Improving Volume Status by Comprehensive Dietary and Dialytic Sodium Management in Chronic Hemodialysis Patients

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Abstract
Chronic volume overload is highly prevalent in chronic hemodialysis patients and leads to hypertension, left ventricular hypertrophy and increased hospitalization and mortality rates. Volume overload is caused primarily by a positive sodium balance and can be improved by sodium restriction. The main sources of sodium excess are a high-sodium diet in the interdialytic period and a positive sodium balance during dialysis. Here we discuss different approaches to achieve neutral or negative sodium balance, including reducing dietary sodium intake, individualizing dialysate sodium prescription, abandonment of sodium profiling, and reducing saline infusion for treatment of intradialytic symptoms and as part of dialyzer rinsing and priming procedures. All of these approaches should be combined for a maximal reduction of volume overload.

Introduction
Volume overload, which is defined as an expansion of extracellular volume (ECV) above normal, is very common in chronic hemodialysis (HD) patients and is associated with adverse outcomes. There is a close relationship between volume overload and hypertension, increased vascular stiffness and cardiac remodeling [1–4]. Moreover, several studies have shown a relationship between volume control and mortality [5–8]. In a recent prospective cohort study, volume status was assessed by multifrequency bioimpedance in 269 chronic HD patients [5]. After adjustments for co-variables, including blood pressure level, age, cardiovascular disease and diabetes, overhydrated patients (defined as the upper quartile of ECV as determined by multifrequency bioimpedance) had a two times higher mortality risk. Other studies did not directly assess volume status, but demonstrated relationships between high interdialytic weight gain or high ultrafiltration rates and increased mortality [6, 7].

The diagnosis of volume overload in HD patients is not straightforward. ‘Dry weight’ is generally assessed based on clinical judgment and may not necessarily represent the optimal volume status. For instance, the presence of pedal edema is frequently used as one of the clinical markers to diagnose volume overload, but is not associated with more objective markers such as the vena cava diameter or biochemical parameters [8]. Bioimpedance spectroscopy is the most promising technique to quan-
tify volume status and is increasingly used in clinical practice [9]. In a recent study, volume status was measured with this technique in 370 randomly selected patients. This study revealed that more than 20% of the patients were overhydrated at the end of dialysis [10]. Identifying these patients is of clinical importance, since they are most likely to benefit from interventions. It has been shown that decreasing the post-dialysis target weight in hypertensive HD patients leads after 4 weeks to significant blood pressure reductions of a similar magnitude to that achieved with a single antihypertensive drug [11]. Long-term observations have suggested that strict volume control also improves left ventricular dimensions [12].

It has been postulated that each individual has an inherent plasma sodium concentration ('sodium set-point') and, as a consequence, any increase in plasma sodium will be followed by a thirst-driven water intake to lower the plasma sodium until the set-point is reached [13, 14]. The pre-dialysis serum sodium concentration remains stable over time in HD patients [15]. In other words, whenever the sodium intake (be it from dietary sources or during dialysis) exceeds the accompanying fluid intake, plasma sodium levels rise above the set-point (i.e., a hypertonic state) and additional intake of fluid occurs. An overall positive sodium balance, taking into account the interdialytic and intradialytic time periods, is therefore the major culprit in fluid-overloaded patients and is a result of a high-sodium diet, a positive sodium balance during dialysis, or, in many cases, the combination of both. The recommended maximum dietary sodium intake of 2.4 g/day (100 mmol sodium/day; 6 g salt [sodium chloride]) [16] is actually an elusive goal for many chronic HD patients. In the few studies in dialysis patients where sodium intake was measured, it did not substantially differ from that in the general population [17]. During HD treatment, most sodium is removed by convection. However, a positive sodium gradient, i.e., the dialysate sodium concentration exceeds the plasma sodium, substantially contributes to a positive sodium balance during treatment by diffusive transport. In addition, inappropriate sodium profiling and excessive saline infusions to treat intradialytic symptoms or as part of dialyzer rinsing and priming procedures may result in sodium loading [18].

Dietary sodium restriction can be combined with adjustments of the dialysis treatment to avoid a positive sodium balance in order to achieve the largest improvements in fluid status, blood pressure level and maybe also long-term outcomes [19]. Remarkably few studies have focused on the effects of such a combined approach [20]. In this article we review current evidence of strategies and clinical benefits of sodium restriction, and discuss the feasibility and potential drawbacks of intensive sodium management in routine practice.

**Dietary Sodium Restriction and Its Relationship to Outcome**

**Dietary Sodium Restriction in Normo- and Hypertension**

The intestinal absorption of dietary sodium is close to 100% [21]. Whenever dietary sodium intake is increased, the antidiuretic hormone and thirst feedback systems are activated, so that the plasma sodium concentration and plasma osmolality are maintained at relatively constant levels. In healthy subjects the resulting increase in ECV is counteracted by appropriate changes in renal sodium and fluid excretion, restoring normohydration [21]. Despite this powerful adaptive mechanism, a chronically high salt intake generally results in an increased ECV.

A clear relation between dietary sodium intake and blood pressure level has been established in the general population [22]. Additionally, it has been shown that blood pressure can be lowered with a low-sodium diet in hypertensive patients [23, 24]. Strict dietary sodium restriction also effectively lowers blood pressure in patients with resistant hypertension, suggesting that an excess of sodium is involved in the development of therapy-resistant hypertension [25]. However, it is controversial whether lowering blood pressure with sodium restriction improves long-term cardiovascular prognosis in subjects with normo- or hypertension. Randomized controlled trials evaluating the effects of dietary sodium restriction in various populations were designed to detect differences in blood pressure level and did not have enough power to analyze clinical events [26]. Data from observational studies are inconsistent and show both the benefits and potential harm of a low-sodium diet [27]. These inconsistencies may be explained by differences in the studied populations and outcomes, substantial inter-individual blood pressure response to sodium restriction, or by potential undesirable side effects of sodium restriction, such as activation of the sympathetic nervous system and the renin angiotensin aldosterone system [27]. In the absence of large clinical trials in well-defined patient populations, it is unlikely that the effects of sodium restriction on clinical outcomes will be fully elucidated.
Dietary Sodium Restriction in Dialysis Patients

Several studies have investigated the effects of dietary sodium restriction in dialysis patients. Despite the fact that these studies were mostly small, had short follow-up or lacked a control group, they consistently showed a decrease in intradialytic weight gain, blood pressure and use of antihypertensive drugs [17]. In a retrospective analysis, 67 hypertensive HD patients were evaluated 8–60 months after a new treatment policy was initiated, consisting of strict volume control by sodium restriction and, if necessary, additional ultrafiltration sessions [28]. This policy resulted in sustained lower blood pressure levels in nearly all patients, with only 3 of 67 (4%) patients needing anti-hypertensive therapy at the end of the follow-up period [28]. In another study by the same investigators, 190 HD patients from a center with strict volume control by means of sodium restriction (center A) was compared with 204 patients from a center that predominantly treated patients with antihypertensive drugs (center B) to control blood pressure [29]. The patient characteristics were not statistically different between the centers; dietary sodium intake was unfortunately not assessed. The patients in center A as compared to center B used less antihypertensive drugs (7 vs. 42%), but had similar average blood pressure levels (126/75 vs. 126/76 mm Hg). Interdialytic weight gain and the number of hypertensive episodes were lower in center A (2.29 vs. 3.31 liters, and 11 vs. 27%, respectively). Cardiac dimensions, including left ventricular mass, were also significantly better in center A, suggesting that long-term intensive volume control by means of sodium restriction may slow down or improve left ventricular hypertrophy. In contrast, a recent retrospective study in 305 incident peritoneal dialysis patients showed an association between a low average dietary sodium intake and increased death risk, independent of caloric intake [30]. As of yet, there are no prospective data on the relation between dietary sodium restriction and clinical events in dialysis patients.

It is underappreciated that certain drugs, such as sodium bicarbonate and antibiotics contain substantial amounts of sodium, thereby potentially contributing to fluid retention [31]. However, in a prospective study in 110 stable HD patients an average intake of 2 g sodium bicarbonate/day (i.e., 0.5 g sodium) was not associated with increases in blood pressure or interdialytic weight gain [32]. This raises the intriguing question whether or not the anion accompanying sodium matters [33]. Although this point is of theoretical interest, its practical relevance is small, since sodium is usually accompanied by chloride.

Summarizing, there is a clear relation between dietary sodium intake and blood pressure level in different patient populations. Conclusive evidence on the relation between sodium intake and cardiovascular events is lacking. In HD patients, sodium restriction improves volume control and blood pressure and is associated with improved cardiac function. Importantly, blood pressure levels within the normal range can be achieved in the majority of the patients by strict dietary sodium restriction, without the need for additional blood pressure-lowering drugs. This justifies increased efforts to restrict dietary sodium in HD patients, especially in those with hypertension and cardiovascular disease.

Sodium Restriction during Hemodialysis Treatment

The dialysis procedure itself can be a major contributor of sodium excess in HD patients. As mentioned above, several causes of a positive sodium balance during treatment and/or a rise in post-dialysis serum sodium concentration can be identified, including: (a) a positive sodium gradient; (b) inappropriately conducted sodium profiling; (c) treatment of intradialytic symptoms with saline solutions, and (d) unnecessary saline administrations during priming and rinsing of the extracorporeal circuit. We describe strategies to avoid a positive sodium balance during HD treatment.

Alignment of Dialysate Sodium with Plasma Sodium Concentration

In patients with a positive sodium gradient, sodium will diffuse from the dialysate to the blood compartment of the dialyzer. Although sodium is mainly removed by ultrafiltration (about 6.9 g sodium chloride/liter ultrafiltrate [34]), a positive sodium gradient may result in a net sodium load during treatment, depending on the ultrafiltration volume and the gradient. Regardless of the presence or absence of net sodium gain, a positive sodium gradient will in most cases result in an increase in post-dialysis plasma sodium levels, resulting in thirst. Subsequent fluid intake may lead to increased interdialytic weight gain, fluid overload and hypertension. A relation between dialysate sodium concentration and interdialytic weight gain and increase in blood pressure was established already long ago. High dialysate sodium concentrations lead to increased interdialytic weight gain and blood pressure levels [35]. Conversely, interdialytic weight gain and blood pressure level can be improved by reducing the dialysate sodium concentration [36].
Previously, we have evaluated the relation between the sodium gradient and clinical parameters in a large cohort of HD patients [37]. We found that a positive sodium gradient was not only associated with interdialytic weight gain and hypertension, but also with increased hospitalization and all-cause mortality. These data indicate that lowering the dialysate sodium concentration is likely to be beneficial in terms of clinical outcome. Notably, a fixed reduction in the dialysate sodium concentration on a facility level will have a different impact for each individual, depending on the serum sodium.

The distribution of pre-dialysis serum sodium levels in January 2010 in 3,445 prevalent patients receiving dialysis at one of the Renal Research Institute dialysis facilities is depicted in figure 1. The mean sodium concentration in this cohort was 140.0 ± 3.3 mmol/l (± standard deviation). With a dialysate sodium concentration of 140 mmol/l, 43% of these patients would have a positive sodium gradient, and even with a dialysate sodium concentration of 138 mmol/l, still 20% would have a positive sodium gradient. Further reducing the dialysate sodium concentration would obviously decrease the number of patients with a positive sodium gradient. On the other hand, the number of patients with a negative sodium gradient would increase, potentially leading to more intradialytic symptoms in some patients. Therefore, dialysate sodium levels should ideally be individualized, aiming at a sodium gradient of zero.

Years ago Murisasco et al. [38] aligned the dialysate sodium level with the patients’ sodium ‘equilibrium point’. The equilibrium point was defined as the dialysate concentration at which no decrease or increase in the plasma sodium during treatment was seen. Applying this approach to 65 chronic HD patients did substantially lower intradialytic morbidity and reduced the number of patients on antihypertensive drugs from 19 (29%) to 6 patients (9%). In another more recent study, the dialysate sodium level was individualized based on pre-dialysis sodium levels in 27 stable patients. After 3 weeks of follow-up, interdialytic weight gain was decreased, thirst scores had improved and blood pressure levels were reduced in the subgroup of patients with uncontrolled hypertension [39]. Moreover, the number of intradialytic symptoms also improved [39]. Although these data are promising, more research is needed before individualized dialysate sodium levels could be applied in clinical practice. Thus far, only stable patients have been investigated and the clinical characteristics of patients with high positive gradients (i.e., patients with low serum sodium levels) have not yet been well studied.

**Avoidance of Inappropriate Sodium Profiling**

Sodium profiling has been developed to facilitate high ultrafiltration rates without being limited by increased intradialytic symptoms. A sodium profile usually consists of a high dialysate sodium concentration at the beginning of the dialysis treatment, leading to a rise in the plasma sodium concentration and facilitating a water shift from the intracellular to the extracellular compartment. This counteracts rapid changes in plasma osmolality due to uremic toxin removal and may limit decreases in blood volume. During the course of the treatment, the dialysate sodium concentration is lowered gradually or stepwise to avoid unnecessary sodium loading [34]. Although sodium profiling can indeed reduce the number of intradialytic hypotensive episodes on the short term, this is largely explained by the positive sodium balance of many of these profiles [40]. Time-averaged dialysate sodium concentrations are generally higher with sodium profiling as compared to dialysis with a fixed dialysate sodium concentration. Not surprisingly, these sodium balance-positive profiles are associated with increased intradialytic symptoms, such as thirst and weight gain [41]. Therefore, there is no role for long-term use of sodium profiling with a positive sodium balance in clinical practice. As of yet, the benefits of sodium profiles with a neutral sodium balance remain unclear. However, decreased hypotensive episodes have been observed in
short-term studies when neutral sodium balance profiles were combined with ultrafiltration profiles [41, 42].

Avoidance of Sodium-Containing Solutions to Treat Intradialytic Symptoms

Intradialytic hypotension and muscle cramps have been reported to occur in up to 30% of all dialysis sessions, although its incidence strongly depends on the patient characteristics, the ultrafiltration rate and the definition that is used [43, 44]. The K/DOQI and European Best Practice Guidelines have proposed to define intradialytic hypotension as a decrease in systolic blood pressure by 20 mm Hg or a decrease in mean arterial pressure by 10 mm Hg associated with clinical events and need for nursing interventions [45]. Cardiac abnormalities, autonomic dysfunction, fluid status, ultrafiltration rates and dialysate temperature may all contribute to the occurrence of intradialytic hypotensive episodes [43, 44]. It is beyond the scope of this article to discuss these factors in more detail.

In clinical practice, hypotensive episodes are usually treated with saline, when placing the patient in Trendelenburg position and lowering the ultrafiltration flow rate do not relieve symptoms. Notably, these saline infusions may significantly contribute to a positive sodium balance. For instance, an infusion of 250 ml isotonic NaCl solution (154 mmol/l sodium chloride) contains 2.2 g sodium chloride, which is almost half of the recommended daily dietary intake. Only a small part of this excess sodium will be removed during the HD session, depending on the sodium gradient and remaining treatment time [34]. Repetitive saline infusions can therefore substantially contribute to sodium loading during dialysis. As a result, interdialytic weight gain may increase, necessitating higher ultrafiltration rates to reach a satisfactory post-dialysis target weight in the next session, and thereby further increasing the risk of intradialytic symptoms in these patients. Some units have adopted a policy to give hypertonic saline solutions (e.g., 5% NaCl) in the event of muscle cramps. Clearly, this practice contributes to intradialytic salt loading.

Several alternative solutions have been successfully applied instead of saline in the acute management of intradialytic hypotension, usually acting as plasma expanders. In stable as well as in cardiac-compromised HD patients blood volume was better preserved with albumin or hydroxyethyl starch in comparison with isotonic saline, whereas the efficacy of hydroxyethyl starch was comparable to albumin [46, 47]. In a randomized crossover study in hypotensive-prone patients saline and albumin were equally effective in the treatment of hypotensive episodes [48]. Another study investigated the effects of hypertonic glucose solutions on blood volume as compared to iso- or hyperosmotic saline solutions in 6 stable HD patients and revealed that hypertonic glucose (20% glucose) resulted in a greater increase in blood volume than equal volumes of the other solutions [49].

Increased attention should also be paid to the prevention of intradialytic hypotension. Several strategies have been proposed, such as accurate dry-weight assessment, low-sodium diet, avoidance of food intake during dialysis, frequent monitoring of heart rate and blood pressure during treatment to anticipate symptoms and cardiac evaluation in patients with frequent intradialytic hypotension [45]. Reducing the temperature of the dialysate is another approach to reduce symptoms, without affecting dialysis adequacy [50]. Lastly, there may be a role for pharmacological interventions with midodrine or vasopressin in hypotensive-prone HD patients [51–53].

Taken together, fluid infusions to treat intradialytic symptoms should be limited by means of preventive measures. If fluid administration is indicated, there are several alternative solutions that are at least equally as effective as saline. To prevent sodium loading, one of these alternatives should be considered, especially in patients with frequent hypotensive symptoms. Hypertonic glucose is cheap and readily available and may therefore be preferable, although there may be some theoretical concerns about its use in diabetics.

Avoidance of Sodium Loading during Priming and Rinsing of the Extracorporeal Circuit

At the beginning of a HD treatment the dialyzer and blood lines are primed with 200–300 ml isotonic saline. In many dialysis facilities this priming volume is not discarded, but routinely administered to the patient. A similar volume is administered at the end of the treatment to rinse the extracorporeal circuit. Generally, the priming and rinsing volumes are accounted for by adjusting the ultrafiltration target weight accordingly to reach the estimated dry weight. The sodium concentration of isotonic saline is approximately similar to the patient’s plasma water sodium concentration, but since the ultrafiltrate is slightly hypotonic [54] priming and rinsing with saline theoretically lead to a positive sodium balance. Conversely, the use of a priming and rinsing fluid with a low sodium concentration would substantially contribute to intradialytic sodium removal. For instance, if 500 ml isotonic saline (containing 77 mmol of sodium) were replaced by a similar volume of a dextrose 5% solution
(containing no sodium), then an additional 77 mmol of sodium (i.e., 1,800 mg sodium) would be removed during treatment, assuming that the sodium concentration in the ultrafiltrate does not change. This amount of sodium corresponds to >50% of the daily recommended dietary intake. To the best of our knowledge, there are no studies thus far evaluating the role of different sodium concentrations of priming and rinsing fluids on intra-dialytic sodium balance, interdialytic weight gain and blood pressure.

Feasibility of Sodium Restriction

Dietary Sodium Restriction

Is it feasible to lower the dietary salt intake of the average dialysis patient to the level as recommended by guidelines [17, 55]? Buying low-sodium products can be challenging, since sodium is added to nearly all manufactured foods [56]. Sodium is often replaced by potassium, making these low-sodium products unsuitable for dialysis patients. Moreover, patient compliance is of major concern, especially since it may take several months before a patient is adapted to the recommended level of sodium intake [17]. The role of the renal dietician is therefore of utmost importance for dietary counseling, taking into account the patients’ personal and cultural dietary habits and signaling unintended weight loss indicative for malnutrition. However, long-term dietary sodium restriction can probably best be achieved with a multidisciplinary approach, where the dietician, nephrologist, dialysis nurse, social worker and facility manager all work together to facilitate behavioral change of dietary habits [17]. Experiences in Tassin (France) and Izmir (Turkey) have shown that long-term sodium restriction is indeed feasible. These encouraging results may be related to the fact that many of the patients in these units actually cook themselves and thus reduce their dependence on processed food [C. Chazot, Tassin, France, and E. Ok, Izmir, Turkey, pers. commun.].

Neutral or Negative Sodium Balance during Dialysis

Abandonment of sodium profiling or minimizing saline infusions for intradialytic symptoms are realistic goals. Alignment of dialysate sodium with the plasma sodium concentration requires frequent pre-dialysis sodium measurements. Ideally, the pre-dialysis sodium concentration should be measured prior to each treatment, which is expensive and time-consuming. Since sodium levels remain stable over time [15], the dialysate sodium concentration could probably be safely aligned with the average of previously measured serum sodium values. Alternatively, conductivity measurements could be used to estimate serum sodium level. Results with such conductivity kinetic models thus far are promising [57]. However, an operationally feasible approach to align dialysate sodium in a large dialysis population is not yet available. Exact alignment of the dialysate sodium concentration is complicated by the relatively limited precision of sodium concentration measurements and by uncertainties in the calculations of the effective plasma water sodium concentration and the Donnan effects [34, 36, 54]. Patients with extremes of sodium concentrations or with unstable glucose levels pose additional challenges. In addition, it should be recognized that the sodium concentration of the dialysis fluid, as given by the dialysis machine and measured by ionic conductance, is not always correctly calibrated with the actual sodium concentration as measured by direct or indirect potentiometry [58].

Potential Drawbacks of Sodium Restriction

A strong correlation between sodium intake and caloric intake has been observed [30]. Hence, strict dietary sodium restriction could potentially lead to nutritional deficiencies. Apart from this, a decline in residual urinary output has been observed after 4 weeks of strict volume control by salt restriction (approximately 4 g/day) and ultrafiltration in peritoneal dialysis patients [59]. There are no data on the effects of volume control by sodium restriction on residual renal function in HD patients. Residual renal function has been associated with improved volume control, less left ventricular hypertrophy and improved survival [60]. The benefits of strict volume control by sodium restriction could thus be attenuated by an increased loss of residual renal function. The relation between volume control and decline of residual renal function deserves further study, especially after long-term interventions. Benefits of sodium restriction on volume status may also be offset by increased activation of the sympathetic nervous system and the renin angiotensin system, as already mentioned above [61]. Finally, blood pressure-lowering drugs should be considered for all patients on HD to reduce cardiovascular morbidity and mortality [62], also if blood pressure control is improved by strict sodium restriction.
**Conclusions**

Fluid overload is common in chronic HD patients and is associated with adverse outcome. In the vast majority of these patients, volume status can be significantly improved with sodium restriction. Dietary sodium restriction reduces blood pressure and interdialytic weight gain. Many patients do not comply with the sodium targets as defined in clinical guidelines. Increased efforts to lower dietary sodium intake have the potential to significantly improve clinical outcomes. Apart from that, a positive sodium balance during dialysis contributes to sodium loading. This can be prevented in almost all patients by individualizing dialysate sodium prescription and refraining from saline solutions during dialysis treatment. We postulate that combined dietary and dialytic sodium restriction is the cornerstone in the prevention and treatment of volume overload in HD patients. Whether such a combined approach is operationally feasible and leads to improved hard clinical outcomes, such as hospitalization and survival, has to be addressed in prospective randomized trials.

**References**


