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Effect of dietary sodium restriction on body water, blood pressure, and inflammation in hemodialysis patients: a prospective randomized controlled study

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Abstract
Purpose Accumulating evidence suggests an association between body volume overload and inflammation in chronic kidney diseases. The purpose of this study was to evaluate the effect of dietary sodium reduction in body fluid volume, blood pressure (BP), and inflammatory state in hemodialysis (HD) patients.
Methods In this prospective controlled study, adult patients on HD for at least 90 days and those with C-reactive protein (CRP) levels $\geq$0.7 mg/dl were randomly allocated into two groups: group A, which included 21 patients treated with 2 g of sodium restriction on their habitual diet; and group B, which included 18 controls. Clinical, inflammatory, biochemical, hematological, and nutritional markers were assessed at baseline and after 8 and 16 weeks.
Results Baseline characteristics were not significantly different between the groups. Group A showed a significant reduction in serum concentrations of CRP, tumor necrosis factor-α, and interleukin-6 during the study period, while BP and extracellular water (ECW) did not change. In group B, there were no changes in serum concentrations of inflammatory markers, BP, and ECW.
Conclusions Dietary sodium restriction is associated with the attenuation of the inflammatory state, without changes in BP and ECW, suggesting inhibition of a salt-induced inflammatory response.

Keywords Inflammation · Sodium · Dietary sodium restriction · Hemodialysis · Blood pressure · Volume

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Introduction

Cardiovascular disease (CVD) is the major cause of death in hemodialysis (HD) patients, with a mortality rate that is 10- to 20-fold higher than that in the general population [1–4]. The mechanisms proposed for the genesis of CVD in HD patients include hypervolemia, hyperhomocysteinemia, and secondary hyperparathyroidism beyond traditional factors [5]. Furthermore, inflammation has been identified as a risk factor for atherosclerosis in these patients [6]. Some potential causes of inflammation in HD patients are blood exposure to dialysis membranes, non-sterile dialysate use, retention of cytokines, acidosis, and unapparent infections [7, 8].

Inflammation and extracellular volume expansion are common in HD patients [9]. There is an increasing evidence that fluid overload may be associated with inflammatory responses. Ortega et al. [10] observed that in chronic kidney disease patients, volume

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expansion assessed by atrial natriuretic peptide is predictive of inflammation. Avila Dias et al. [11] demonstrated that in peritoneal dialysis (PD) patients, ECV is independently associated with inflammation. Among PD patients, those with circulatory congestion have malnutrition and higher median C-reactive protein (CRP) levels [12]. Niebauer et al. [13] found that in patients with congestive heart failure, those with peripheral edema had significantly higher concentrations of endotoxins, and after diuretic treatment, endotoxin concentrations were significantly reduced. These authors suggested that intestinal wall edema associated with volume expansion would favor the translocation of bacterial endotoxins and trigger an inflammatory response.

Dietary sodium restriction is associated with lower interdialytic weight gain (IDWG) and blood pressure (BP) reduction [14–18]. We hypothesized that sodium restriction affects the inflammatory state. To the best of our knowledge, no intervention study has assessed the effect of low-sodium diets on the inflammatory state in dialysis patients. Therefore, the purpose of this study was to evaluate the effect of dietary sodium reduction in body water volume and inflammatory markers in HD patients.

Methods

This study included patients aged ≥18 years on HD for at least 90 days. Inflammation was defined as CRP levels ≥0.7 mg/dl, which was the median of CRP levels of 119 HD patients treated in our dialysis unit at baseline. Exclusion criteria were acute inflammatory processes, chronic inflammatory diseases, antibiotic use within the past 2 months, malignancies, and central venous catheter use. The Institutional Research Ethics Committee approved the study protocol, and the patients signed an informed consent.

Patients were randomly allocated into two groups: group A, which received a prescription of 2 g of sodium reduction in their habitual diet; and group B, which included patients who maintained their usual dietary habits (controls). All patients were monitored by the same nutritionist throughout the study and were followed up for 16 consecutive weeks. At baseline, and on the 8th and 16th weeks, demographical, clinical, laboratory, and nutritional data were assessed.

Clinical and demographical data (underlying renal disease, time on dialysis, sex, age, presence of diabetes, smoking status, medications in use, BP, and interdialytic weight gain) were retrieved from the patients' medical records. Systolic and diastolic BP was estimated by the average of the last 10 routine pre-dialysis measurements.

Dietary intervention and nutritional assessment

For group A patients, sodium reduction of 2 g corresponded to 5 g of salt withdrawal in the patient's daily diet, in relation to the actual intake, considering the salt used in food preparation and during meals. The amount of salt to be removed was converted to household measures for better understanding. Dietary instructions and encouragement were provided to patients and family at all assessment points. Dietary intake was based on a 72-h alimentary registry.

Body weight, height, and single-frequency bioelectrical impedance analysis (BIA) measurements were performed 30 min after HD sessions. The BIA device (Biodynamics® analyzer) measures resistance (ohms) and reactance (ohms) directly and stores the information. This information was used by an internal microprocessor to perform subsequent calculations of phase angle, total body water, and extracellular water (ECW) according to previously validated equations [19, 20].

Laboratory measurements

Pre-dialysis blood samples were collected for measurement of biochemical (serum levels of albumin, sodium, creatinine, urea, glucose, cholesterol, HDL cholesterol, triglycerides, and bicarbonate), inflammatory (serum CRP, tumor necrosis factor-α [TNF-α], and interleukin-6 [IL-6]), and hematological markers (hematocrit and hemoglobin). TNF-α and IL-6 levels were determined by ELISA using commercial kits (R&D® Systems, Minneapolis, MN, USA). The remaining tests were performed using standard methods.

Dialysis parameters

All patients were dialyzed three times per week, for 3.5–4 h per session using low-flux polysulfone dialyzers and dialysate with bicarbonate buffer and a

sodium concentration of 138 mEq/l. Prescribed dialysis doses (Kt/V) were at least 1.4.

Statistical analysis

Results are expressed as mean ± standard deviation, median (interquartile range), or percent as appropriate. Basal characteristics were analyzed by the unpaired *t* test, Mann–Whitney *U* test, or chi-squared test. Parametric data were analyzed by ANOVA for repeated measures, whereas nonparametric data were assessed by the Friedman's test. The significance level was set at $p < 0.05$.

Results

Fifty-three subjects, enrolled between April 2007 and February 2009, were allocated into the two groups as follows. Group A included 30 patients and group B included 23 patients. During the follow-up, nine subjects in group A and five in group B were excluded because of acute infections. Therefore, 39 patients (21 in group A and 18 in group B) completed the study period. No significant differences were observed between the groups regarding basal characteristics (Table 1).

Table 1 Patients' baseline characteristics

Characteristic	Group A ($n = 21$)	Group B ($n = 18$)	p
Age (years)	56.00 ± 11.91	60.22 ± 13.96	0.31
Males (*n*) (%)	12 (57.1)	3 (83.3)	0.10
Time on dialysis (months)	30.90 (8.75; 105.5)	49.50 (26.0; 58.0)	0.88
Diabetics (%)	6 (28.5)	6 (33.33)	1.00
Active smoking (%)	5 (23.8)	5 (27.7)	1.00
Hypertensive nephrosclerosis (%)	8 (38)	4 (22.2)	0.32
Diabetic nephropathy (%)	4 (19)	6 (33.3)	0.46
Chronic glomerulonephritis (%)	4 (19)	7 (38.8)	0.28
Use of statins (%)	10 (47.6)	12 (66.7)	1.00
Use of angiotensin-converting inhibitors (%)	11 (52.4)	12 (66.7)	0.82
Systolic blood pressure (mmHg)	149 ± 13.70	142 ± 19.30	0.23
Diastolic blood pressure (mmHg)	87.24 ± 10.99	84.31 ± 13.06	0.45
Serum albumin (g/dl)	3.79 ± 0.26	3.84 ± 0.28	0.57
Serum C-reactive protein (mg/dl)	1.10 (0.90; 1.40]	1.15 (0.90; 1.50)	0.47
Glycemia (mg/dl)	90 (84; 140)	108 (93; 179)	0.12
Hemoglobin (g/dl)	11.4 (10.7; 12.5)	11.7 (9.7; 12.6)	0.88
Serum bicarbonate (mEq/l)	21.53 ± 3.11	22.97 ± 2.68	0.14
Body weight (kg)	64.6 (57.6; 69.2)	70.8 (62.6; 76.0)	0.10
Total body water (l) (BIA)	32.72 ± 6.38	33.83 ± 8.19	0.64
Extracellular water (l) (BIA)	14.95 ± 2.99	15.36 ± 3.41	0.69
Anurics (%)	95.2	77.7	0.16

BP, IDWG, and serum sodium

BP and IDWG showed no significant changes among the groups during the follow-up. The median sodium serum concentration did not change in group A, and it was significantly elevated in group B between the 4th and 8th week (Table 2).

Medications

All patients received recombinant human erythropoietin, and the proportion of patients treated with iron hydroxide remained unchanged in both groups throughout the study. During the follow-up, the proportion of subjects using statins (group A, $p = 0.94$; group B, $p = 1.00$) or angiotensin-converting enzyme inhibitors (ACEIs) (group A, $p = 0.82$; group B, $p = 1.00$), and the median number of hypertensive classes (group A, $p = 0.37$; group B, $p = 0.09$) were not significantly different between the groups.

Biochemical, inflammatory and hematological markers

Biochemical and hematological markers did not significantly change in both groups at all assessment points. In group A, serum CRP levels significantly decreased between baseline and the 8th week and remained stable up to the 16th week. Significant reductions in median TNF-α and IL-6 concentrations

Table 2 Blood pressure (BP), interdialytic weight gain (IDWG), and serum sodium concentrations in group A ($n = 21$) and group B ($n = 18$)

	Baseline	Week 8	Week 16	p
Group A				
Systolic BP (mmHg)	148.8 ± 13.7	147.4 ± 9.22	147.5 ± 18.25	0.45
Diastolic BP (mmHg)	87.24 ± 10.99	85.73 ± 6.21	87.38 ± 11.91	0.71
IDWG (kg)	2.50 (2.34; 3.48)	3 (2.14; 3.45)	2.76 (2.17; 3.59)	0.95
Serum sodium (mEq/l)	138 (134; 142)	139 (136; 143)	138 (136; 141)	0.54
Group B				
Systolic BP (mmHg)	142.33 ± 19.3	148.5 ± 19.56	149.22 ± 20.44	0.17
Diastolic BP (mmHg)	84.3 ± 13.1	85.4 ± 11.0	83.6 ± 22.9	0.73
IDWG (kg)	2.64 (1.78; 3.5)	2.34 (1.84; 2.92)	2.79 (1.44; 3.22)	0.11
Serum sodium (mEq/l)	139 (135; 140)	141 (137; 144)*	140 (137; 142)	0.04

* $p < 0.05$ versus baseline

Table 3 Serum biochemical, inflammatory, and hematological markers in group A ($n = 21$)

	Baseline	Week 8	Week 16	p
Albumin (g/dl)	3.79 ± 0.26	3.85 ± 0.22	3.92 ± 0.36	0.14
Creatinine (mg/dl)	10.40 (9.20; 12.30)	10.70 (9.30; 12.10)	10.90 (9.20; 12.00)	0.85
Urea (mg/dl)	109 (93; 126)	99 (92; 119)	116 (91; 132)	0.41
Glucose (mg/dl)	90 (84; 140)	103 (83; 131)	97 (82; 141)	0.26
Cholesterol (mg/dl)	134.94 ± 21.67	135.86 ± 26.96	132.24 ± 25.17	0.65
HDL cholesterol (mg/dl)	38.76 ± 8.89	39.30 ± 10.84	37.43 ± 8.87	0.09
Triglycerides (mg/dl)	155.33 ± 82.91	153.09 ± 67.75	139.05 ± 54.02	0.29
Bicarbonate (mEq/l)	21.53 ± 3.11	23.08 ± 2.72	22.59 ± 2.58	0.09
Hemoglobin (g/dl)	11.40 (10.70; 12.50)	11.80 (10.70; 12.60)	11.90 (11.10; 13.00)	0.31
Hematocrit (%)	34.82 ± 5.19	36.2 ± 5.42	36.5 ± 5.73	0.31
Lymphocytes (cells/mm^3)	1,795.0 (1,386; 2,036)	1,507.0 (1,345; 1,856)	1,531.0 (1,267; 1,777)	0.13
C-reactive protein (mg/dl)	1.1 (0.90; 1.40)	0.7 (0.30; 1.10)*	0.6 (0.30; 1.30)*	0.022
TNF-α (pg/ml)	691 (633; 760)	542 (476; 628)*	443 (386; 530)*, **	<0.001
IL-6 (pg/ml)	5.47 (4.96; 5.86)	3.87 (3.33; 4.92)*	307 (2.42; 3.90)*, **	<0.001

* $p < 0.05$ versus baseline; ** $p < 0.05$ versus week 8

were observed between baseline and the 8th week and between the 8th and 16th weeks. In group B, there were no significant changes in inflammatory marker concentrations throughout the study (Tables 3, 4).

Nutritional assessment

Protein and caloric intake measurements remained unchanged in both groups at all assessment points. Sodium intake significantly decreased in group A between baseline and the 8th week and between the 8th week and the 16th week, while no significant changes were observed in group B. BIA measurements did not significantly change in both groups (Table 5).

Discussion

The results of this study showed that dietary sodium restriction was associated with a reduction in inflammatory marker concentrations, while body volume markers, IDWG, and BP remained unchanged. Our results are difficult to interpret. However, it is possible that the intervention used, dietary sodium restriction alone, was not sufficient to achieve reduction in these parameters. In the majority of studies that showed a reduction in systolic BP and IDWG with dietary sodium restriction, this intervention was used in combination with intensified ultrafiltration [14, 15] or reduced dialysate sodium [16, 17]. One study examining dietary sodium restriction alone showed a

Table 4 Serum biochemical, inflammatory, and hematological markers in group B (n = 18)

	Baseline	Week 8	Week 16	*p*
Albumin (g/dl)	3.84 ± 0.28	3.92 ± 0.34	3.94 ± 0.39	0.40
Creatinine (mg/dl)	10.15 (8.9; 12.1)	10.35 (9.3; 12.3)	9.95 (9.0; 11.6)	0.70
Urea (mg/dl)	105 (76; 117)	107 (86; 143)	93 (83; 120)	0.45
Glucose (mg/dl)	108 (91; 115)	116 (92; 155)	108 (91; 115)	0.85
Cholesterol (mg/dl)	143.17 ± 34.65	145.0 ± 29.3	148.39 ± 41.8	0.54
HDL cholesterol (mg/dl)	36.1 ± 12.1	37.6 ± 13.2	37.2 ± 12.8	0.58
Triglycerides (mg/dl)	210.1 ± 159.7	199.3 ± 114.1	192.8 ± 122.6	0.92
Bicarbonate (mEq/l)	22.9 ± 2.7	23.4 ± 2.3	23.8 ± 3.2	0.85
Hemoglobin (g/dl)	11.75 (9.7; 12.6)	11.25 (10.0; 12.6)	11.15 (10.1; 11.9)	0.74
Hematocrit (%)	35.2 ± 4.6	34.9 ± 4.85	34.9 ± 3.7	0.94
Lymphocytes (cells/mm^3)	1,762.5 (1,398; 2,112)	1,768.0 (1,601; 1,930)	1,698.5 (1,306; 2,279)	0.85
C-reactive protein (mg/dl)	1.15 (0.90; 1.50)	0.80 (0.30; 1.30)	0.80 (0.50; 1.70)	0.30
TNF-α (pg/ml)	645 (594; 714)	684 (610; 780)	689 (624; 748)	0.18
IL-6 (pg/ml)	5.83 (5.31; 6.0)	5.75 (5.31; 6.00)	5.75 (5.31; 6.01)	0.49

Table 5 Nutritional assessment in group A ($n = 21$) and group B ($n = 18$)

	Baseline	Week 8	Week 16	*p*
Group A				
Food intake				
Protein (g/kg/d)	0.99 ± 0.26	1.05 ± 0.25	1.01 ± 0.38	0.59
Calories (kcal/kg/d)	23.4 ± 5.4	24.4 ± 5.11	22.7 ± 7.4	0.34
Sodium (g/d)	9.25 ± 1.47	7.56 ± 1.97*	6.74 ± 1.29**	<0.001
Total body water (l)	32.7 ± 6.4	32.5 ± 6.4	32.25 ± 6.4	0.70
Extracellular water (l)	14.95 ± 2.9	14.95 ± 2.9	15.3 ± 2.9	0.49
Phase angle (°)	6.1 (5.4; 7.1)	6.2 (5.4; 6.9)	6.0 (5.3; 6.8)	0.72
Group B				
Food intake				
Protein (g/kg/d)	0.97 ± 0.24	0.99 ± 0.26	1.02 ± 0.31	0.84
Calories (kcal/kg/d)	23.7 ± 5.0	23.8 ± 6.1	22.6 ± 5.3	0.95
Sodium (g/d)	9.54 ± 1.6	9.33 ± 1.2	9.24 ± 1.28	0.64
Total body water (l)	33.8 ± 8.2	35.1 ± 8.7	33.7 ± 7.0	0.70
Extracellular water (l)	15.3 ± 3.41	15.95 ± 3.5	15.6 ± 2.1	0.49
Phase angle (°)	6.4 (5.1; 6.9)	6.3 (5.0 7.3)	5.6 (5.0; 6.7)	0.35

* $p < 0.05$ versus baseline;
** $p < 0.05$ versus week 8

reduction in systolic BP and IDWG; however, only 15 patients were enrolled [18]. Interestingly, McCausland et al. [21] recently reported that higher dietary sodium intake is associated with higher mortality, but not with BP.

With regard to the mechanisms involved in the attenuation of the inflammatory state, our findings suggest an additional mechanism by which sodium can directly promote inflammatory response. Some evidence supports the hypothesis that sodium induces gene expression of inflammatory response mediators. Investigators from the University of Colorado repeatedly showed that human peripheral blood mononuclear cell exposure to hyperosmolar conditions by sodium chloride addition increases gene expression for IL-1a, IL-1b, and IL-8 and promotes

phosphorylation of mitogen-activated protein kinase (MAPK p38) [22–24]. Therefore, the link between inflammation and salt intake could include hyperosmolar sodium chloride triggering MAPK p38 phosphorylation and stimulating inflammatory cytokine synthesis.

This study has some limitations. In particular, we had a small number of patients, and there was no accurate method to evaluate the amount of sodium consumed and body water beyond dietary registry and BIA measurements. The main strength of our study is its prospective and randomized design. To the best of our knowledge, our study is the first to examine the effects of dietary sodium restriction alone on BP, body volume, and inflammation in HD patients.

The results of this intervention study show that sodium restriction is associated with inflammatory-state attenuation in HD patients and suggest that sodium plays an independent role in the genesis of this condition. Therefore, dietary sodium restriction appears to provide an effective strategy for improving HD patients' prognosis, particularly in terms of cardiovascular events.

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Conflict of interest The authors declare that they have no conflicts of interest.

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