB	5.15	8.60	5.62	4.09	0.155
	GA	4.22	6.15	4.62	2.28	(219)
Cholesterol, mg/dl	GB	161.12	197.97	171.0	43.63	0.599
	GA	154.95	190.89	168.0	42.56	(262.5)
Albumin, g/dl	GB	3.35	3.96	3.80	0.72	0.352
	GA	3.37	3.80	3.60	0.51	(243)
MIS	GB	3.39	6.27	4.0	3.41	0.001
	GA	6.41	9.43	7.50	3.57	(125.5)
UF, l/day	GB	1.54	2.44	1.80	1.07	0.373
	GA	1.73	2.30	2.0	0.67	(245)
Hcy, μM	GB	16.26	20.54	18.95	5.06	0.226
	GA	17.76	22.96	19.52	6.16	(234)
Pro-BNP, pg/ml	GB	–1,806.58	12,943.2	686.0	17,465.2	<0.001
	GA	4,261.37	22,290.3	6,760.0	21,348.1	(91)
TropT, ng/ml	GB	0.01	0.06	0.0100	0.06	0.002
	GA	0.03	0.06	0.0365	0.042	(139.5)

U = U of the Mann-Whitney test; Hct = hematocrit; UF = ultrafiltration rate; Hcy = homocysteine.

out cardiovascular disease; in addition, patients in the former group were significantly older, had a longer history of hemodialysis, higher prevalences of hypertension and vascular grafts and displayed a more severe inflammatory pattern and malnutrition state. Patients with normal BMI presented a worse nutrition status as assessed by the MIS score. In patients without cardiovascular disease, malnutrition was more common in patients with vascular grafts, while pro-BNP levels were lower in obese patients.

There is an undeniable relationship between renal failure and cardiovascular risk [27, 28]. However, many large, randomized controlled trials have failed to show that increasing dialysis dose or nutrition delivery, correcting anemia or hypercholesterolemia or reducing vascular remodeling would add any patient survival benefit [29–34]. Finally, in the hemodialysis population, Framingham risk factors for cardiovascular disease only partially explain this phenomenon [35, 36].

We found that the degree of malnutrition was independent of BMI. Patients with cardiovascular disease and BMI <25 (range 18–24.9) presented a higher MIS (table 5). In GB (table 6), the nutritional status was worse in those patients who had vascular grafts, and there was also a trend towards a more inflammatory milieu. As MIS diminished and nutritional status improved, a negative correlation was found with CRP, hematocrit levels, albumin, creatinine and cholesterolemia (table 4). We were unable to show any significant correlation between higher CRP levels and pro-BNP or TropT with respect to the kind of vascular access (table 6), as described by others [37], when AVFs were compared with PTFE grafts. However, when catheters were included with PTFE grafts as a group and compared with AVFs, CRP levels were higher and a more severe malnutrition assessment was determined in patients with cardiovascular disease, coupled with a trend towards elevated pro-BNP levels in patients with fistulae (table 7). In GB, patients with prostheses showed the same inflammatory and malnutrition profile, while pro-BNP levels were similar and much lower than in GA. This could be related to a worse clinical condition when prostheses are employed, particularly in patients with catheters, who are more labile and clinically unstable and have a greater predisposition to infections and inflammation.

Table 4. Spearman correlation analysis

	Pro-BNP	TropT	Hcy	MIS	CRP	Hct	Creat	Chol	Alb
UF									
rho	0.135	0.338	0.165	0.148	0.020	0.071	0.095	0.009	0.110
p	0.179	0.009	0.132	0.158	0.446	0.316	0.260	0.475	0.228
Pro-BNP									
rho		0.539	0.321	0.502	0.199	–0.138	0.022	–0.074	–0.147
p		0.000	0.013	0.000	0.087	0.174	0.441	0.308	0.159
TropT									
rho	0.539		0.322	0.317	0.160	–0.028	0.075	–0.177	–0.006
p	0.000		0.013	0.014	0.138	0.426	0.305	0.114	0.484
MIS									
rho	0.502	0.317	0.145		0.511	–0.236	–0.358	–0.105	–0.253
p	0.000	0.014	0.162		0.000	0.053	0.006	0.239	0.042
Hcy									
rho	0.321	0.322		0.145	0.054	0.157	–0.007	0.101	0.128
p	0.013	0.013		0.162	0.358	0.143	0.480	0.248	0.192
CRP									
rho	0.199	0.160	0.054	0.511		0.143	–0.099	0.053	0.026
p	0.087	0.138	0.358	0.000		0.335	0.252	0.361	0.430
Hct									
rho	–0.138	–0.028	0.157	–0.236	–0.063		–0.188	0.217	0.240
p	0.174	0.426	0.143	0.053	0.335		0.100	0.069	0.050
Creat									
rho	0.022	0.075	–0.007	–0.358	–0.099	–0.188		0.015	0.154
p	0.441	0.305	0.480	0.006	0.252	0.100		0.460	0.148
Chol									
rho	–0.074	–0.177	0.101	–0.105	0.053	0.217	0.015		0.252
p	0.308	0.114	0.248	0.239	0.361	0.069	0.460		0.042

UF = Ultrafiltration rate; Hct = hematocrit; Creat = creatinine; Chol = cholesterol; Alb = albumin.

Interestingly, in patients without overt cardiovascular disease, subjects with normal BMI had the best nutritional status and lowest intragroup pro-BNP levels. In contrast, GB patients with normal BMI displayed the worst nutritional status and the highest pro-BNP levels. Finally, in this group, patients with low or high BMI presented with low pro-BNP levels (table 5). In this regard, a possible explanation could be the active and dynamic interaction between adipose tissue and pro-BNP molecules.

Pro-BNP, a 134-amino acid hormone secreted by the heart in response to chamber stretching, is excreted by the kidney and only scarcely removed by hemodialysis [38, 39]. Thus, pro-BNP levels are elevated in renal failure patients and further increased in the presence of hypervolemia and hypertension [39, 40]. Pro-BNP levels also increase with age and are inversely related to BMI, malnourishment and systolic function [41, 42]. Interestingly and unexpectedly, considering that pro-BNP is a biomarker of myocardial parietal stress, pro-BNP levels were not associated with a higher intradialytic ultrafiltration rate (table 5). This phenomenon could be explained by the fact that in patients with cardiovascular disease, water removal during hemodialysis is often lower because they have lower tolerance for ultrafiltration, or it may be due to better compliance as they cannot sustain fluid overload. With respect to pro-BNP and adipose tissue, it has been shown that adipocytes possess an increased number of membrane pro-BNP receptors that remove it from circulation, explaining why pro-BNP levels are not increased in obese patients through elevated adipocytic clearance

Table 5. Relationships between pro-BNP, BMI and MIS in GA and GB

	BMI		Pro-BNP, pg/ml		MIS	
	GA	GB	GA	GB	GA	GB
BMI						
<25	22.9 (8)	23.7 (9)	8,840 (8)	451 (9)	11 (8)*	4 (9)*
25–30	27.9 (14)	27.5 (6)	4,950 (14)	1,103 (6)	6 (14)	5 (6)
>30	30.9 (2)	32 (9)	9,185 (2)	659 (9)	6.5 (2)	4 (9)

Figures shown in parentheses are numbers of patients. * $p < 0.001$.

Table 6. Relationships between CRP, MIS, BMI, pro-BNP and vascular access

Access	GA				GB			
	CRP mg/dl	MIS	BMI	pro-BNP pg/ml	CRP mg/dl	MIS	BMI	pro-BNP pg/ml
AVF	1	6	26.75	11,220	0.4	4	26.5	659
PTFE	1.1	8	25.8	2,320	1	6	28.3	930
p	0.26	0.50	0.55	0.08	0.06	0.02	0.32	0.48

Table 7. Relationships between pro-BNP, CRP, MIS, BMI and native fistulae versus prostheses

Vascular access	GA				GB			
	CRP mg/dl	MIS	BMI	pro-BNP pg/ml	CRP mg/dl	MIS	BMI	pro-BNP pg/ml
AVF	1	6	26.75	11,220	0.4	4	26.5	659
Prosthesis (catheter or PTFE)	1.7	10	26.1	2,570	1.3	9	28.8	990
p	0.04	0.03	0.52	0.09	0.04	0.01	0.28	0.29

[43, 44]. In patients with cardiovascular disease, the opposite phenomenon appears to occur, probably because pro-BNP adipocytic clearance is functionally decreased due to a higher inflammatory state, because cardiac stress is proportionally higher than pro-BNP adipocyte depuration [43], or reduced secretion of natriuretic peptides from diminished myocardial hormone release or impaired synthesis occurs [45, 46]. Obese patients have circulating pro-BNP levels that are inappropriately low with respect to their hypertensive status. The loss of this protective mechanism could certainly predispose these patients to salt retention, adrenergic overstimulation and high blood pressure [47]. Finally, it has recently been shown that natriuretic peptides bind to their receptors on adipocytes, thus inducing lipolysis [48]. Therefore, low natriuretic peptide levels may lead to reduced lipolysis, contributing to volume and saline retention and perpetuating the obese state [43, 49]. After the recent interesting findings of Drechsler et al. [50] on adiponectin and cardiovascular events and mortality in diabetic hemodialysis subjects, which show that adiponectin levels correlate positively with pro-BNP and negatively with BMI and are associated with sudden death and stroke, we believe that further research is needed to unravel the role adipose tissue plays in end-stage renal disease. In that study, in agreement with our findings, it was found that as BMI

increases, pro-BNP and adiponectin levels decrease. Moreover, natriuretic peptide infusion appears to stimulate adiponectin concentrations [51].

With respect to TropT levels, they correlate with the prescribed ultrafiltration rate and with the MIS (table 4). The value of TropT as a predictor of mortality in renal failure patients is well established [52–54], in contrast to pro-BNP [55, 56]. The correlation between TropT, ventricular mass and cardiac function is less clear [57, 58].

Homocysteine levels were not different between the two groups due to the fact that all patients were on folic acid and vitamin B12 supplementation. However, despite vitamin treatment, a positive correlation was found between homocysteine and pro-BNP and TropT, other cardiovascular biomarkers (table 4). This could suggest that vitamin therapy could contribute to a better nutritional status, leading to homocysteine levels in both groups not higher than 20 μM (table 3).

These results must be interpreted with caution due to the small number of patients studied. Our findings suggest that when elevated, pro-BNP is a cardiovascular biomarker that presents a strong and positive correlation with malnutrition as assessed by MIS, and with inflammation. The previously reported lower mortality rates in obese hemodialysis patients may be related to low pro-BNP levels, which may be due to the impact of the higher adipocyte mass and its augmented clearance and is possibly counterbalanced by interactions with cardioprotective cytokines such as adiponectin. Patients with vascular grafts and tunneled catheters presented a higher degree of malnutrition and inflammation in both groups.

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