Effects of lowering dialysate sodium on flow-mediated dilatation in patients with chronic kidney disease

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Abstract

Objective. This study examined the effects of low dialysate sodium on endothelial dysfunction (ED) as measured by flow-mediated dilatation (FMD) of brachial artery in haemodialysis (HD) patients.

Methods. Thirty HD patients (17 men; mean age: 48.4 ± 17.8 years) were studied. Subjects underwent two consecutive 6-week HD periods. Dialysate sodium was 143 mEq/L in the first period (standard Na HD) and 137 mEq/L in the second period (low Na HD). After each period, we performed FMD, echocardiographic evaluation and 24-h ambulatory blood pressure monitoring (ABPM). Interdialytic weight gain (IDWG), levels of pre- and post-dialysis blood pressure (BP), and dialysis-related symptoms were monitored during the study.

Results. Per cent FMD was significantly greater (P < 0.05) after low Na HD (9.3 ± 6.2) compared with standard Na HD (5.7 ± 6.2). IDWG was significantly lower during low Na HD (2.35 ± 0.86 kg versus 2.71 ± 0.89 kg; P < 0.001). BP control was improved during low Na HD, as assessed by ABPM (128.2/77.5 mmHg versus 132.4/80.8 mmHg). Dialysis-related symptoms were more frequent during low Na HD (P < 0.05). There was no change in left ventricular mass after reducing dialysate sodium.

Conclusions. Reducing dialysate sodium concentration reduced ED, and provided better control of IDWG and BP, but increased dialysis-related symptoms.

Keywords: endothelial dysfunction; flow-mediated dilatation; ambulatory blood pressure monitoring; dialysate sodium

Introduction

Although numerous in vivo and in vitro studies have shown that endothelial dysfunction (ED) is common in patients with chronic kidney disease (CKD), the underlying mechanisms remain unknown [1–6]. Other work has demonstrated that the endothelium is directly affected by sodium, and that this is independent of blood pressure (BP) increases [7, 8]. The most widely used method for evaluating endothelial function is the measurement of flow-mediated dilatation (FMD) in the brachial artery using high resolution ultrasound [9, 10].

Little is known about which type of treatment reverses impaired endothelial function in patients with CKD [11, 12]. Rat and human studies that included normotensive overweight subjects have shown that ED is improved by restricted sodium intake and worsened by high dietary sodium [7, 13–16]. Salt consumption in CKD patients is determined not only by diet but also by the sodium concentration of the dialysate [17, 18]. Excessive interdialytic weight gain (IDWG) has been associated with high BP and left ventricular hypertrophy (LVH), and both of these are major risk factors for cardiovascular disease [19–21]. The main cause of IDWG is the salt and water intake that occurs between two dialysis sessions. A lowering of the dialysate sodium concentration has been shown to provide more effective diffusive sodium removal that may also reduce thirst and IDWG [22].

The current study aimed to determine whether a lowering of dialysate sodium levels exerts reversible effects on ED, LVH, IDWG and BP levels. We also recorded intradialytic symptoms, such as hypotensive attacks or cramps, that indicate a reduced tolerance to low sodium haemodialysis (HD).

Methods

Patients

We included 32 adult patients that had been on HD for at least 6 months. Twenty-seven of the patients with no residual renal function were on HD three times weekly, and the remaining patients with an average daily urine output of 500 mL received HD twice weekly. Hypotension-prone patients and patients with malignancy, active infection, chronic liver disease or haemoglobin levels <8 g/dL were excluded from the study. All patients were receiving HD with standard dialysis prescription as follows: blood flow: 300 mL/min; dialysate flow: 500 mL/min; membrane: polysulfone FX7 or FX6, (Fresenious Medical Care, Germany) and duration of HD session: 4–4.5 h. Medications, dietary salt intake and dialysis prescription were not changed during the study.

Using medical records, we obtained data on patient demographics, cause of end-stage renal disease, hepatitis status, history of diabetes mellitus, hypertension, cardiovascular disease, smoking, number of antihypertensive medications, serum sodium, serum albumin, haemoglobin levels and serum lipid profiles.
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Control subjects

Thirty healthy age-and gender-matched controls with no history of vascular disease (17 men, mean age: 45.3 ± 4.7 years) were included in the study. All control subjects underwent FMD evaluation.

Study protocol

Patients were evaluated during two 6-week periods, with each patient acting as his/her own control. In the first 6-week period (standard Na HD), all patients were dialysed against a sodium concentration of 143 mEq/L. In the second 6-week period (low Na HD), the dialysate sodium concentration was reduced from 143 to 137 mEq/L. The dialysis composition except for Na was: HCO₃:33.35 mEq/L, K:2.18 mEq/L, Mg:2.18 mEq/L, acetate:2.85 mEq/L, and was the same for all patients throughout the study. At the end of the two study periods, FMD, ambulatory blood pressure monitoring (ABPM) and echocardiography were performed during an interdialytic day. Echocardiographic and FMD evaluation were performed by the same operator who was unaware of subject status.

IDWG, dry weight, as well as pre- and post-dialysis BP levels were recorded for each HD session during the two study periods. IDWG was defined as the change in body weight between two consecutive HD sessions and was calculated by subtracting the dry weight from the weight before dialysis. The pre- and post-dialysis BP values were averaged from all consecutive sessions of each 6-week period. Changes in pre- and post-dialysis BP levels occurring from week to week in each period were also assessed.

During dialysis sessions, systolic and diastolic blood pressures (SBP, DBP), as well as dialysis-related symptoms such as cramps or hypotensive attacks and requirement for saline infusion because of hypotensive attacks/cramps were monitored. Hypotensive attacks were defined as a reduction in SBP by 20 mmHg associated with symptoms requiring emergency medical attention, trendelenburg position or saline infusion. Cramps were defined as symptoms that required emergency medical attention or saline infusion because of hypotensive attacks/per cent FMD was significantly higher during the low Na period, P < 0.001. Decreasing the sodium values in the different subgroups. A P-value of < 0.05 was considered statistically significant.

Results

Thirty-two patients were enrolled, and 30 patients (17 men and 13 women) completed the study. Two patients withdrew because of intradialytic hypotensive attacks associated with low Na HD. Baseline clinical and laboratory data of the subjects are given in Table 1.

Eleven patients (36.7%) had hypertension and were receiving antihypertensive medications. The average number of antihypertensive drugs per patient was 1.27 ± 0.47. Three of the hypertensive patients required two antihypertensives for controlling BP, and the remaining hypertensives received one drug. The most prescribed antihypertensive medication was calcium channel blockers, followed by angiotensin receptor blockers and beta blockers. Two hypertensive patients required discontinuation of antihypertensives during the low Na HD period.

Endothelium-dependent dilatation was significantly impaired in dialysis patients compared with controls (14.2 ± 4.8% for controls versus 5.7 ± 6.2% for patients during the standard Na period, P < 0.001 and 9.1 ± 6.1% for patients during the low Na period, P = 0.001). Decreasing the dialysate sodium concentration from 143 to 137 mEq/L caused an improved FMD % in 23 patients. The average per cent FMD was significantly higher during the low Na HD period than the standard Na HD period (Figure 1). The multiple linear regression model was not significant (R² = 0.081, P = 0.52). Pre-dialysis BP (β = 0.002, P = 0.355),
post-dialysis BP ($\beta = -0.001, P = 0.677$), and the difference between the dialysate sodium and serum sodium ($\beta = -0.007, P = 0.260$) did not affect the improvement in FMD. There was no significant difference in plasma sodium levels between patients with and without improved FMD (135.7 ± 2.2 mEq/L versus 135.7 ± 4.1 mEq/L; $P > 0.05$).

Although 24-h ABPM decreased from 132.4/80.8 to 128.2/77.5 mmHg during the low Na HD period, this fall was not statistically significant. There were no significant differences in daytime and night-time BP levels between the two study periods (Table 2). Pre- and post-dialysis SBP and DBP levels were also similar during the two periods (Table 2). There were no differences between pre-dialysis BPs measured during each week in both dialysate groups. Similarly, there were no differences between post-dialysis BPs measured during each week in both dialysate groups. There were no significant differences in plasma sodium or the gradient between dialysate sodium and plasma sodium concentration between patients with and without decreased BP (135.4 ± 2.6 versus 136.4 ± 3.3 mEq/L, $P > 0.05; 1.65 \pm 2.55$ mEq/L versus $0.60 \pm 3.27$ mEq/L, $P > 0.05$).

IDWG decreased significantly during the low Na period compared with the standard Na period (2.35 ± 0.86 kg versus 2.71 ± 0.89 kg, $P < 0.001$) (Figure 2). Hypotensive attacks and cramps were more frequent during the low Na HD period (Table 2). The amount of infused saline solution that was necessary due to HD-related symptoms was significantly higher during the low Na HD period than in the standard HD period (Table 2). There was no relation between serum sodium levels and complications observed during dialysis sessions. Serum sodium levels in patients with and without increased cramps (135.6 ± 2.9 mEq/L versus 135.8 ± 2.6 mEq/L, $P > 0.05$) and in patients with and without increased hypertensive attacks (134.2 ± 3.1 mEq/L versus 136.2 ± 2.4 mEq/L, $P > 0.05$) were not significantly different.

LV EF and LV mass remained unchanged at the end of the low Na HD period (EF: 61.2 ± 11.6% versus 61.3 ± 9.9%, $P > 0.05$; LV mass: 203.3 ± 59.6 g versus 203.2 ± 58.4 g, $P > 0.05$).

**Discussion**

In this study, we demonstrated that low Na HD reduced ED as measured by FMD of the brachial artery. To our knowledge, this is the first demonstration that lowering dialysate sodium will cause improved endothelial function. Previous
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studies have examined the effects of dietary salt restriction on ED in normotensive and hypertensive subjects [7, 13, 25, 26]. Dickinson et al. [25] reported a reduction in ED in normotensive overweight subjects at the end of a 2-week sodium-restricted diet. In a study that included normotensive subjects, Fang et al. [14] showed that high salt consumption (18 g salt/day for 7 days) was associated with a reduction in plasma nitric oxide (NO) synthesis, which was caused by high asymmetric dimethylarginine (ADMA) levels. It is well documented that a high salt intake decreases plasma NO levels in hypertensive patients [27–29]. In addition, it has been shown that salt loading increases ADMA levels, an endogenous inhibitor of nitric oxide synthase [13, 14, 30].

One of the most important findings of the present study was the significant fall in IDWG that occurred during low Na HD. It is well known that low IDWGs provide more comfortable dialysis sessions because of the decreased amounts of hourly fluid removal required during dialysis. In contrast with this, we observed that lower IDWG during low Na was associated with a higher frequency of dialysis-related symptoms. In several previous studies, there were no differences in frequency of hypotensive attacks or cramps between standard Na HD and low Na HD, which suggested that low dialysate sodium concentrations were well tolerated [31–34]. Similarly, Davenport [33] showed that a lowering of dialysate sodium caused reductions in IDWG and dialysis-related hypotension. Ozturk et al. [35] lowered dialysate sodium from 140–153 mEq/L in 17 HD patients and found significant increases in the frequency of cramps, hypotensive attacks and saline infusion requirements during dialysis. The increased saline requirement was similar to that in our study. Recent studies have suggested that a lowering of dialysate sodium concentration to predialysis serum sodium levels (individualized Na dialysis) may reduce IDWG and intradialytic symptoms [36].

Decreased dialysate sodium concentration, which is an important determinant of sodium loading in HD patients, is associated with improved BP control. Several previous studies demonstrated that a lowering of dialysate sodium by 5 mEq/L for 2 weeks [34, 37] or for 15–20 weeks [38] will cause a fall in BP. Furthermore, Davenport [33] observed that patients from dialysis centres that used higher dialysate sodium concentrations required greater numbers of antihypertensive medications. Our study showed that a lowering of dialysate sodium from 143 to 137 mEq/L for 6 weeks was accompanied by a reduction in predialysis SBP and mean 24-h ambulatory BP. However, unlike the two previous studies, our reductions in BP did not reach statistical significance. To explain this difference, the two previous studies used shorter periods with reduced dialysate sodium, which may have resulted in more significant falls in BP [34, 37]. There are several factors that may explain these differing BP findings. First, we modified only dialysate sodium without altering dietary sodium intake during the low Na HD period. Second, there was a possibility that less antihypertensive medications would be required since our patients would have lower BP levels. Nevertheless, an important outcome for our studies was that two of our hypertensive patients no longer required antihypertensive medication during the low Na period.

Strict volume control is the predominant factor for reducing LVH [39, 40]. A regression of LVH has been achieved through prolonged and frequent dialysis, nocturnal HD, daily HD, as well as strict dietary sodium restriction [40–42]. Sayarlio et al. [43] showed that a low sodium dialysate given for >8 weeks reduced the effects of volume load on the heart, as assessed by significant decreases in inferior vein cava diameter, pulmonary artery pressure and EF. In our study, we did not find reductions in EF or LV mass index at the end of low Na HD, although IDWG was lower in this period. This lack of effect on LVH in our study may be explained by the lack of significant BP reductions or by the shorter time interval of our low Na HD period.

In conclusion, we have shown for the first time that a lowering of dialysate sodium concentration is consistently effective for reducing ED. We also demonstrated that low Na dialysis caused a reduction in IDWG and provided better BP control; however, it increased the frequency of intradialytic hypotensive episodes and cramps.

Conflict of interest statement. None declared.

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