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REVIEW ARTICLE

Volume Control

Sodium and ultrafiltration profiling in hemodialysis: A long-forgotten issue revisited

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Abstract

Sodium and ultrafiltration profiling are method of dialysis in which dialysate sodium concentration and ultrafiltration rate are altered during the course of the dialysis session. Sodium and ultrafiltration profiling have been used, commonly simultaneously, to improve hemodynamic stability during hemodialysis. Sodium profiling is particularly effective in decreasing the incidence of intradialytic hypotension, while ultrafiltration profiling is suggested to decrease subclinical repeated end organ ischemia during dialysis. However, complications such as increased interdialytic weight gain and thirst due to sodium excess have prevented widespread use of sodium profiling. Evidence suggest that different sodium profiling techniques may lead to different clinical results, and preferring sodium balance neutral sodium profiling may mitigate adverse effects related to sodium overload. However, evidence is lacking on the long-term clinical outcomes of different sodium profiling methods. Optimal method of sodium profiling as well as the utility of sodium/ultrafiltration profiling in routine practice await further clinical investigation.

KEYWORDS
hemodialysis, interdialytic weight gain, sodium profiling, ultrafiltration

INTRODUCTION

End-stage kidney disease (ESKD) is a major cause of morbidity and mortality. Over 60% of patients with ESKD use hemodialysis (HD) as their renal replacement therapy, with a total of more than 500,000 patients receiving HD in the United States alone.[1] While many factors contribute to the high mortality seen in HD patients (165 per 1000 patient-years),[1] various HD factors are known to affect the outcomes in different ways. Intradialytic hypotension (IDH) is a common complication and has a prevalence of up to 40%.[2] While IDH has a major impact on quality of life, it has also been associated with cardiovascular events and mortality.[2,3] Sodium is the main extracellular ion and defines osmolality and size of the extracellular volume. Sodium mass balance in HD is primarily dependent on two factors: dietary salt intake and sodium removal during dialysis. One of the most important goals of the dialysis therapy is to remove exactly the mass of sodium that has been accumulated in the interdialysis period in order to reach a zero sodium mass balance. Sodium profiling is a technique in which dialysate sodium concentration is gradually decreased over the course of the dialysis session from hypernatremic to hyponatremic dialysate. Such intervention alleviates the acute decline in intravascular volume during ultrafiltration (UF) as well as the decline in intradialytic plasma osmolarity and the consequent disequilibrium

syndrome.[4] Sodium profiling has potential benefits in terms of intradialytic morbidity and mortality as well as quality of life and long-term cardiovascular events; nevertheless, it may also predispose to interdialytic hypernatremia and increased interdialytic weight gain (IDWG) and hypertension.[5] Another method to avoid intradialytic hemodynamic instability is UF profiling. In it, a larger portion of total UF volume is extracted during the first part of a dialysis session, after which the UF rate is decreased in order to maintain hemodynamic stability.[6] This article reviews the existing evidence on the potential benefits and drawbacks of sodium and UF profiling.

SODIUM PROFILING

Sodium profiling is a method of dialysis in which dialysate sodium follows a time-dependent gradient. High sodium dialysate is used to maintain intravascular volume, which is followed by low sodium dialysate to counteract excess sodium gain. During HD, the accumulated water and electrolytes are removed by UF and diffusive clearance. While the fluid mainly accumulates in the extravascular space, UF primarily removes fluid from the intravascular space, acutely reducing the circulating plasma volume and predisposing to hypotension. The acute drop in plasma osmolarity further decreases fluid refill from the extravascular space, aggravating hemodynamic instability. Sodium profiling enhances the internal plasma refill rate and helps to stabilize the blood pressure,[7,8] thus decreasing the risk of IDH.[9–11] It is imperative to limit or prevent IDH since it does not only affect the patient's comfort but also increases the risk of vascular access thrombosis,[12] myocardial fibrosis and stunning,[13] cardiovascular events, and mortality.[2,14–17] However, interdialytic complications, particularly IDWG, fatigue and thirst have been reported with sodium profiling and the resulting sodium overload.[18]

Several sodium profiling methods are available (Figure 1). Increasing, decreasing, or alternating sodium concentrations may be used, although decreasing profiling has been the most accepted. The decrease in dialysate sodium concentration may be linear, stepwise, or exponential (Figure 2). The stepwise method was shown to be the most reliable method to decrease both IDH[9] and muscle cramps[19,20] in various studies. Linear profile was also reported to reduce IDH[19,21,22] and muscle cramps in several studies,[19] nevertheless not consistently.[9,23] Both

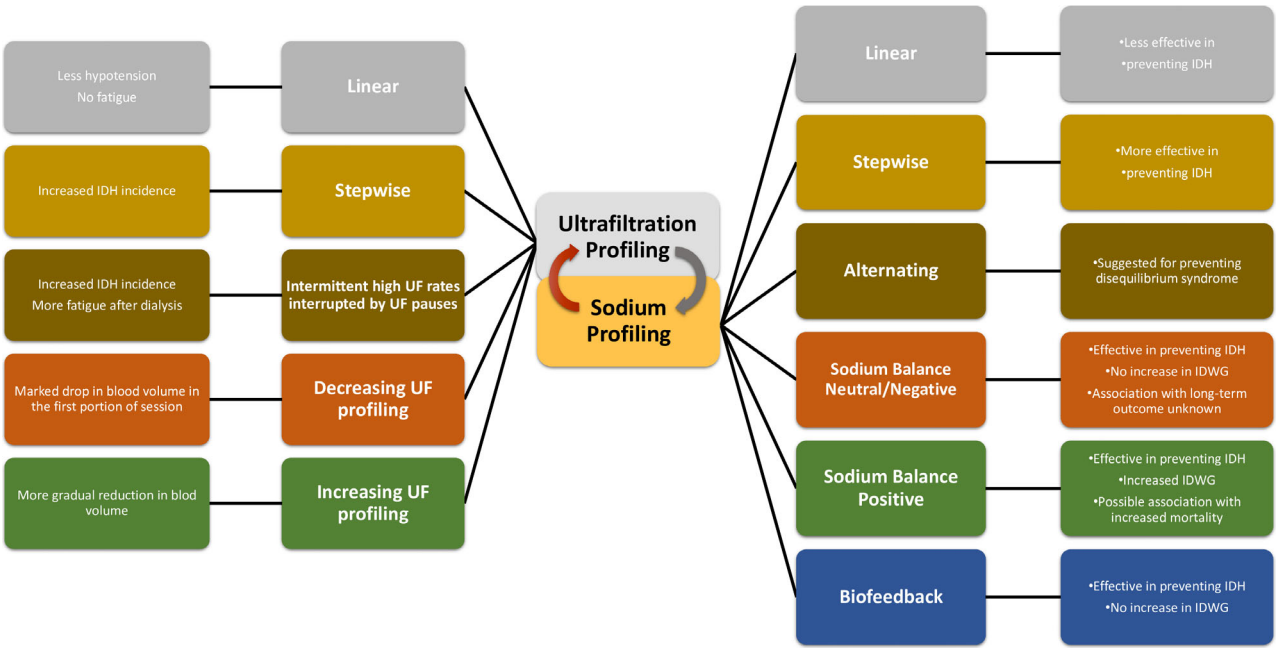

FIGURE 1 Methods of sodium profiling. Sodium profiling can broadly be categorized in terms of the change curve of dialysate sodium concentration. Most commonly, concentrations are decreased linearly, stepwisely or alternatingly. Studies suggest that stepwise profiling is the most effective method for decreasing the incidence of IDH, while alternating profile may be more effective against symptoms of disequilibrium syndrome. Sodium profiling can be further categorized according to the net sodium change in the patients. While sodium balance positive profiling was the generally used profiling method historically, studies have shown that sodium balance neutral or negative profiles do not cause IDWG, a major concern for sodium profiling. While one cohort has found that sodium profiling was associated with increased mortality, the profiles used were suggested to be sodium balance positive. Biofeedback models utilizing sodium profiling have shown to be safe and effective in preventing IDH [Color figure can be viewed at wileyonlinelibrary.com]

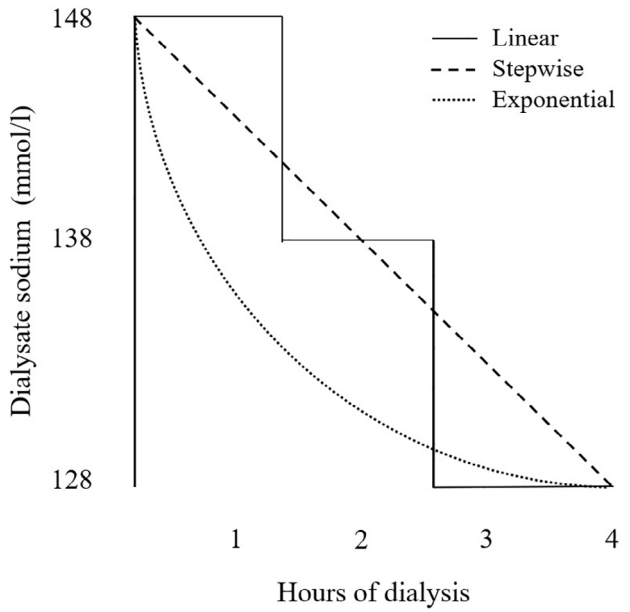

FIGURE 2 Graphic presentation of the three different methods of sodium profiling; linear, stepwise, and exponential ramping

methods have been associated with increased IDWG[19,22] and thirst.[19] Alternating profile, on the other hand, shifts between high and low sodium dialysates throughout the dialysis session, therefore inducing solvent drag and encouraging elimination of toxins. As a result, alternating profile was proposed to decrease the occurrence of disequilibrium syndrome.[24,25] Among the profiles, stepwise profiling is the most commonly used method. A cohort consisted of 2272 HD patients in 24 facilities revealed that more than 28% used sodium profiling. Among the profiles used, nearly 60% were stepwise and 40% linear algorithms.[26]

Sodium profiling can be further classified according to the net sodium change that occurs in the serum at the end of the dialysis session: sodium balance positive, sodium balance neutral, and sodium balance negative sodium profiling. The profile is called sodium balance positive if there is a net gain of sodium, and sodium balance negative if there is a net loss of sodium during the session. Sodium balance neutral profiling does not alter the serum concentration and osmolarity and therefore regarded as the most physiologic form.[25] Higher dialysate sodium is known to increase IDGW,[27] hypertension[28] with a resulting increased mortality among stable patients.[28,29] Specifically, Mc Causland et al. found that dialysate sodium >140 mmol/L was associated with higher IDGW.[26] Higher IDWG, in return, requires higher UF rates in the subsequent sessions and increases the risk of IDH,[27] which renders the efforts for sodium profiling counterproductive. Furthermore, aggressive UF may lead to myocardial stunning and cardiac arrhythmias.[30] Therefore, the net sodium balance during sodium profiling has been gaining more attention recently. Currently, there is no consensus on sodium concentrations that should be used for profiling and various studies use different concentrations (Table 1). While Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines advise against using high dialysate sodium concentrations, it does not provide a specific recommendation of an optimal concentration or a reference sodium profiling method due to lack of consistent evidence.[46]

In order to sustain neutral sodium balance in profiling HD, the temporarily high dialysate sodium should be compensated by a sufficient subsequent decrease, usually to below 130 mmol/L. For example, alternation of dialysate sodium concentration between 140 and 160 mmol/L every hour for 5 h without ultrafiltration leads to a net sodium gain of 26 g, commensurate with more than a 10 mmol/L increase in serum sodium concentration in an average patient. On the other hand, alternating the dialysate sodium between 125 and 160 mmol/L would theoretically lead to no imbalance in serum sodium concentrations.[18] However, achieving a correct intradialytic sodium balance is a much more difficult task in clinical practice. With the advances in technology, automatic computer-based programs can be used today to calculate intradialytic sodium removal. These models use real-time data from patients and are being used to reach end-dialysis sodium, weight, and blood volume targets. Such biofeedback systems enable to achieve sodium balance neutral sodium profile and UF profile automatically.[47–49] Currently, there are various commercial dialysis systems that calculate dialysate and UF profiles with algorithms based on the prescribed decrease in body weight and sodium mass.[50]

EVIDENCE FOR EFFECTS OF SODIUM PROFILING ON INTRADIALYTIC AND INTERDIALYTIC MORBIDITY

To date, large-scale clinical trials to assess the long-term effects of sodium profiling are lacking. The existing evidence is primarily from small crossover clinical trials and observational studies (Table 1), where sodium profiling is compared with conventional HD or particular profiling methods are compared. For instance, a crossover study randomizing 22 patients to receive stepwise and linear sodium profile for 12 consecutive sessions showed that the incidence of intradialytic adverse effects was 48% in control while 34% and 36% in stepwise and linear profiles, respectively ($p < 0.001$). Interestingly, IDWG was

TABLE 1 Summary of the clinical studies that investigated the sodium profiling in hemodialysis

Author and year	Design of the study	Subject number	Intervention	Sodium profiling	Dialysate sodium concentration (mmol/L)	Duration	Interdialytic weight gain	Intradialytic hypotension	Special notes
Meira et al. (2010)[31]	Crossover	22	Control versus step versus linear sodium profiling	Step wise and linear	Initial 147 End 138	12 consecutive dialysis sessions for each period	IDWG did not change	Decreased in both linear and step profiling	
Oliver et al. (2001)[10]	Crossover	33	Control versus sodium with ultrafiltration profiling	Exponential	Initial 152 End 142	2 weeks for each period	Greater during profile (0.3 kg) ($p < 0.01$)	Decreased (OR 0.6, 95% CI 0.39–0.96)	
Hamidi et al. (2020)[32]	Crossover	32	Control versus linear Na profile with UF versus step wise sodium profile with UF	Linear and stepwise	Initial 146 End 138	Three dialysis sessions in each method		Decreased in both linear and step profiling	
Hamzi et al. (2012)[23]	Crossover	14 patients prone to IDH	Control versus linear sodium profiling versus sodium profiling with UF profiling	Linear	Initial 147 End 131	10 dialysis sessions in each method	No difference	No difference	No difference in delivered dialysis dose
Song et al. (2005)[33]	Crossover	11 patients prone to IDH	Control versus sodium balance positive step down Na profile vs sodium balance positive step down Na profile with UF profile vs sodium balance neutral step down Na profile with UF	Step wise and alternate	Initial 148 End 138	6 week for each period	Increased in sodium balance positive protocols, no difference in sodium balance neutral profiles	Decreased in all treatment protocols	Significantly increased subjective discomfort and weight gain in the interdialytic period in the sodium balance positive profiling, with or without UF profiling
Zhou et al. (2006)[21]	Crossover	8	Control versus linear sodium profiling versus UF profile versus sodium profiling with UF profiling	Linear	Initial 148 End 131	10 dialysis sessions for each group	Increased in Na with UF profiling group	Decreased in in Na with UF profiling group	More stable mean BP and large UF volume in Na with UF profiling group
Moret et al. (2006) [34]	Crossover	12 patients prone to IDH	Control versus linear sodium profile versus blood volume controlled feedback vs plasma concentration controlled feedback	Linear	Initial 150 End 140	Four dialysis sessions for each group	No difference	No significant change	

(Continues)

TABLE 1 (Continued)

Author and year	Design of the study	Subject number	Intervention	Sodium profiling	Dialysate sodium concentration (mmol/L)	Duration	Interdialytic weight gain	Intradialytic hypotension	Special notes
Tang et al. (2006)[22]		13 patients prone to IDH	Control versus linear sodium profile	Linear	Initial 150 End 140	4 weeks	Increase in Na profile	Decrease in Na profile	Dialysate sodium concentration ramped from 150 mmol/L to 140 mmol/L at the end of dialysis.
Meira et al. (2007)[35]	Crossover	18 patients who were prone to develop IDH	Control versus step-wise sodium profile	Step wise	Initial 147 End 139	12 dialysis sessions	Reduction in Na profile	Decrease that did not reach significance level	Significant decrease in muscle cramps in Na profile
Straver et al. (2002)[36]	Observational	8	Control versus sodium profiling versus UF profiling	Alternating	Initial 152 End 130	One dialysis session for each group	N/A	MAP was lower in control compared to Na profiling but not UF profiling	
Zhai et al. (2017)[37]	Placebo-controlled crossover	60	Control versus sodium profiling	Linear	Initial 148 End 132	3 months for each group	No difference	No difference	Lower ambulatory blood pressure and lower antihypertensive medication dosage in profiling
Donauer et al. (2000)[38]		53	Control versus linear UF profiling versus stepwise UF profiling versus intermittent high UF rates interrupted by UF pauses	Linear, step wise and other	The same as of previous sessions (ranging from 132 to 142)	One dialysis session for each group		Increased in step wise and other UF profiling compared to control and linear UF profiling	Alternating UF profiling group had signifncantly more nausea
Shahgholian et al. (2011)[39]	Crossover	24	Control versus sodium profile with UF profile	Sodium profiles (not indicated)	Not indicated	Three dialysis sessions for each group	N/A	No difference	
Dominic et al. (1996)[40]	Crossover	22	Control versus linear low sodium profile with UF profile	Linear, sodium balance negative	Initial 137 End 128	Seven dialysis sessions for each group	Decrease in Na profiling	Decreased in Na profiling	Dialysate Na was decreased from 137 to 128 mEq/L
Locatelli et al. (2012)[41]	Crossover	55	Control versus HFR-Aeq	Biofeedback	Adapted differently for each patient based on plasma sodium	2 months for each group	No difference	Decrease in HFR-Aeq	

(Continues)

TABLE 1 (Continued)

Author and year	Design of the study	Subject number	Intervention	Sodium profiling	Dialysate sodium concentration (mmol/L)	Duration	Interdialytic weight gain	Intradialytic hypotension	Special notes
Franssen et al. (2005)[42]	Crossover	12 patients prone to IDH	Control versus biofeedback profile	Biofeedback	Adapted differently for each patient based on plasma sodium	3 weeks for control and first biofeedback session, 6 weeks for the second biofeedback period	No difference	Decrease in biofeedback	Biofeedback with blood volume tracking to continuously modifying the weight loss rate and dialysate conductivity
Santoroet al. (2002)[43]	Crossover	36 patients prone to IDH	Control versus biofeedback profile	Biofeedback	Adapted differently for each patient based on plasma sodium	4 months for each group	No difference	Decrease in biofeedback	Biofeedback with blood volume tracking to continuously modifying the weight loss rate and dialysate conductivity
Dasgupta et al. (2019)[44]	Prospective cohort	10,898 from DOPPS cohort study	Control versus routine use of sodium profiling	N/A	N/A	Median follow-up 1.4 years			Higher cardiovascular and all-cause mortality and higher cardiovascular events in routine Na profiling
Hecking et al. (2012)[45]	Prospective cohort	29,593 from DOPPS study	Correlation of dialysate Na concentrations with outcomes	N/A	N/A	Median follow-up 16.5 months	Higher dialysate Na correlated with higher IDWG		Higher dialysate Na associated with lower risk of overall hospitalization and hospitalization due to fluid overload

Abbreviations: BP, blood pressure; CI, confidence interval; DOPPS-Dialysis Outcomes and Practice Patterns Study; HFR-Aeq, hemodiafiltration aequilibrium; IDGW, interdialytic weight gain; MAP, mean arterial pressure; Na, sodium; IDH, intradialytic hypotension; N/A, not applicable; OR, odds ratio; UF, ultrafiltration.

not different between the periods, and postdialysis systolic blood pressure was lower in the linear profile than both control and stepwise profile. Stepwise profile was found to be superior in decreasing episodes of symptomatic IDH, while patients in the period with linear profile had fewer cramps.[31]

In another randomized cross over clinical trial, 32 patients underwent three sessions by conventional HD, three sessions by linear sodium profile with UF and three sessions by stepwise sodium profile with UF. The mean of adequacy of dialysis (Kt/V) scores were 1.12, 1.24, and 1.31 in conventional HD, the stepwise method and linear method, respectively ($p < 0.05$). The incidences of HD complications, with IDH being the most common, were 44%, 26%, and 30% in conventional HD, stepwise and linear profile methods, respectively. The dialysate sodium at the beginning of dialysis was 146 mmol/L, which was reduced to 135 mmol/L at the end of dialysis.[32]

However, linear sodium profiling has failed to show clinical benefits in other studies. In a study including 14 patients who were prone to IDH, either linear sodium profiling alone or in combination with UF profiling failed to improve the incidence of IDH, mean IDWG, and delivered dialysis dose.[23] A recent study reported no difference in IDWG or IDH with linear sodium profiling for 3 months, although significant decreases in ambulatory blood pressure and antihypertensive medication dosage were found.[37] Indeed, a recent meta-analysis of 10 studies comparing stepwise profiling versus linear sodium profiling showed that stepwise profiling significantly reduced the incidence of IDH, while linear sodium profiling did not.[5]

The effects of sodium profiling seem to be directly related to the net sodium balance in many studies. An early crossover trial compared the effects of three sodium profile with different time-averaged concentration of dialysate sodium (TAC): conventional HD with sodium = 138 mmol/L, sodium profile with sodium ranging from 145 to 135 mmol/L (TAC = 140 mmol/L) and sodium profile with sodium ranging from 158 to 130 mmol/L (TAC = 147 mmol/L). Both sodium profiles increased serum sodium concentrations. The sodium profile with TAC 147 mmol/L further increased the predialysis serum sodium at the end of the 6-weeks follow-up period. The results demonstrated that net sodium gain was directly correlated with the sodium TAC, and using low dialysate sodium at the final hours could not compensate the high dialysate sodium used at the beginning of the session.[25]

Another double blind crossover study of 22 patients evaluated sodium balance negative linear sodium profile in which dialysate sodium was reduced from 137 to 128 mmol/L along with UF profiling for seven consecutive dialysis sessions. As opposed to other sodium profiles, sodium balance negative profile resulted in decreased IDWG, thirst and serum sodium levels. Importantly, it also decreased the incidence of IDH. Self-reported well-being scores were higher during the interdialytic period of sodium profile.[40]

In a randomized controlled crossover study including 264 dialysis sessions from 11 HD patients who were prone to IDH, Song et al. compared conventional HD to sodium balance positive stepdown sodium profiling HD, sodium balance positive stepdown sodium profiling HD with UF profiling and sodium balance neutral stepdown sodium profiling with UF profiling. Prescribed sodium concentrations were 143 and 138 mmol/L and starting sodium concentrations were 148 and 145 mmol/L for sodium balance positive and sodium balance neutral sodium profiling, respectively. After 6-week maintenance of each treatment, diffusive sodium gain and postdialysis sodium concentration as well as IDWG were significantly increased in sodium balance positive profiling protocols compared to conventional HD and neutral sodium balance profiles regardless of UF profile. The incidence of intradialytic complications was decreased with all treatment protocols compared with conventional HD. However, this benefit was offset by significantly increased subjective discomfort and weight gain in the interdialytic period in the sodium balance positive profiling, with or without UF profiling. It is important to underline that these undesired side effects were not seen in sodium balance neutral sodium profiling HD while intradialytic hemodynamic benefits of sodium profiling were maintained.[51]

Other studies have also supported that sodium balance neutral sodium profiling is effective in decreasing the risk of IDH without increasing the dialysate sodium concentration. In a study of eight HD patients and a total of 320 dialysis sessions, sodium balance neutral linear sodium profiling combined with linear UF profile was significantly associated with decreased incidence of IDH and higher stability of stroke volume variation and preservation of mean blood pressure. The sodium with UF profiling group also had significantly reduced postdialysis body weight with higher UF volume compared with the control, while no difference was seen in either sodium or UF profiling alone.[21]

It should be noted that, in most of these studies, the target in sodium profiling was achieving the preset sodium balance. Nevertheless, dialysate sodium concentrations were not patient tailored in such cases. Biofeedback systems, which will be discussed in the subsequent sections, were mainly used to automatically profile dialysate sodium concentrations based on individual plasma sodium level, although some also profiled total dialysate conductivity.[34,41]

EVIDENCE FOR EFFECTS OF SODIUM PROFILING ON LONG-TERM OUTCOMES

Most of the research on sodium profiling has focused on the efficacy of profiling in limiting intradialytic adverse effects, while its impact on long-term outcomes, including cardiovascular morbidity and mortality are of utmost importance to determine whether sodium profiling should be adopted in routine practice. Some facilities have already adopted the use of sodium profiling in their routine dialysis practice to limit or prevent IDH. Nevertheless, evidence is currently lacking on the benefits of such routine use. The analysis of data from 10,898 HD patients obtained from the Dialysis Outcomes and Practice Patterns Study (DOPPS) cohort study assessed the long-term effects of routine use of sodium profiling in a median follow-up time of 1.4 years. Medical directors from 10 different dialysis facilities answered to a questionnaire to evaluate the practices of each facility. Results showed that routine use of sodium profiling was associated with higher cardiovascular (HR 1.34. 99% CI, 1.04–1.73) and all-cause mortalities (HR 1.36, 99% CI 1.14–1.63) as well as higher cardiovascular events (HR 1.21, 99% CI 1.03–1.43).[44] However, it is crucial to note that the study did not establish which sodium profiling methods were used and the extend of the practice due to the intrinsic limitation of the study design. As the authors also have implicated, the widespread use of sodium balance positive sodium profiling may have led to increased IDWG,[33] which is independently associated with fluid overload-related hospitalization, cardiovascular events, and mortality.[52]

Another cohort consisting of 2272 patients with a median follow up time of 2.4 years did not find a significant difference in mortality between patients receiving sodium profiling and patients receiving fixed higher dialysate sodium (>140 mmol/L), although mortality was trended to be lower in profiled patients. The study analyzed sodium profiling within the overall higher dialysate sodium subgroup, since it was assumed that most of the sodium profiling would be sodium balance positive. Given that sodium profiling may be prescribed selectively to hemodynamically instable patients, it should be noted that patients with sodium profiling had a similar survival to those who had a fixed higher dialysate at baseline.[28]

While assessing the effects of sodium balance in profiling, the possible long-term benefits as well as side effects of low and high sodium dialysates independent of sodium profiling should also be mentioned. Dialysate sodium appears to have an alternating interaction with mortality. The evidence shown by Mc Causland et al. indicated that higher dialysate sodium (>140 mmol/L) was associated with increased mortality in high predialysis serum sodium concentrations, while no association was seen at lower predialysis serum sodium.[26] Furthermore, the results of a recent meta-analysis suggest that low dialysate decreased IDWG and interdialytic blood pressure, which are known to be associated with better outcomes. However, the concomitant increased incidence of IDH and reduced serum sodium concentrations may also lead to increased mortality risk.[53]

An earlier analysis of 29,593 eligible patients from the DOPPS study also investigated the association of dialysate sodium concentration with IDWG, hospitalization and mortality. The analysis revealed that the dialysate sodium prescription did not correlate with baseline serum sodium concentration, indicating that the dialysate prescription was not tailored individually in the 960 facilities. Analysis showed that dialysate sodium prescriptions over 142 mmol/L were associated with significantly higher IDWG. IDWG increased by 0.17% of postdialysis body weight per 2 mmol/L increase in dialysate sodium concentration (95% CI, 0.15%, 0.20%).[45] Although the authors did not find a correlation between higher dialysate sodium and mortality, other studies have associated higher IDWG with higher mortality risk.[54] As such, the prevalence of high dialysate sodium prescription among facilities using sodium profile should be assessed before a hard conclusion can be reached.

Sodium profiling was also suggested to modulate the renin-angiotensin system activation. Papasotiriou et al. investigated the impact of sodium profiling on plasma renin levels during HD and HDF. Results showed that plasma renin levels significantly increased during constant sodium dialysate and decreased during sodium profiling, which was independent of UF volume. Additionally, the plasma renin reduction seen with sodium profiling was more pronounced in the HDF group.[55] Unfortunately, the abstract did not report on intradialytic hemodynamics and IDH incidences.

SODIUM PROFILING AS A PART OF DIALYSIS MODALITIES AND BIOFEEDBACK

As different sodium profiling methods may have distinct impacts, different dialysis modalities may also affect the outcome of profiling. Although not as commonly used, hemodiafiltration (HDF), which utilizes convective clearance in addition to diffusion, may change the results of sodium profiling. As HDF predisposes to additional sodium retention by infusing sodium through substitution fluid and boosting the Donan effect induced by high UF rates, which decreases the sodium concentration

available for diffusion, higher the transmembrane sodium gradients are required to counterbalance these effects and reach the target sodium balance.[56]

As the biofeedback dialysis systems has become more available, the algorithms provide individual computation of sodium and UF profiling. Many studies showed the efficacy of such dialysis models in decreasing intradialysis adverse effects and benefits.[50] Using the "Profiler" algorithm to calculate the sodium and UF profiling[57] in 55 patients with IDH for 6 months, Colì et al. showed that the use of automatic dialysis system was associated with a marked decrease in IDH (from 59% to 0.9%, $p < 0.001$) and other disequilibrium symptoms including headache and nausea. Importantly. IDWG and predialysis serum sodium levels were not changed during the 6-months follow-up period.[57] Another study by Colì et al. also showed that profiled HD performed with "Profiler" led to significant reduction in IDH, cramps and significant increase in heart index in a 8-month period.[58] In a single-arm trial assessing their latest modification of Profiler, the automatic adaptive system dialysis (AASD), Coli et al. reported a profound decline in the incidence of IDH from 59% to 1% without any changes in IDWG or presession plasma sodium levels.[50]

The application of real-time sodium sensor (Natrium sensor) in biofeedback further enables recalculation and adjustment of the sodium profile and ultrafiltrate conductivity during the dialysis session. The system that uses sodium sensor in hemofiltration with endogenous reinfusion is called hemodiafiltration Aequilibrium (HFR-Aeq).[47] In a randomized crossover multinational study, Locatelli et al. reported that significantly less symptomatic IDH was seen in HFR-Aeq, and the effect was significantly greater in unstable patients. No evidence of sodium or water overload was detected with the intervention.[41]

Coli et al. utilized their mathematical model to automatically determine the dialysate sodium and ultrafiltration profiles based on the sodium mass to be removed during the session, which is assessed via two methods. In majority of the patients, sodium mass to be removed was given a priori depending on the cumulative evaluation of many clinical variables including IDWG, intra and interdialytic BP and intradialytic symptoms. In the alternative method, AAD calculated the mass as a function of the natremia target (end-session natremia), which was set as the mean plasma sodium concentration in the last 12 dialysis sessions using standard dialysis.[50] For HFR-Aeq, the natremia target was similarly defined as the mean plasma natremia observed during the previous 1 month of standard dialysis.[41] In both strategies, the main goal is obtaining the natremia target consistently at the end of each session. A major objective of hemodialysis is to keep the total body water volume and total plasma water sodium concentrations, which are the two determinants of total sodium mass, constant at the end of each session to maintain a neutral sodium balance.[59] By persistently achieving constant end-dialysis weight and plasma sodium concentrations at the end of the dialysis sessions, end-dialysis sodium mass can be ensured to be constant.[60] Via calculating the dialysate sodium concentration needed to obtain the natremia target and ultrafiltration to obtain target weight, these mathematical models help to preserve the neutral sodium balance.

Other biofeedback systems using sodium and UF profiling were also shown to be effective in decreasing intradialytic complications and improving hemodynamic stability without compromising IDWG and blood pressure.[42,43,49,61]

Using plasma conductivity controlled feedback as a surrogate for plasma sodium, Moret et al.[34] investigated the effects of profiling through adjustments of dialysate conductivity adjustments rather than direct dialysate sodium. In this randomized crossover study, the target of profiling was to achieve a plasma conductivity of 14.0 mS/cm at the end of the dialysis. The results showed that neither plasma conductivity- nor blood volume-controlled feedbacks significantly altered the frequency of symptomatic hypotensive episodes. These feedback treatments did not affect IDWG or predialytic blood pressures as well, suggesting their safety.

Individual on-line prescription of electrolytes in biofeedback may also compensate for the interindividual and intraindividual differences in serum sodium levels without requiring frequent blood sampling.[62] Since the effects of dialysate sodium level seem to be partially dependent on predialysis serum sodium levels, such intervention may prevent the development of excess sodium gain because of profiling.

UF PROFILING

Rapid intravascular fluid removal via UF has been associated with higher all-cause and cardiovascular mortality,[63,64] possibly due to end-organ damage by hemodynamic instability.[65,66] Repeated subclinical ischemia leads to myocardial stunning and predispose to heart failure in long-term HD patients.[65] UF profiling is a practice to remove the greatest amount of fluid at the beginning of a HD session and gradually decrease the UF rate. UF profiling is a potential method to prevent UF-associated hemodynamic instability and consequent end-organ ischemia. UF profiling is often used concomitantly with sodium profiling due to their intrinsic connection. The two determinants of the change in plasma sodium

are the diffusive flux, which depends on the dialysate sodium controlled by sodium profiling, and the convective flux, which depends on the UF rate controlled by UF profiling. As a main component of osmolality, plasma sodium regulates the vascular refilling rate, which in return limits the UF rate. Sodium profiling with a higher dialysate sodium at the beginning of the session ensures an adequate vascular refill, which enables safe UF profiling. Therefore, UF profiling is most useful when used concurrently with sodium profiling and trials studying the effects of UF profiling independent of sodium profiling are sparse.

Intradialytic effects of different UF profiling methods were compared by Donauer et al. in a study including 53 patients. The study compared five different UF profiles, including linear, stepwise, as well as three other profiles with intermittent high UF rates interrupted by UF pauses. Compared to the control, all UF profiles except linear UF profile caused significant increases in IDH incidence (17%, 42%, and 36% in control, stepwise and other profile, respectively). The increased occurrence of IDH was possibly related to using a UF rate 1.5 times higher than standard UF at the beginning of the sessions in these UF profiles, as the hypotensive episodes were associated with a rapid decline in relative blood volume in the first 20 min of the dialysis session. Furthermore, UF profiles with intermittent high UF rates caused significantly more fatigue after the dialysis session, while no fatigue was reported in control and linear UF profile groups. While the study was limited by the small number of patients and assessment of each profile only once, the linear UF profile showed a trend toward less hypotension, although not statistically significant.[38]

Another study including 10 patients by Morales-Alvarez et al. compared the hemodynamic response to decreasing UF profiling with the response to increasing UF profiling. The study showed that the alterations in mean values of blood pressure monitoring, echocardiographic changes, heart rate, cardiac output, and peripheral vascular resistance were similar in the two UF profiles. Furthermore, IDWG did not differ significantly between the profiles. Nevertheless, increasing UF profile led to a more gradual reduction in blood volume, while decreasing UF profile caused a marked drop in blood volume in the first portion of the session.[67]

Mancini et al. have developed a blood pressure-controlled biofeedback system for UF profiling to prevent severe IDH episodes. The system utilizes BP monitorization at 5-min intervals to control the UF rate instantaneously but does not provide sodium profiling. Implementation in patients prone to IDH showed a significant reduction in the frequency of severe but not mild IDH episodes.[68]

There is an ongoing crossover trial that will compare the incidence of IDH, predialysis and postdialysis troponin T, left ventricular systolic function and development of intradialytic left ventricular stunning between conventional UF and UF profiling (ClinicalTrials.gov Identifier: NCT03301740).[69]

EVIDENCE FOR EFFECTS OF SODIUM AND UF PROFILING ON QUALITY OF LIFE

Improvements in HD techniques have increased survival, although the quality of life in patients on chronic HD has not improved substantially, largely due to the extensive symptom burden.[70] While the extend of intradialytic and interdialytic complications may provide an indirect indicator of quality of life, no studies have assessed the impact of profiling on quality of life directly until today. To address the lack in literature, Gerrish et al. compared conventional HD with sodium profiling and UF profiling in 27 patients by a quantitative and qualitative crossover study. The study showed no significant difference between the mean arterial pressure, delta value between pre- and post-dialysis blood pressures, IDWG or IDH among the treatments, although IDH showed a not significant increase in UF profiling and a not significant decrease in sodium profiling. The latter caused a significant increase in the incidence of intradialytic cramps. Nevertheless, some patients reported less cramps during sodium profiling in the self-reported questionnaire. Interestingly, the analysis of total scores for the perceived positive and negative side effects of different interventions recorded on the questionnaires indicated that respondents showed widely conflicting opinions. While a group of participants reported that sodium profiling increased adverse effects and disliked it, others reported to find it beneficial. Interestingly, sodium profiling scored the highest for all positive as well as all negative effects but scored the lowest in the "no change noticed" question. These answers indicated that patients were noticeably affected by sodium profiling, in either a positive or negative way. The authors noted that the range of predialysis serum sodium levels varied greatly between 131 and 143 mmol/L, whereas the base dialysate sodium concentration was constant at 135 mmol/L which could account for some of the interpersonal differences in response. Notably, although the reported scores for positive and negative effects changed greatly, sodium profiling scored more than two times higher than UF profiling and more than three times higher than conventional HD for an improvement in "feeling well" between dialysis sessions.[71]

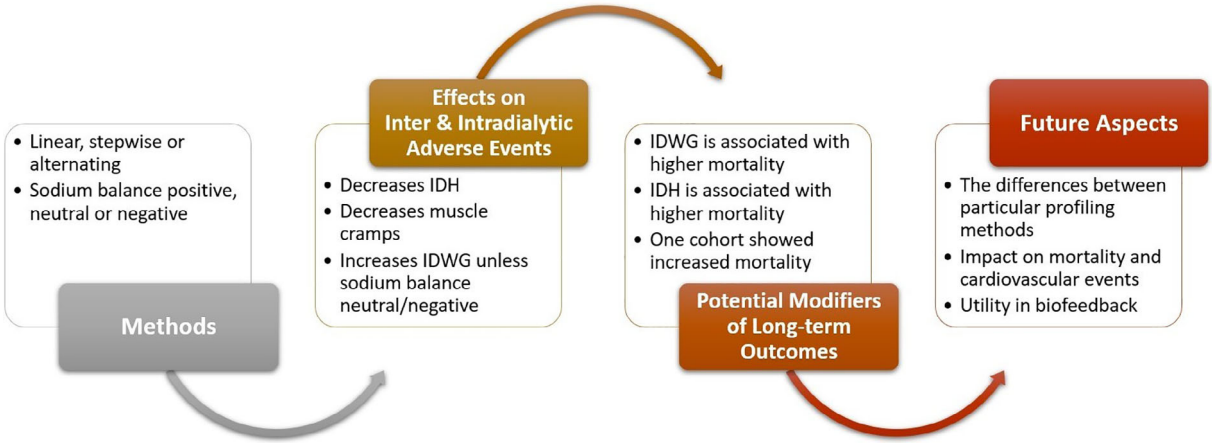

FIGURE 3 Knowns and unknowns about sodium profiling. Sodium profiling can be classified in two different categories. Sodium profiling has been associated with decreased incidence of IDH, muscle cramps and increased IDWG in various studies. No effect on IDWG was seen in sodium balance neutral and negative profiling. To date, there has been only one study on the association of mortality and sodium profiling. Nevertheless, IDH and IDWG, which are profoundly affected by profiling, are known to be associated with mortality, implicating that sodium profiling may modify long-term outcomes. Future studies should assess the relationship with mortality, compare different sodium profiling methods and confirm the utility of sodium profiling in biofeedback models [Color figure can be viewed at wileyonlinelibrary.com]

Further studies are needed to examine the factors that change the subjective effects of profiling in HD patients and individualize HD treatments to maximize patient comfort.

RECOMMENDATIONS

As many studies have shown, sodium profiling is a potentially effective and safe method to limit or prevent intradialytic adverse effects, while these results are not free of uncertainty. The traditional methods of sodium profiling have a high risk of leading to increased IDWG and subsequent long-term complications. More research is needed to establish whether specific profiling methods are more efficacious in preventing specific symptoms and which profiling method has the most utility in routine clinical practice. Furthermore, more qualitative data is warranted for subjective analysis of quality of life and personal well-being. Sodium profiling should only be used in sodium balance neutral or negative profiles; otherwise excess sodium appears to counteract the benefits of profiling. Biofeedback systems using profiling may guide in correctly arranging the sodium balance and avoiding complications of profiling. Further research is needed to determine the utility of sodium profiling in biofeedback systems and in patients receiving HDF. While UF profiling has been widely used along with sodium profiling in clinical practice, its value by itself is questionable. Large-scale double blind clinical trials are needed to verify the clinical benefits of sodium/UF profiling, its associations with quality of life and mortality.

CONCLUSIONS

Sodium and UF profiles have been shown to be effective in improving intradialytic hemodynamic stability and limit adverse effects (Figure 3). Although such interventions can lead to increased IDWG and associated complications, a careful sodium balance can mitigate such effects. Intradialytic monitoring systems and biofeedback models may help with optimization of profiling. Extra care should be given to prevent positive sodium balance, as high sodium dialysate levels have been shown to result in negative long-term consequences including mortality.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICS STATEMENT

This article does not contain any studies with human participants or animals performed by any of the authors.

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