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OBSERVATIONAL STUDY

Residual urinary output in high body mass index individuals on chronic hemodialysis: A disregarded life vest?

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Abstract

AIM: To assess residual diuresis and diverse variables according to body mass index (BMI).

METHODS: Cross-sectional study (n = 57), with 3 groups. Group A: BMI < 25, n = 22; Group B: BMI 25-30, n = 15; Group C: BMI > 30, n = 20. Diuresis, hematocrit, albumin, C-reactive protein, Malnutrition inflammatory score, Pro-BNP, Troponin T, leptin and insulin levels are expressed as median and ranges (r).

RESULTS: Albumin (g/dL): GA *vs* GC, 3.70 (r2.20-4.90) *vs* 3.85 (r3.40-4.90), P = 0.02. Diuresis (mL/d): GA 690 (r0-1780); GB 660 (r60-1800); GC 840 (r40-2840). Diuresis GA *vs* GC, P = 0.01. Leptin (ng/mL): GA *vs* GC, 3.81 (r0.78-69.60) *vs* GC, 32.80 (r0.78-124.50), P < 0.001. Insulin (μU/mL): GA *vs* GB, 7 (r2-44) *vs* 11.50 (r4-38), P = 0.02; GA *vs* GC, 7 (r2-44) *vs* 19.5 (r5-155), P = 0.0001. Troponin T and Pro-BNP levels were not different. Significant correlations: GC, Insulin-UF: ρ = 0.53; P = 0.03; TroponinT-diuresis: ρ = -0.48, P < 0.05; Pro-BNP-diuresis: ρ = -0.39, P < 0.01; Troponin T-ProBNP: ρ = 0.77, P < 0.0001; albumin-Troponin T: ρ = -0.66, P < 0.0001; albumin-ProBNP: ρ = -0.44, P < 0.05.

CONCLUSION: High BMI associated positively with higher diuresis and albuminemia, and negatively with TropT and Pro-BNP. High BMI-associated better survival may be explained by better urinary output, lowering cardiovascular stress.

Key words: Hemodialysis; Residual diuresis; Body mass index; Troponin T; Pro-BNP; Insulin

Core tip: Cardiovascular disease is the major cause of death in hemodialysis, while residual diuresis and increased body mass index (BMI) are associated with better survival. We found that an elevated BMI > 30 associated positively with higher diuresis, insulin levels and albuminemia. This higher urinary output dialysis individuals with BMI > 30%, may reflect water retention, in part due to hyperinsulinemia, hyperleptinemia and secondary higher ultrafiltration rates. The ability to excrete water correlates negatively and significantly with Troponin T and Pro-BNP levels, reflecting lower myocardial and vascular overload. High BMI-associated better survival may be explained by better diuresis, and lower cardiovascular stress.

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INTRODUCTION

The International Task Force has established that worldwide 1.5 billion adults are overweight or obese, with nearly 500 million being obese[1]. Only in the United States, a third of the adult population is overweight and another third is obese[2]. In the general population, obesity is associated with higher rates of hypertension, diabetes, metabolic syndrome, cardiovascular disease, and death[3,4]. Morbidly obese adults present a 6-fold higher risk of diabetes compared with their lean peers[5]. Moreover, approximately 70% of hypertension can be attributed to excess weight[6,7]. Because a large proportion of chronic kidney disease is attributed to both diabetes and hypertension, conditions associated with high body mass index (BMI), it seems logical to suppose that obesity should be associated with bad prognosis in hemodialysis (HD) individuals. However, in HD patients obesity is independently associated with reduced all-cause mortality[8-11]. In this regard, there is a negative correlation between BMI and death, generally referred to as the obesity paradox[12]. In hemodialysis individuals, obesity seems to act as a protective factor[13,14] and in general, obese subjects display a better nutritional status, regardless of portraying a more severe cardiac condition[15]. While diabetes and obesity are two usually associated conditions, in HD diabetics tend to present increased morbidity and mortality rates but obesity has been reported to display better survival. Many variables have been ascribed as potential factors that could explain this apparent paradox about obesity in HD: A better nutritional status, higher albumin levels, and a lower inflammatory milieu as assessed by C-reactive protein (CRP), among other factors[8-11].

In end stage kidney disease, residual renal function or remnant diuresis is considered an important variable associated with better survival[16-18]. Besides a better volume management, residual diuresis has been associated with better preserved renal functions, such as calcium, phosphorus and vitamin D homeostasis, erythropoietin levels, and removal of middle molecules[19-24]. In this regard, residual renal function has been shown to present a greater influence on dietary protein intake and nutritional status[25-27]. However, with respect to urinary output, in obese hemodialyzed people the reported results are scant or controversial. In this regard, some studies have found an inverse association between obesity and diuresis, while this association has also been reported to be inconclusive[28,29].

In addition, insulin and particularly hyperinsulinemia itself due to peripheral tissue resistance and deeply involved in the pathogenesis of metabolic syndrome and obesity, has been reported to be elevated in high BMI individuals on HD[15,30]. Insulin causes myocardial hypertrophy and water and salt retention and is associated with diabetes and hypertension, conditions that contribute to high morbidity and mortality rates, particularly in end stage kidney disease[31]. Finally, leptin and insulin not only present similar metabolic and hemodynamic actions, but also display the same patterns of distribution with respect to BMI in HD[30,32].

We investigated cardiac and metabolic biomarkers in HD subjects with respect to urinary output, and propose another potential protective cardiovascular mechanism high BMI individuals display in HD. Finally, a consideration is addressed with respect to the importance of defining elevated body weight in hemodialysis, as obesity may not always be the case when other factors intervene, as fluid overload or muscle wasting.

MATERIALS AND METHODS

Design

Cross-sectional, prospective, observational study undertaken in 57 chronic clinically stable HD individuals.

Patients

The Teaching and Research Committee of the Hospital Británico de Buenos Aires approved this observational study. Each patient signed the respective informed consent. Fifty-seven patients with more than 3 mo of HD were enrolled. Exclusion criteria: Patients younger than 18 years old, or with an active cancer, acute infections, hepatopathy, non-treated hypothyroidism, anuria or BMI > 40 kg/m^2. Anuria was defined as a urinary output < 140 mL/d and proteinuria was considered positive when the daily excretion was > 0.15 g/d. One included patient was HIV positive and another one was HbsAg positive. Failed transplant patients were excluded. The population was divided into three groups as to BMI tertiles as described above. Group A, BMI < 25 (n = 22); Group B, BMI 25-30 (n = 15) and Group C, BMI > 30 (n = 20). Median age (range): Group A: 65 (36-83) years; Group B: 71 (26-88) years; Group C: 63 (33-79) years, P = 0.61. Moreover, the three groups were not different with regard to gender, time on chronic HD, estimated glomerular filtration rate at the beginning of HD, etiology of kidney disease, hypertension, diabetes mellitus, CRP levels, nutritional status evaluated by the malnutrition inflammatory score (MIS), daily diuresis, ultrafiltration rates and no difference in mean estimated GFR in the three groups when dialysis was initiated (Table 1). The rates of decline of diuresis were 13%, 17% and 6 %, respectively. Determinations: Mean automatic intradialytic ultrafiltration rates, mean average blood pressure per session, Troponin T (TropT), Pro-BNP, albumin, insulin levels and HOMA. Serum concentrations of albumin and CRP were measured by routine procedures. TropT levels were determined by electrochemoluminiscence, Cobas e411, Roche Diagnostics, Indianapolis, IN, United States, (normal value: < 1 ng/mL); Pro-BNP levels were measured by chemiluminescence, VITROS 5600®, Johnson and Johnson, New Jersey, United States: (reference values: < 125 pg/mL for subjects < 75 years and < 450 pg/mL for those > 75 years). Insulinemia was measured by electrochemoluminiscence, Cobas e411, Roche Diagnostics®, Indianapolis, Indiana United States, (normal value: 2-15

Table 1 Patient characteristics *n* (%)

Variable	Group A	Group B	Group C
N	22	15	20
Male gender	10 (45)	9 (60)	14 (70)
Diabetics	4 (18)	3 (20)	10 (50)
Hypertensives	15 (68)	12 (80)	17 (85)
Median age (yr)	65	71	63
Range	36-83	26-88	33-79
Median time on HD (mo)	12	26	15.5
Range	4-101	9-92	4-55
BMI (Mean ± SD) (kg/m2)	21.3 ± 2.4[b]	27.6 ± 1.4[b]	33.9 ± 4.2[b]
Median MIS	5.5	4	3
Range	1-21	2-8	0-13
Causes of ESRD			
Glomerulonephritis	8	7	11
Diabetes	2	2	3
Nephroangiosclerosis	7	3	4
Obstructive uropathy	1	0	1
Interstitial nephritis	1	1	1
Polycystic kidney disease	3	2	0
Median C-Reactive protein (mg/dL)	1.2	1.1	1.1
Range	0.50-12	0.20-8	0-4.5
Median urinary output (mL/d)	690	660	840
Range	140-1780	160-1800	140-2840
Median initial urinary output (mL/d)	790	800	890
Range	170-1860	180-1970	940-2900
Median albumin (g/dL)	3.70[a]	3.8	3.85[a]
Range	2.2-4.9	3.2-4.4	3.4-4.9

[b]$P = 0.001$, [a]$P = 0.02$. MIS: Malnutrition Inflammatory Score; ESRD: End-stage renal disease; HD: Hemodialysis.

μUI/mL). HOMA was calculated as follows: (Insulin x glycemia)/405. Leptin levels were determined by ELISA, Millipore®, Missouri United States.

Blood samples were obtained in fasting condition prior to the dialysis session. Depending on the dialysis schedule, 24-h urine samples were collected on Sundays or Mondays. All the determinations were performed at the Hospital Británico.

Hemodialysis aspects

High-flux biocompatible membranes were employed in the hemodialysis sessions (Polyflux 21 R®, Gambro, Sweden and Sureflux 190®, Nipro, Japan). Dialysis was performed using bicarbonate bath with a mean blood flow: 450 ± 50 mL/min, and a dialysate flow: 500 mL/min; mean time of the sessions lasted 4.0 ± 0.5 h. The ultrafiltration rate recorded was the one obtained by the automatic dialysis machines (Surdial 190, Nipro® Japan or Diamax, Nipro® Japan) in coincidence with the session when the blood samples were obtained.

Medications

The majority of the patients were receiving aspirin, beta-blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, and other commonly used drugs in HD: Subcutaneous erythropoietin, iv iron, calcium salts, potassium chelators, folic acid, vitamins, iv L-carnitine, statins, proton-pump inhibitors and benzodiazepines.

Statistical analysis

The results are expressed as the median (range), unless explained otherwise. Fisher exact test or Student test were used to determine categoric variables; for continuous variables, Mann-Whitney test was employed; for intervariable correlations Spearman Rank and ρ coefficient were calculated. *P* values ≤ 0.05 were accepted as statistically significant. To compare the different variables with respect to BMI, χ^2 coefficients were calculated and the Kruskal-Wallis test was used.

RESULTS

Groups were not different as to age, gender, time on HD, hematocrit, ultrafiltration rates (UF), inflammation status evaluated by CRP levels and MIS (Table 1). Median glomerular filtration rates (mL/min) were: GA: 10 (r: 7-15), GB: 9 mL/min (r: 8-17), GC: 10 (r: 8-14), mL/min. Although the nutritional status, assessed by MIS, was not different among groups, albumin levels were statistically different between subjects with low BMI compared to those with BMI > 30: GA *vs* GC, 3.70 g/dL (r 2.20-4.90) *vs* 3.85 g/dL (r 3.40-4.90), $P = 0.02$ (Table 1). Urinary outputs measured in ml/day were also different between both groups: GA 690 (r 0-1780) *vs* GC 840 (40-2840), $P = 0.01$ (Table 1). Leptin levels increased significantly from GA to GC and correlated significantly with insulin (Tables 2 and 3). Insulin levels increased positively and significantly with BMI determi-

Table 2 Blood measurements and ultrafiltration rates in all groups

Group	TropT (ng/mL)	UF rates (L)	Pro-BNP (pg/mL)	Insulin (μU/mL)	HOMA	Leptin (ng/mL)
GA	40	2	4970	7.00[a,b]	1.30[c,b]	3.81[b,d]
	(9-1081)	(0.8-4)	(216-234000)	(2-44)	(0.3-22.4)	(0.8-69.6)
GB	48	2.5	2180	11.50[a]	2.50[c]	18.60[d]
	(5-179)	(0.8-4)	(226-102000)	(4-38)	(1.10-9.30)	(4.7-47.40)
GC	41	3	2040	19.50[b]	3.75[b]	32.80[b]
	(4-186)	(0.5-4.0)	(139-166000)	(5.0-155.0)	(1.0-59.3)	(0.78-124.80)

[a]$P = 0.02$; [b]$P = 0.0001$; [c]$P = 0.03$; [d]$P = 0.01$. UF: Ultrafiltration; Pro-BNP: Pro-brain natriuretic peptide.

Table 3 Different correlations in Groups A and C

	GA BMI < 25	GC BMI > 30
VARIABLE	**ρ; *P***	**ρ; *P***
Insulin-ultrafiltration rate	0.21; 0.44	0.53; 0.03
TroponinT-diuresis	-0.46; 0.07	-0.48; < 0.05
Pro-BNP-diuresis	-0.43; 0.09	-0.39; < 0.01
TroponinT-proBNP	0.44; 0.09	0.77; < 0.0001
Albumin-TropT	-0.04; 0.87	-0.66; < 0.0001
Albumin-proBNP	-0.1; 0.72	-0.44; < 0.05
Leptin-insulin	0.34; 0.26	0.52; < 0.03

Pro-BNP: Pro-brain natriuretic peptide.

nations (μU/mL): GA *vs* GB, 7 (r 2-44) *vs* 11.50 (4-38), $P = 0.02$; GA *vs* GC, 7 (r 2-44) *vs* 19.5 (r 5-155), $P = 0.0001$ (Table 2). With respect to cardiac and hemodynamic biomarkers, TropT and Pro-BNP levels were not different amongst groups (Table 2). However, the following significant correlations were observed, all in high BMI patients: In GC, TropT-diuresis: $\varrho = -0.48$, $P < 0.05$; Pro-BNP-diuresis: $\varrho = -0.39$, $P < 0.01$; TropT-ProBNP: $\varrho = 0.77$, $P < 0.0001$; insulin-UF rate: $\varrho = 0.53$, $P = 0.03$; albumin-TropT: $\varrho = -0.66$, $P < 0.0001$; albumin-ProBNP: $\varrho = -0.44$, $P < 0.05$ (Table 3).

DISCUSSION

In the present study, we observed that subjects with high BMI displayed higher diuresis, albumin, leptin and insulin levels. In this group, higher urinary outputs correlated significantly with lower TropT and Pro-BNP levels. Albumin inversely and significantly correlated with TropT and Pro-BNP. As expected, insulin levels raised accordingly with BMI, but correlated significantly with UF rates only in individuals with high BMI. Besides, all groups were not different according to the time on HD, and initial urinary outputs were similar in the whole cohort (Table 1). Noteworthy, the rates of decline in diuresis were lower in patients with high BMI (6%) in comparison with those from either Groups A (13%) or B (17%).

In the literature, many manuscripts refer to obesity as a variable associated with a better survival in HD subjects[8-11,33]. Many causes have been attributed to explain this phenomenon. It is possible that one variable associated with good prognosis could be remnant dieresis. In the present work, this association occurred independently of the time on HD (Table 1). However, many studies have reported that obese subjects on HD present with low renal residual function[28,29]. In addition, in our study patients with BMI > 30 presented significantly higher albumin levels that correlated with better residual kidney function. This clinical picture of a better oncotic pressure coupled with a preserved diuretic function could lead to a lower vascular stress. Consequently, a smoother hemodynamic scenario would originate. According to our findings, higher albumin levels could not be ascribed to a better nutritional status, as MIS was not different among groups, or to a better inflammatory milieu, as CRP levels were similar in all subjects (Table 1). Noteworthy, residual renal function has been associated with higher albumin levels[25-27]. However, notwithstanding the cause, these higher albumin levels in GC could be exerting a more efficient intravascular oncotic pressure, removing more interstitial water. As a consequence, vessels could be better replenished, being more volume delivered to the kidneys. The result would be a higher urinary output. This hemodynamic situation is also illustrated by the fact that albumin is negatively correlated with TropT and Pro-BNP, two cardiovascular biomarkers that are increased in overfilling states and myocardial stretching[34-39] (Table 3). Although we reported significantly low ProBNP levels in high BMI individuals, we could not demonstrate this phenomenon in the present work[15] (Table 2). It is possible that this smoother hemodynamic setting could explain in part one of the causes of a higher survival rate in high BMI subjects. Finally, it could also contribute to the absence of hypertension in GC, which in the general population is associated with elevated BMI[40,41]. Interestingly, Trop T can increase not only due to vascular causes as myocardial infarction, vascular shear stress, endothelial damage, cardiomyocyte hypertrophy, but also due to muscular wasting in obese subjects on HD[35,36,42,43]. In this regard, TropT is a non-specific marker of cardiovascular origin. Taken together, we propose that in obese subjects on HD, the higher urinary output that patients with high BMI present is correlated with lower TropT and Pro-BNP levels. A better residual renal function could also contribute to lower TropT levels, as this molecule is cleared by the kidneys[35,36,42].

Moreover, an interesting additional factor that could play a role in preserved remnant diuresis in obesity is in-

sulin. As it occurred in one of our previous publications, in subjects with BMI > 30, insulin is again associated with higher UF rates in high BMI patients, albeit UF rates were not different amongst groups[30]. As expected, insulin increased in parallel with BMI, but did not correlate significantly with any other variable except fluid removal and only in high BMI individuals (Table 3). This phenomenon could be related to the ability of insulin to retain salt and water[44]. In turn, this fluid retention would be the trigger for a pressure-diuresis phenomenon and a maintained urinary output, probably potentiated by higher albumin levels. This increase in insulin could also reflect an insulin-resistant state in high BMI patients, which is inherent to obese individuals[44,45]. In addition, in our study high BMI was associated with lower Pro-BNP levels, which is in agreement with other publications that report the association between hyperinsulinemia and low Pro-BNP patients in obesity[15,45-47].

In our study, leptin is significantly high in GC, where its correlation with insulin is positive and significant. Recently, insulin has been reported to upregulate leptin gene expression. With respect to leptin sodium and water handling, the results are controversial. While some studies have shown leptin presents natriuretic effects, many others have reported its association with water and salt retention, sympathetic nervous system activation and hypertension, which could add to insulin hemodynamic effects[32,48]. With respect to the cardiovascular system, leptin (as insulin) is involved in the pathogenesis of myocyte hypertrophy[32,48].

Finally, the obesity paradox in hemodialysis has always been related to an elevated weight and assumed to be due to fat. However, BMI correlates with body fatness or density[49], but in these studies and in our present manuscript, the increase in body weight has not been discriminated in tissue compartments. An elevated BMI could be due to an increase in fat, water, bone density and/or muscle mass[50]. Therefore, increased body weight, particularly in end-stage kidney disease patients, is not a synonymous of obesity. Moreover, assuming overweight dialysis patients as obese, may be a misleading statement. We assume our GC subjects as obese due to high leptin and insulin levels and an elevated HOMA index, a characteristic profile encountered in obesity (Table 2).

Our manuscript contains several pitfalls. It is a cross-sectional study including a limited number of patients. Our findings must be interpreted with caution, as it joins previous studies with respect to the evaluation of body tissue and fluid composition and distribution. We call the attention of future authors to make the appropriate distinction when overweight patients are studied in the dialysis setting. Obesity is not a synonymous of high BMI in renal failure. Water retention and muscle wasting are to be addressed. Finally, these variables can operate simultaneously in these individuals. In this regard, bioimpedancy studies are mandatory. It is possible that whether this issue is taken into account, the obesity paradox in hemodialysis may not be such. In this regard, residual renal function would be more related to fluid overload and a pressure-diuresis forced situation.

In conclusion, our study shows that high BMI HD patients display higher diuresis rates, albumin and insulin levels. This higher urinary output dialysis individuals with BMI > 30 present, may reflect water retention, in part due to hyperinsulinemia, hyperleptinemia and secondary higher UF rates. The ability to excrete water correlates negatively and significantly with TropT and Pro-BNP levels, which would reflect a lower myocardial and vascular stress and a better hemodynamic status. Whether these events are associated with a better survival rate in HD should be appropriately assessed.

COMMENTS

Background

Cardiovascular disease is the most important cause of mortality in dialysis, while residual diuresis and increased body mass index (BMI) are associated with better survival. The authors studied residual diuresis and diverse variables according to BMI.

Research frontiers

To be able to discern between BMI and fluid retention in dialysis patients. Residual diuresis may be an important in outcome in these subjects, and high BMI subjects may display higher dieresis rates, lowering cardiovascular stress.

Innovations and breakthroughs

High BMI hemodialysis patients display higher diuresis rates, albumin and insulin levels. This higher urinary output dialysis individuals with BMI > 30 present, may reflect water retention, in part due to hyperinsulinemia, hyperleptinemia and secondary higher ultrafiltration rates rates. The ability to excrete water correlates negatively and significantly with TropT and Pro-BNP levels, which would reflect a lower myocardial and vascular stress and a better hemodynamic status.

Applications

In the every-day assessment of dialysis subjects, this paper suggests that obesity may not always be the reflection of a fat tissue, but the fluid overload must be taken into account. This water retention may explain the residual renal function this group may display, in relation with the pressure-diuresis phenomenon.

Terminology

The obesity paradox in dialysis states that this cohort of patients do better than other groups with lower BMIs. This is in contradiction with what occurs in the general population. The authors state that an elevated BMI may not always be a mere reflection of a higher fat tissue mass, but to an accumulation of water. The residual renal function displayed by these subjects may be due to a pressure-diuresis phenomenon.

Peer review

The present study aimed to investigate the associations between several cardiac and metabolic biomarkers as well as residual diuresis with BMI in chronic dialysis patients. The study is interesting and it could be published provided that the discussion should be re-written taking into account that some differences between groups.

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