The relevance of dietary sodium in hemodialysis

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ABSTRACT

Since the earliest days of hemodialysis, dietary sodium restriction has been recommended as a therapeutic means to mitigate problems of extracellular volume overload, hypertension and inter-dialytic weight gain. Recently, there has been a proliferation of human subjects’ research examining the potential effects of dietary sodium curtailment. Herein we examine the available evidence with respect to the effects of dietary sodium restriction on clinically relevant endpoints among hemodialysis patients.
INTRODUCTION

Sodium is the most abundant extracellular cation, the major determinant of plasma osmolality and one of the most important electrolytes involved in the homeostatic control of extracellular volume and blood pressure [1]. In humans, the control of sodium balance is tightly regulated by several neurohormonal axes in order to maintain the constancy of the internal environment [2]. In healthy individuals, the kidneys are the primary end-organs that regulate sodium homeostasis. Renal capacity for natriuresis varies across a broad range so as to be able to account for variability in dietary sodium intake and effective circulating volume status.

In light of their minimal residual renal function, hemodialysis patients cannot adequately excrete sodium loads and are predisposed to states of sodium and extracellular volume overload. Therefore, dietary sodium gain must be counterbalanced by dialytic removal in order to maintain neutral sodium balance. The aim of this manuscript is to critically review the literature pertaining to the epidemiology of dietary sodium intake in maintenance of hemodialysis patients, and the association of dietary sodium restriction with clinical outcomes.

DIETARY SODIUM: ASSOCIATIONS IN THE NON-DIALYSIS POPULATION

Many studies of non-dialysis populations have found associations between greater dietary sodium intake and adverse outcomes. For example, Intersalt studied 10,074 individuals across 32 countries and found that each 2.3 g (~100 mmol) increment in 24-h urinary sodium excretion was independently associated with 6/3 mmHg higher blood pressure [3]. Forman et al. [4] reported that each 2.3 g increment in daily salt intake (~1 g or 44 mmol sodium) was associated with a 6% greater adjusted risk of developing hypertension, among participants of the Prevention of Renal and Vascular End Stage Disease (PREVEND) study. Lin et al. [5] reported that, compared with the lowest quartile (3.9 g salt/day; ~1.7 g or 75 mmol sodium), those in the highest quartile (5.5 g salt/day; ~2.4 g or 106 mmol sodium) of estimated dietary salt intake had 52% greater odds of developing incident chronic kidney disease (defined as estimated glomerular filtration rate decline ≥30%) during an 11-year period of follow-up. A meta-analysis of observational studies reported a 20% greater adjusted risk of stroke per 2.3 g increment in estimated daily dietary salt intake (~1 g or 44 mmol sodium) [6]; while others have reported a J-shaped association between 24-h urinary sodium excretion and cardiovascular outcomes [7]. Meta-analyses of randomized trials have reported disparate results, depending on the trial selection criteria utilized [8, 9]. In terms of randomized studies, the Dietary Approaches to Stop Hypertension-Sodium (DASH-Sodium) trial randomized participants to a control diet (low in fruit, vegetables and dairy, but high in fat) or the DASH diet, and further randomized each of these groups to a high, intermediate or low sodium diet for 30 consecutive days. Among individuals consuming the control diet (typical of the intake in the USA), a reduction in daily dietary salt intake from 7.4 to 5.5 g (~3.2 to 2.4 g or 141 to 106 mmol sodium) was associated with a 2.1 mmHg reduction in systolic blood pressure (SBP); while reduction in daily dietary salt intake from an average of 5.5 to 3.7 g (~2.4 to 1.6 g or 106 to 64 mmol sodium) was associated with a 4.6 mmHg reduction in SBP [10].

Accumulating evidence suggests that sodium may be stored in a non-osmotic form (without concomitant water retention) in association with glycosaminoglycans [11]. In this interstitial environment, sodium accumulation may have an important influence on the regulation of surrounding cells, providing a novel mechanism for potential up-regulation of pro-inflammatory pathways and detrimental effects mediated by pathways other than extracellular volume status [12]. These findings are important avenues for future research in maintenance of hemodialysis patients.

DIETARY SODIUM RESTRICTION IN HEMODIALYSIS

During the infancy of hemodialysis, it was noted that the combination of dietary sodium and fluid restriction provided a means by which to limit volume accumulation and minimize hypertention between dialytic treatments [13, 14]. Interestingly, following initiation of renal replacement therapy of the first reported chronic hemodialysis patient, Scribner et al. [13] described a decline in the 24-h urinary sodium excretion from 2.3 to 0.5 g/day (100 to 23 mmol/day), suggesting that the loss of residual renal function may play an important role in the tendency to sodium and volume accumulation in oligo-anuric patients. The subsequent institution of dietary sodium restriction by healthcare providers has thus prevailed through the subsequent decades and remains a mainstay of dietary advice to hemodialysis patients [15], despite a relative paucity of supporting evidence.

WHAT IS THE AVERAGE DIETARY SODIUM INTAKE IN HEMODIALYSIS PATIENTS?

Not surprisingly, the estimated average dietary sodium intake in hemodialysis patients appears to be quite variable, which probably reflects both inaccuracies in assessment tools and dietary differences between populations and between individual patients. Attempts have been made to estimate inter-dialytic sodium and water intake based on changes in serum sodium and body weight between dialysis sessions. In one study, based on calculations using physiological balance principles, the authors suggested that sodium intake accounted for the majority of inter-dialytic weight gain (IDWG) in nine non-diabetic patients and half of IDWG in seven diabetic subjects [16]. However, this approach is likely over-simplified, as it does not account for dietary potassium intake, non-dietary exogenous sodium sources or for non-osmotic sodium storage.
Oligo-anuric patients present a unique set of challenges in deriving accurate measurements of dietary sodium intake, with dietary recall being the most common assessment tool utilized in reports to date. In a study of eight stable Japanese hemodialysis patients, the authors reported an average daily salt intake of 12.6 g (~5.5 g or 240 mmol sodium), based on dietary records [17]. An average daily salt intake of 10 g (~4.3 g or 189 mmol sodium) was reported among 17 Spanish patients, estimated from mass transfer equations [18]. In a study of 17 American patients, the authors reported an average daily salt intake of 9.7 g (~4.2 g or 183 mmol sodium), with no significant differences in estimates obtained from dietary recall compared with those obtained from balance formulae in a subgroup of seven patients [16]. In our post hoc analysis of the Hemodialysis (HEMO) Study, we reported an average daily dietary salt intake of 5.15 g (~2.24 g or 99 mmol sodium), based on 2-day diet diary-assisted recalls [19]. The Tassin group in France, renowned for their low incidence of hypertension and strict volume control, reported an average estimated salt intake of 3.8 g/day (~1.7 g or 75 mmol sodium) based on 3-day food questionnaires [20].

**STUDIES EXAMINING THE ASSOCIATION OF DIETARY SODIUM INTAKE WITH OUTCOMES IN HEMODIALYSIS PATIENTS**

There has been a paucity of research examining the association of dietary salt restriction in isolation among hemodialysis patients. Potential reasons for this include the inability to accurately assess dietary sodium intake and years of accumulated clinical experience suggesting that a multi-pronged approach is required to address the problems of IDWG and sodium excess. Among those studies that have been published, few have been prospective and none was randomized.

**Dietary salt restriction and ultrafiltration**

Early literature supporting an association between sodium restriction and improved blood pressure among hemodialysis patients came from observational studies where dietary measures were instituted in combination with strict volume control. In 1972, Craswell et al. reported their experience with 89 individuals who were enrolled in their home hemodialysis program in London, England. This regimen comprised thrice-weekly nocturnal dialysis for 10 h, in addition to dietary sodium and water restriction. The dietician estimated that individual daily dietary salt consumption was 2 g (~1 g or 45.5 mmol sodium); the average SBP was 103.5 mmHg, which was recorded between 16 and 28 h post-dialysis [21]. Covic et al. also reported their experience with 286 patients during the period from 1968 to 1986, all of whom were prescribed low salt diets 2.2 g/day (~1.1 g or 50 mmol sodium). When averaged over the preceding 5 years for each individual, the mean SBP was 136/81 mmHg and only 7.4% were taking regular anti-hypertensive medications [22]. More recent examples include an audit of 105 chronic hemodialysis patients who were receiving thrice-weekly 4 h sessions against 140 mmol/L dialysate sodium concentrations. Following initial data collection, and among other interventions that included patient education and dry weight probing, patients were advised to ingest a low salt diet of <2 g/day (~0.4 g or 18 mmol sodium). At the follow-up data collection point, 74.3% of individuals achieved target pre-dialysis blood pressures of <140/80 mmHg compared with 38.0% at baseline, while IDWG had decreased from 5.3 to 3.2 kg, respectively. Dietary sodium intake was not directly assessed as part of this audit, limiting the ability to determine the independent role it played in these changes [23]. A larger series of 218 thrice-weekly maintenance hemodialysis patients from Turkey were analyzed following adoption of an institutional strategy consisting of dietary salt restriction, cessation of blood pressure medications and intensification of ultrafiltration. Analysis of food consumption patterns estimated a mean daily dietary salt intake of 3.2 g (~1.6 g or 70 mmol sodium). At the end of the observation period (mean 47 months), the mean pre-dialysis SBP had declined from 150 to 121 mmHg and IDWG had declined from 1.44 to 0.93 kg. Of note, extra UF sessions were required in 28% of individuals, which may have confounded these results [24]. Ozkayhaz et al. examined the effect of intensified ultrafiltration in combination with dietary salt restriction on changes in echocardiographic measurements of left ventricular hypertrophy in 15 patients. After the mean follow-up of 37 months, SBP had fallen from 139 to 116 mmHg and calculated left ventricular mass index had fallen from 175 to 105 g/m², despite the absence of a significant change in the left ventricular ejection fraction [25]. However, no estimation of dietary salt intake was recorded in this study.

The above data appear to suggest that the combination of dietary salt restriction with strict volume control may be useful in achieving blood pressure and estimated dry weight targets. However, they are limited by lack of power, short follow-up, inconsistent and possibly inaccurate estimation of dietary sodium intake, as well as by possible effects of other concomitant dietary interventions.

**Dietary sodium restriction and reduced dialysate sodium concentration**

A report of five hemodialysis patients examined the effect of 6–8 g daily dietary salt restriction (~2.4–3.2 g or 106–140 mmol) in combination with a reduction in dialysate sodium from 142 to 135 mmol/L. Without change in dry weight, post-dialysis SBPs declined from 174 to 118 mmHg with these interventions [26]. Similarly, a report of eight hemodialysis patients highlighted improved blood pressure control following dietary counseling (6 g/day dietary salt restriction; ~2.4 g or 106 mmol sodium) and graded reduction in dialysate sodium concentration. Without change in dry weight, the average pre-dialysis SBP declined over the observation period from 147 to 136 mmHg [27]. Kayikcioglu et al. reported data from a cross-sectional study from Turkey that leveraged practice pattern differences between two dialysis centers, one of which (Center A) promoted dietary salt restriction (5 g/day; 2 g or 88 mmol sodium) and intensive ultrafiltration for BP control; the other (Center B) used anti-hypertensive medications unless edema was present. Despite
the similar session length, dialysate sodium concentration and dialyzer use, Center A had lower IDWG (2.3 versus 3.3 kg; P < 0.001) and less left ventricular hypertrophy (74 versus 88%; P < 0.001) by echocardiographic assessment. However, there were no detectable differences in SBP or diastolic blood pressures between the two centers [28].

In the aforementioned studies, the actual dietary sodium intake was not reported, which limits the interpretation of the independent association of this factor with the outcomes of interest and again, caution must be applied when interpreting and extrapolating results from observational data.

**Dietary sodium restriction alone**

One of the few studies to examine dietary sodium restriction alone involved a cross-over study of 15 patients, where sodium intake was estimated by sodium mass transfer and conductivity measurements. All dialysis parameters and dry weight were held constant; salt intake pre- and post-dietary intervention was estimated at 10.2 versus 7.1 g/day (∼4.1 versus 2.8 g or 180 versus 123 mmol sodium), respectively. The corresponding SBP change was from 138.7 to 131.8 mmHg (P < 0.01), with IDWG decreasing from 2.26 to 1.87 kg (P < 0.001) [29].

**Association of dietary sodium with mortality**

In our analyses of the HEMO Study, we examined the association of three different metrics of estimated dietary sodium intake (dietary sodium alone, sodium:calorie intake ratio and sodium:potassium intake ratio; n = 1770) with predefined clinical outcomes of interest (pre-dialysis SBP, IDWG and all-cause mortality) [19]. The reason for considering these three metrics of exposure is related to the known correlation between dietary sodium intake and intake of other macronutrients, which may also affect survival [30]. Notable exclusions of the HEMO Study included those with a baseline albumin <2.6 g/dL, the presence of end-stage comorbid conditions, those with significant residual renal function and those who failed to achieve target dose parameters required for trial purposes [31]. Dietary sodium intake was assessed by 2-day diet diary-assisted recalls. We found that diet-Na (g/day) and sodium:calorie (mg/kcal/day) were only modestly associated with greater UF requirements in adjusted analyses (0.14 and 0.17 L, respectively; P < 0.001) and inconsistently associated with pre-dialysis SBP (1.58 mmHg; P < 0.001 and 1.65 mmHg; P > 0.05, respectively). Differences in our findings compared with prior studies may be related to the lack of concomitant changes in dry weight (which were not mandated in the HEMO Study) and to unmeasured exogenous sources of sodium excess, e.g. from the use of higher dialysate sodium concentrations. Nevertheless, all dietary sodium intake metrics were associated with a greater adjusted risk of all-cause mortality (aHR 1.12; 95% CI 1.03–1.20 per 1 g increment in diet-Na; aHR 1.14; 95% CI 1.02–1.28 per mg/kcal increment in sodium:calorie ratio; and aHR 1.12; 95% CI 1.02–1.24 per mg/mg increment in sodium:potassium ratio), which accentuated following additional adjustment for nutritional-related parameters.

Many prior reports have suggested that dietary recall instruments have a tendency to underestimate actual nutrient intake [32–35]; an observation that may extend to dietary sodium intake among hemodialysis patients. However, in our analyses, in order to account for this and for potential differences in dietary habits, we indexed reported sodium intake to caloric intake; this exposure may be less subject to bias, and provide greater confidence in observed associations. It must be noted that, although our data support the construct that less sodium intake is better, they cannot be used to identify a ‘safe’ upper limit for sodium intake, if such even exists among hemodialysis patients.

Our data also provide indirect evidence that unintended concomitant compromises in other macronutrient intake that occur in the setting of dietary sodium curtailment may partially offset the benefits of dietary sodium limitation. Specifically, HEMO Study patients who ingested less sodium also had lower intake of protein and calories. Therefore, the associations between sodium intake and mortality were more pronounced when caloric and protein intake were adjusted for in the statistical model (i.e. estimating survival differences between patients with discrepant sodium intake but equivalent protein and caloric intake), than when these factors were not adjusted for (i.e. estimating survival differences between patients with discrepant sodium intake but not necessarily with equivalent protein and caloric intake). Although manipulations of dietary sodium intake may be simulated mathematically in the context of a statistical model, they may not be readily implemented in clinical settings—at least through conventional dietary counseling—without unintended compromise of global macronutrient intake. This may be particularly relevant to consider in dialysis patients suffering from protein–energy malnutrition. Further research is needed to identify clinical paradigms by which the beneficial effects of sodium restriction may be best realized.

Soberingly, we found that prescribed dietary sodium restrictions were poorly adhered to. Dietary sodium intake was only 200 mg/day less among patients prescribed more restrictive (in most cases 2 g/day) versus more liberal (in most cases 3–4 g/day) dietary sodium. This suggests that even in the context of a dedicated clinical study—where oversight is high—current paradigms of dietary counseling are inadequate. Likely as a consequence, a more restrictive dietary sodium prescription was associated with only modestly lower UF requirement (∼0.17 L), and was not associated at all with differences in predialysis SBP or mortality. However, because nearly all patients in the HEMO Study were prescribed some dietary sodium restriction, these results should not be extrapolated to imply that even a more liberal dietary sodium prescription is safe. Adherence to dietary advice may also vary according to residual renal function—we found that the average reported dietary salt intake was 5.5 g/day in subjects with >200 mL/day residual urine output versus 5.1 g/day in those with ≤200 mL/day urine output (∼2.4 versus 2.2 g or 106 versus 97 mmol sodium; P-difference < 0.01). However, we observed no significant difference when the average daily sodium:calorie ratio was compared between non-oliguric and oliguric subjects (1.52 versus 1.49 mg/kcal/day; P = 0.39), likely reflecting better
overall health status and appetite in those with significant residual urine output compared with those without. Diuretic therapy may provide additional means by which to promote natriuresis in dialysis patients with residual urine output. Prior studies have reported mixed findings associated with the use of diuretic therapy in hemodialysis patients. On the one hand, data from the Dialysis Outcomes and Practice Patterns group found that diuretic use was associated with reduced IDWG, fewer intra-dialytic hypotensive episodes and reduced cardiac-specific mortality; on the other hand, there was no significant association between diuretic use and reduced all-cause mortality [36]. In our analyses of the HEMO Study, we found no evidence for effect modification of the effect of dietary sodium intake or sodium:calorie ratio on all-cause mortality according to residual urine output (P-interaction > 0.75 for both), although the analyses may have been underpowered in this regard owing to a paucity of enrolled patients with residual urine output.

**EXOGENOUS SODIUM FROM HIGHER DIALYSATE SODIUM CONCENTRATIONS**

In addition to dietary sodium intake, another potential source of exogenous sodium loading is in the form of higher dialysate sodium concentrations. Higher dialysate sodium has previously been associated with improved hemodynamic stability [37, 38], but these findings have been offset by associations with greater thirst [39], IDWG [40] and blood pressure [41]. However, we and others have reported that the harmful effects of higher dialysate sodium concentrations are primarily observed among patients with high-normal or high, but not low, pre-dialysis serum sodium levels [42, 43]. Clearly, further research is needed to understand the mechanistic underpinnings of this phenomenon.

**CONCLUSION**

The heterogeneity across studies, lack of gold standard assessment of dietary sodium intake and absence of randomized feeding trials are major limiting factors in determining the optimal sodium intake in the high-risk population of chronic hemodialysis patients. However, the evidence to date supports the assertion that greater dietary sodium intake is associated with higher blood pressure, greater IDWG and greater all-cause mortality on a population-wide basis in chronic hemodialysis patients. In the absence of controlled feeding studies, individualization of dietary sodium intake is often necessary, taking into account the IDWG, extracellular volume status, hemodynamic stability and the gross nutritional state of each individual patient.

**CONFLICT OF INTEREST STATEMENT**

F.R.M.C. is supported by a research fellowship from the National Kidney Foundation (2011–13). S.S.W. has received grant support from Astellas for an investigator-initiated study of hyponatremia and participated in an advisory board meeting for Otsuka. He is supported by DK075941 and U01DK085660. S.M.B. has served as an advisor to Amgen, CB Fleet Company and Proctor & Gamble. He has received speaking honoraria from Fresenius Medical Care North America. His spouse is employed by Astra Zeneca.

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Received for publication: 14.8.2012; Accepted in revised form: 28.8.2012