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In hemodialysis, adiponectin, and pro-brain natriuretic peptide levels may be subjected to variations in body mass index

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Abstract

Adiponectin exerts cardiovascular protective actions, although some studies have shown the opposite. In hemodialysis, obese subjects display lower mortality rates despite hypoadiponectinemia, while higher adiponectin concentrations correlate with an elevated cardiovascular risk in nonobese subjects. The aim of the study is to suggest that adiponectin level variations are associated with differences in the body mass index (BMI). The interplay between adiponectin and pro-brain natriuretic peptide (Pro-BNP) levels may vary according to body fat mass. Fifty-two chronic hemodialysis patients were divided into three groups. Group A, BMI<25 (n=20); Group B, BMI 25 to 30 (n=21), and Group C, BMI>30 (n=11). Diabetics: Group A 10%; Group B 6 29%; Group C 55%, P=0.027. Determinations: Adiponectin, Pro-BNP, insulin, insulin resistance (HOMA), troponin T, nutritional status, ultrafiltration rates, C-reactive protein (CRP), vascular accesses, and echocardiography. Group A: adiponectinemia positively and significantly correlated with Pro-BNP, CRP, and troponin T. As BMI increased, adiponectin, Pro-BNP, and malnutrition significantly decreased, while insulin, HOMA, and ultrafiltration rates significantly increased. Cardiac restriction was significantly higher in obese patients. In all groups, Pro-BNP and troponin T displayed a strong positive correlation. In low-BMI subjects, high Pro-BNP and adiponectin, low myocardial restriction, and worse nutritional status were prevalent. In obesity, hypoadiponectinemia stimulates cardiac remodeling, cardiac hypertrophy, and decreased stretching, rendering Pro-BNP levels low despite high ultrafiltration rates. Thus, adiponectin correlates inversely with BMI, probably playing different cardiovascular roles as BMI changes.

Key words: adiponectin, Pro-BNP, body mass index, malnutrition inflammatory score, insulin, hemodialysis, cardiovascular disease, restrictive cardiomyopathy

INTRODUCTION

Adiponectin is an adipokine with antiatherogenic properties.[1,2] Obesity, coronary artery disease, and diabetes are characterized by hypoadiponectinemia.[3–5] However, some studies have demonstrated that high rather than low adiponectinemia may be associated with adverse outcomes in diabetics and heart failure patients.[6–8]

Limited data exist on adiponectin levels in chronic dialysis patients. As highlighted recently by Drechsler et al., in advanced chronic kidney disease, the pattern and composition of risk is changing.[9] Although some studies have

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Table 1 Patient characteristics

Variable	Group A N=20 BMI<25	Group B N=21 BMI 25-30	Group C N=11 BMI>30	P
Age (years)*	59.9 ± 20.6	68.8 ± 11.6	65.2 ± 7.5	NS
Gender (males)	10 (50%)	17 (81%)	9 (82%)	NS
Time on HD (months)	26.9 ± 24.6	27.76 ± 22.6	29.55 ± 18.2	NS
Nephroangiosclerosis	7 (35%)	8 (38%)	4(36%)	NS
Glomerulonephritis	8 (57%)	3 (21%)	3 (27%)	NS
Diabetic nephropathy	2 (10%)	5 (24%)	2 (18%)	NS
PKD	2 (10%)	3 (14%)	2 (18%)	NS
Hypertensives	12 (60%)	14 (67%)	6 (56%)	NS
Diabetics	2 (10%)	6 (29%)	6 (55%)	0.027
CVD	11 (55%)	13 (62%)	4 (36%)	NS
Restrictive echocardiographic findings	8 (40%)	10 (48%)	9 (82%)	0.011

*Kruskall-Wallis test used; otherwise, the Pearson chi square test.
BMI=body mass index; HD=hemodialysis; PKD=polycystic kidney disease; CVD=cardiovascular disease; NS=nonsignificant.

shown a favorable and protective association between hyperadiponectinemia and cardiovascular disease in chronic kidney failure subjects,[10–12] others have found the opposite.[13] Hypoadiponectinemia and insulin resistance, typical findings in obese subjects, are associated with cardiac disease. Moreover, as addressed in chronic renal failure, there exists an inverse correlation between body mass index (BMI) and mortality, often called the *obesity paradox*.[14] In hemodialysis patients, obesity appears to confer a protective role[15,16] and obese patients tend to show a better nutritional profile, despite more severe cardiac abnormalities such as systolic and diastolic dysfunction.

We correlated adiponectin levels with insulinemia, with cardiac biomarkers and echocardiographic patterns, with nutritional scores and inflammatory markers, and try to explain the variations of adiponectinemia in relation to changes in BMI and cardiovascular biomarkers, particularly pro-brain natriuretic peptide (Pro-BNP).

METHODS

Design

Cohort, transversal, prospective, observational comparative study on 52 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 cross-sectional study. Informed consent was obtained from each patient enrolled. Fifty-two chronic hemodialysis patients with more than 3 months under treatment were included. Patients under age 18 or over 85, or with a history of neoplasia, acute infection, hepatopathy, nontreated hypothyroidism, or BMI > 40 kg/m^2 were excluded. No patients with HIV, HBV, or HCV were positive. No failed transplant patients were included. Mean age (years): Group A: 59.86+20.53; Group B: 68.76+11.57; Group C: 65.21+7.54, P=ns.

Patients were divided into three groups according to BMI. Group A, BMI < 25 (n=20); Group B, BMI 25 to 30 (n=21); and Group C, BMI > 30 (n=11).

Groups were not different with respect to age, gender, time on hemodialysis, cause of renal disease, hypertension, and cardiovascular disease. Diabetes mellitus patients and restrictive echocardiogaphic findings were different (Table 1). Blood measurements: C-reactive protein (CRP), hematocrit, insulin, HOMA, albumin, MIS, Pro-BNP, TropT, adiponectin, and mean intradialytic ultrafiltration rate. Nutritional assessment was performed with the Malnutrition Inflammation Score (MIS),[17,18] 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 albumin were measured using routine procedures. High-sensitivity CRP (normal value: < 0.3 mg/dL) was calculated by immunoturbodimetry VITROS 5.1®, Johnson & Johnson (New Brunswick, NJ, USA). For Pro-BNP, a chemoluminiscence method was used, VITROS ECi®, Johnson & Johnson: (normal values: < 125 pg/mL < 75 years; < 450 pg/mL for subjects older than 75 years). Troponin T was measured by electrochemoluminiscence, Cobas e411, Roche Diagnostics (Indianapolis, IN, USA) (normal

value: < 0.01 ng/mL). Insulin was determined by electrochemoluminiscence, Cobas e411, Roche Diagnostics (normal value: 2 to 15 μUI/mL). HOMA was calculated as follows: (insulin × glycemia)/405. Adiponectin was determined by DIAsource ELISA KAPME09, Linco Corp, USA (normal values: female 10.2+4.6 μg/mL; male 6.8+4.1 μg/mL).

Blood was drawn in the fasting condition previous to the hemodialysis session. All biochemical measurements were performed at the Central Laboratory of the Hospital Británico.

Hemodialysis aspects

Thrice-weekly hemodialysis sessions were performed using biocompatible membranes (Polyflux 10 L®, Gambro, Sweden) and a bicarbonate bath and with a mean blood flow QB: 450 ± 50 mL/min, dialyzate flow QD: 500 mL/min, and a mean duration per session of 4.0 ± 0.5 hours. The ultrafiltration rate used in this study was the one registered by automatic dialysis machines (Surdial 190, Nipro®, Matsubara, Tatebayashi, Japan) when the blood samples were collected.

Arteriovenous accesses

Arteriovenous access was fistulae in 29 patients (56%), polytetrafluoroethylene grafts (Gore-tex® vascular graft, W.L. Gore & Associates Inc., Newark, DE, USA) in 10 patients (19%), and tunneled catheters (Tesio®, Medcomp Pennsylvania USA or Quinton® Permcath™, Covidien AG, Mansfield, MA, USA) in 13 patients (25%). Non-significant differences according to access distribution were reported among the three groups.

Hypertension

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

Cardiovascular disease

Cardiovascular disease was defined as the presence, based on clinical grounds, imaging, and laboratory results, of cardiac ischemic disease and/or peripheral vascular disease and/or cerebrovascular disease at the time of the study.

Echocardiographic findings

All patients have at least one Doppler cardiac sonogram performed yearly. Three abnormal left ventricular filling patterns were taken into account to consider diastolic dysfunction: impaired relaxation (associated with remodeling and compensatory hypertrophy), pseudonormalization, and restriction (linked to increased left ventricular volume and myocardial stiffness). Ventricular wall thickness was considered hypertrophic if > 10 mm.

Medications

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

Statistics

Results are expressed as the median (range), unless explained otherwise. The Fisher exact test or chi square was used for categorical variables. For continuous variables, the Mann-Whitney test was used, and for intervariable correlations, the Spearman rank and ρ-coefficient was calculated. P values < 0.05 were considered significant. In Table 3, for comparisons of different variables according to BMI, chi square coefficients and the Kruskal-Wallis test were used.

RESULTS

As shown in Table 1, patients were not different as to the general characteristics, except for the fact that there were significantly more diabetics as BMI increased: Group A: 2 (10%) vs. Group B: 6 (29%) vs. Group C: 6 (55%), P = 0.027. In addition, echocardiographic myocardial hypertrophy and restriction augmented significantly with BMI increases (Table 1).

The types of vascular accesses were non-different among the groups: Fistulae: Group A, 10 (50%); Group B, 12 (57%); Group C, 7 (64%). Polytetrafluoroethylene grafts: Group A, 2 (10%); Group B, 5 (23%); Group C, 3 (27%). Catheters: Group A, 8 (40%); Group B, 4 (20%); Group C, 1 (9%).

A significant decrease in adiponectin levels was found as BMI increased: Group A: 17.03 ± 9.49 μg/mL; Group B: 12.57 ± 6.19 μg/mL; Group C: 5.43 μg/mL, P < 0.0001. This change was associated with a nonsignificant decrease in Pro-BNP and troponin T levels and a significant decrease in the MIS. Insulin levels changed inversely and significantly as BMI increased. Finally, ultrafiltration rates increased significantly as BMI increased (Table 2).

In Group A, adiponectinemia positively and significantly correlated with Pro-BNP, CRP, and troponin T levels. As BMI increased, adiponectin, Pro-BNP, and

Table 2 Distribution and comparison of the different variables according to BMI

Variable	Group	n	Mean	Median	SD	Mínimum	Maximum	Interquartile amplitude	P
Adiponectin (μg/mL)	IMC < 25	20	17.03	16.00	9.49	4.039	44.330	14.20575	
	IMC 25–30	21	12.57	11.40	6.19	4.272	23.321	10.02230	0.0001
	IMC > 30	11	5.43	3.87	2.88	2.660	11.436	4.07960	
Albumin (g/dL)	IMC < 25	20	3.82	3.95	0.58	2.6	4.7	0.950	
	IMC 25–30	21	3.95	3.90	0.36	3.2	4.6	0.600	NS
	IMC > 30	11	4.00	4.00	0.15	3.8	4.3	0.200	
Hematocrit (%)	IMC < 25	20	35.55	35.50	5.77	25	46	9.50	
	IMC 25–30	21	35.57	36.00	3.86	30	42	7.50	NS
	IMC > 30	11	34.73	34.00	4.59	25	40	6.00	
Insulin (ng/mL)	IMC < 25	20	8.56	7.00	6.82	2	31	5.75	
	IMC 25–30	21	11.84	7.00	11.34	4	50	7.00	0.003
	IMC > 30	11	22.63	19.00	10.07	15	46	8.00	
HOMA	IMC < 25	20	1.83	1.30	2.06	0.1	9.1	1.100	
	IMC 25–30	21	3.05	1.60	3.80	0.8	16.5	2.800	0.002
	IMC > 30	11	9.90	5.00	10.44	3.1	31.0	14.325	
	IMC > 30	11	3.82	3.00	1.40	2	6	2.00	
MIS	IMC < 25	20	6.20	6.00	2.63	3	11	4.75	
	IMC 25–30	21	4.24	4.00	2.14	2	9	3.00	0.011
	IMC > 30	11	3.82	3.00	1.40	2	6	2.00	
Pro-Brain (pg/mL)	IMC < 25	20	26836.7	2605	57169	38	228000	17943	
	IMC 25–30	21	18823.1	4040	36218	149	158000	18055	NS
	IMC > 30	11	2991.0	929	3863	428	11800	2105	
Trop T (ng/mL)	IMC < 25	20	0.042	0.033	0.0372	0.010	0.140	0.049	
	IMC 25–30	21	0.066	0.0370	0.0794	0.010	0.336	0.0495	NS
	IMC > 30	11	0.045	0.0380	0.0307	0.010	0.110	0.036	
UF (L)	IMC < 25	20	1.94	2.00	1.00	0.5	3.5	1.83	
	IMC 25–30	21	2.41	2.20	0.78	0.9	4.0	1.0	0.003
	IMC > 30	11	3.26	3.50	0.79	2.0	4.0	1.50	

Statistics: Kruskal-Wallis test.
BMI = body mass index; SD = standard deviation; CRP = C-reactive protein; MIS = malnutrition inflammatory score; Pro-BNP = Pro-Brain natriuretic peptide; TropT = Troponin T; UF = ultrafiltration; NS = non-significant.

Table 3 Group A significant correlations (BMI < 25)

Variable	HOMA	Pro-BNP	CRP	TropT	UF
Adiponectin					
ρ		0.586	0.403	0.383	
P		0.003	0.039	0.048	
Insulin					
ρ	0.938				
P	0.0001				
Pro-BNP					
ρ			0.758	0.702	0.437
P			0.0001	0.0001	0.027
CRP					
ρ				0.756	0.390
P				0.0001	0.044

BMI = body mass index; HOMA=Insulin resistance; Pro-BNP = Pro-Brain natriuretic peptide; CRP = C-reactive protein; TropT = Troponin T; UF = ultrafiltration.

malnutrition significantly decreased, while insulin, HOMA, and ultrafiltration rates significantly increased (Table 3). Cardiac restriction was significantly higher in obese patients (Table 1). In all groups, Pro-BNP and troponin T displayed a positive and strong correlation: Group A: $\rho = 0.702$, $P < 0.0001$; Group B: $\rho = 0.325$, $P < 0.04$; Group C: $\rho = 0.642$, $P = 0.017$. From Tables 3 to 5, Group A to C additional significant correlations are, respectively, shown. In Fig. 1, most of the measurements are displayed in relation to BMI indexes.

DISCUSSION

In the present manuscript, we report a significant decrease in adiponectin levels as BMI increased, in agreement with previous published data.[3] This phenomenon was associated with a nonsignificant but noteworthy de-

Table 4 Group B significant correlations (BMI 25–30)

	HOMA	Pro-BNP	Trop T
MIS			
ρ		0.474	
P		0.015	
Insulin			
ρ	0.895	−0.393	
P	0.0001	0.048	
CRP			
ρ			0.452
P			0.020

BMI=body mass index; MIS=malnutrition inflammatory score; HOMA=Insulin resistance; Pro-BNP=Pro-Brain natriuretic peptide; CRP=C-reactive protein; TropT=Troponin T.

crease in Pro-BNP and troponin T levels, biomarkers of cardiac stress, and a significant increase in insulinemia. However, despite significantly higher fluid dialysis removal as BMI increased, the Pro-BNP levels remained disproportionately low. Finally, malnutrition status improved with increases in BMI (Table 2).

In this hemodynamic and metabolic conundrum, two usual questions—among many others—remain unanswered in the dialysis universe: the contradictory role of adiponectin as both an antiatherogenic[1,2] or a pro-atherogenic adipokine [6–8]and the *obesity paradox* encountered in chronic hemodialysis patients, among whom the obese display better survival rates than nonobese individuals.[14] It is also peculiar that being an adipokine, and as such secreted by adipocytes, adiponectin levels are usually low in obesity. If hemodialysis subjects with elevated BMI live more than those with low BMI, it may not be due to the cardioprotective role of adiponectin, whose secretion rate is diminished. It is probable that other factors may play more relevant roles in this situation, as a better nutritional status, which may be one candidate, according to our results.

Table 5 Group C significant correlations (BMI > 30)

Variable	Trop T	UF
Insulin		
ρ	0.795	0.618
P	0.009	0.051
Trop T		
ρ		0.689
P		0.009

BMI=body mass index; ProBNP=ProBrain natriuretic peptide; TropT=Troponin T; UF=Ultrafiltration.

Our study also confirms the findings that in chronic hemodialysis subjects with a low BMI, malnourishment, inflammation, high Pro-BNP, and adiponectin levels are prevalent findings. This is correlated with low echocardiographic myocardial patterns of damage. It is possible that in this phenotypic spectrum of the disease, adiponectin high levels exert a protective cardiovascular compensatory effect, stimulated by high Pro-BNP concentrations after cardiac stretching. Again, it is probable that a poor nutritional and inflammatory status overcomes high adiponectin levels.

In obesity, adiponectinemia is negatively regulated by the accumulation of body and visceral fat.[3,19] This low adiponectin level would, in turn, render cardiovascular remodeling and fibrosis pathways unhindered, stiffening cardiac chambers and decreasing ventricular stretching. Consequently, and despite higher volume removal rates, Pro-BNP levels cannot increase appropriately. Finally, Pro-BNP stimulation of adiponectin is also altered in obesity, due to a higher clearance of Pro-BNP by adipocytes, contributing to the decreased plasma concentration of this cardiac biomarker in high BMI patients.[20,21]

Interestingly, the negatively regulated adiponectin release by body fat may[3,19] be more important than the stimulation natriuretic peptides exert on adipocyte receptors, inducing lipolysis and stimulating adiponectin secretion.[22,23] Obesity-related diseases are associated with pathological cardiac remodeling and myocardial hypertrophy, probably due to hypoadiponectinemia.[24–26] The considerably higher adipocyte mass could decrease Pro-BNP levels, perpetuating its characteristically low levels.[20,21,27] This phenomenon could also contribute to a low adiponectin secretion. Despite low Pro-BNP levels, cardiac parietal stress is a reality in obese subjects, as the high ultrafiltration rates encountered significantly and positively correlated with troponin T, another biomarker of cardiac stress (Table 2).[28]

Obesity-related diseases are associated with cardiac remodeling and diastolic dysfunction, defined by echocardiographic myocardial hypertrophy, impaired relaxation, and restriction.[24,29] Experimental studies have shown that adiponectin is protective against its development. Adiponectin-knockout mice develop severe concentric cardiac hypertrophy and exhibit increased mortality.[30] Conversely, overexpression of adiponectin attenuates cardiac hypertrophy in mice.[30] Adiponectin would apparently increase AMP-activated protein kinase activation (AMPK),[30] an intracellular mediator with vascular protective properties, which normally inhibits TGF-beta-mediated fibrosis.[31] Moreover, adiponectinemia deficiency causes upregulation of NOX-4, a NADPH oxidase highly expressed in the

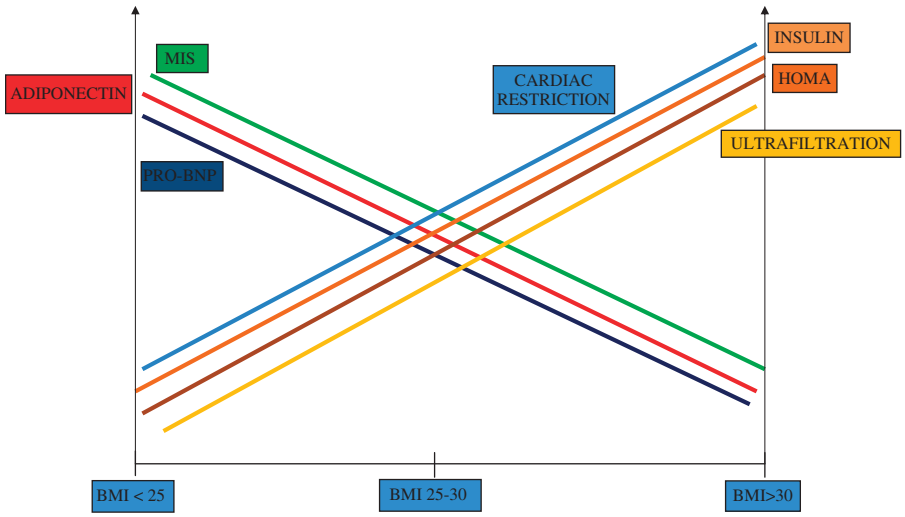

Figure 1 Conceptual framework of the significant variable differences according to variations in body mass index.

kidney and related to insulin resistance, oxidative stress, and inflammatory pathways.[32] Collectively, these findings suggest that in cardiac myocytes, the adiponectin-AMPK axis functions to limit cardiac remodeling in obesity-linked conditions. Others have found that adiponectin may mediate its antiatherogenic properties increasing HDL-C concentrations.[33] At non-different blood pressure determinations between the three groups, we assume that low adiponectin levels may be in part relevant to cardiac restriction.

In our study, in low-BMI subjects, high Pro-BNP and adiponectin and low myocardial restriction were prevalent. In these patients, high Pro-BNP levels could, through its lipolytic effect, contribute to low weight status and stimulate the release of adiponectin.[8,34] The clearance of Pro-BNP could also be decreased due to a lower adipocyte mass. Moreover, weight loss increases adiponectinemia.[34] Therefore, is adiponectin just a marker of the wasting process associated with the increased mortality observed in this subgroup of patients, or is it that adiponectin levels are not able to compensate the already triggered inflammatory and catabolic process? In agreement with other studies, we have found a strong and positive correlation between Pro-BNP and adiponectin.[8,23,25] However, we have also found a strong correlation between CRP levels and the Pro-BNP-adiponectin binomium only in low-BMI subjects, where the inflammatory pattern seems to be more important. In patients with cardiovascular disease, the Pro-BNP adipocyte clearance is functionally decreased due to a higher inflammatory state, because cardiac stress is proportionally higher than Pro-BNP adipocyte depuration.[20] Moreover, it has been shown that adiponectin may antagonize the proinflammatory properties of molecules such as CRP, interleukin-6, and tumor necrosis factor alpha.[35,36] Finally, adiponectin has also been found not only to protect against fibrosis and inflammation, but could also increase energy expenditure, apparently through a direct effect on the brain.[37–39] This interesting finding may suggest that in low-BMI patients, adiponectin could also play a role in catabolic processes and contribute to low weight.

In this study, malnutrition, as assessed by MIS, significantly worsens as BMI reduces, contributing to the morbidity observed in these subjects. Inflammation and malnutrition could overcome hyperadiponectinemia cardioprotective antiatherogenic and antifibrotic roles, notwithstanding the fact that adiponectin can also cause weight loss by itself.[34] Similar reports with respect to adiponectin's role in patients with congestive heart failure have been published.[40]

Finally, adiponectin has been found to improve hepatic and muscular insulin sensitivity.[41,42] In our work, it is shown that, as expected, obese patients present significantly different levels of insulin and HOMA with respect to the other two groups (Table 2). In obesity, hypoadiponectinemia would contribute to insulin resistance at its highest expression.

Drechsler et al. state that high basal adiponectin levels in dialysis patients reflect a consequence of disease circumstances, playing a counter-regulatory role, and that pro-BNP has a confounding effect.[9] We believe that the interplay of Pro-BNP and adiponectin is crucial in the

development of cardiovascular effects, and is dependent on the BMI, mainly due to the amount of body and visceral fat. The nutritional and inflammatory status dialysis patients display, which improves as BMI increases, may also exert a key influence on the mortality rates found in this population.

With regard to the second question of this conundrum, how can the *obesity paradox* then be explained in dialysis? The *obesity paradox* on hemodialysis patients could be explained by a better nutritional score and a lower inflammatory milieu obese subjects generally display, which would be more important than the adiponectin, Pro-BNP, and echocardiographic patterns of cardiac dysfunction. In our study, the obese group presented a higher albeit nonsignificant number of native vascular accesses, which could have contributed to a lower inflammatory milieu. As expected, the percent of diabetics was higher as BMI increased (Group A: 10%; Group B: 29%; Group C: 55%), coupled with higher insulin levels and HOMA (Tables 1 and 2).

To conclude, this cross-sectional study is limited by a small but homogeneous number of patients and the parameters are analyzed at one time-point. However, our results may provide some suggestions on how to interpret the different and apparent contradictory roles adiponectin may play in dialysis patients. According to our results, an explanation for the *obesity paradox* and Pro-BNP, adiponectin, and the inflammatory-nutritional status is also proposed. In chronic hemodialysis, BMI must be used to interpret the fluctuations and close interactions Pro-BNP and adiponectin display in conjunction with inflammatory biomarkers and nutritional scores.

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