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RESEARCH ARTICLE

Update and Perspectives in the Personalized Management of Sodium, Water, Volume and Hemodynamic Disorders of Dialysis Patients

Bernard Canaud[1,2], Carsten Hornig[3], Sudhir Bowry[4]

[1] Global Medical Office, Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany
[2] Montpellier University, UFR Medicine, Montpellier, France
[3] Health Economics & Market Access, Fresenius Medical Deutschland GmbH, Bad Homburg, Germany
[4] Dialysis-at-Crossroads (D@X) Advisory, Wilhelmstraße 9, 61231 Bad Nauheim, Germany

* bernard.canaud@fmc-ag.com

ABSTRACT

Sodium and water-related disorders are major components of chronic kidney disease (CKD) and contribute significantly to cardiovascular (CV) complications and mortality. Usually, they are marked by gradual accumulation of sodium, water and have hemodynamic consequences (i.e., fluid overload, hypertension and cardiac disorders) along with the progression of kidney failure culminating in end stage kidney disease. Renal replacement therapy which is then required to sustain life is intended to restore sodium, fluid and pressure disorders along with the objective of reducing the uremic toxin load. Unfortunately, the intermittent nature of conventional short hemodialysis relying on a so called 'dry weight' probing approach, only partially restores the sodium-water overload related disorders, thereby exposing patients to further multi-organ damage through the resultant dialysis-induced systemic stress (DISS).

Fluid volume management in dialysis patients has emerged as a very challenging condition that requires further attention and more precise tools. Furthermore, recent findings indicate that the physiology of sodium is more complex than that previously summarized by the kidney-centric two-compartment model (volemia and Interstitium) linked to osmotically active sodium (water-bound sodium). A third tissue compartment (skin, muscle) of sodium has now been identified, taking the form of free-water sodium [glycosaminoglycans (GAGs) or gel-like component] with newly-identified pathophysiologic metabolic consequences.

All these findings suggest that restoration of sodium homeostasis in dialysis-dependent chronic kidney disease patients should encompass a more holistic approach to improve cardiac health and reduce cardiovascular burden in this highly vulnerable population.

In this context, new tools for monitoring and managing dialysis patients to ensure a more precise and personalized control of their sodium and water homeostasis, volemic and hemodynamic disorders are needed. Several monitoring and management tools (e.g., bioimpedance, lung ultrasound, blood volume control, thermal balance control) are already available with potential value. The conductivity measurement-based automated sodium control module represents the latest and very appealing addition to this list of innovative tools. Although establishing the clinical value of these tools requires further outcome-based studies, current clinical use of this new tools has shown promising indications towards the goal of reducing CV morbidity and mortality in kidney dialysis patients.

A brief review of these new pathophysiologic findings as well as clinical interests of these new tools is provided in this narrative review.

Keywords: Sodium and fluid disorder- Volume overload- Hypertension - Hemodialysis, Dialysis Adequacy- Cardiovascular complications

1. Introduction

Sodium and water disorders in chronic kidney disease (CKD) patients reflect homeostasis imbalance secondary to degradation of renal functions and alteration of internal milieu composition as part of uremic disorders. Sodium and water accumulation with their consequences (fluid overload, hypertension, hemodynamic response) are major components of CKD pathophysiology that contribute to cardiovascular complications[1]. A gradual accumulation of salt and water is observed along CKD progression reaching an acme point at the late stage of chronic kidney disease (CKD5) and support of renal replacement therapy (RRT) and progressive loss of diuresis. In this context, depending on diet, patient compliance and treatment response, volume overload and hypertension tend to develop with well-known deleterious cardiovascular (CV) consequences.

The intensity of these disorders and cardiovascular disease (CVD) associated risks can be mitigated by salt dietary restriction and appropriate antihypertensive medications therapy including loop diuretics. It is well recognized that time exposure, intensity of disorders (fluid overload, blood pressure levels) but also response and adhesion to therapy, greatly condition cardiovascular complications of CKD patients.

However, CV complications remain the leading cause of morbidity and mortality in CKD patients. This risk is observed at all stages of CKD but with a logarithmic increase after stage 3 CKD. Schematically, CV risk is 10 to 100 times higher in CKD5 patients than that of a control population depending on the patient age groups[2]. Curiously, CVD risk persists or even worsens with RRT, whether this is during hemodialysis (HD) therapy or even after a successful kidney transplant (KTP). As shown by various international registries, CVD-related complications account for more than half of the causes of death in HD patients with a particular incidence of severe arrhythmic disorders and sudden cardiac deaths.

In addition, the presence of hypertension is predominant in advanced CKD patients. Although hypertension involves multifactorial components and pathways (sympathetic tone, renin angiotensin aldosterone system; endothelial dysfunction), salt sensitivity is a prominent feature in stage 5 CKD patients. Sodium excess and fluid imbalance are usually corrected by dialysis treatment prescription through ultrafiltration and dialysate sodium and diet adjustment. As shown in several studies, hypertension may be adequately controlled by dry weight probing approach in up to 70% of dialysis patients. However, hypertension may persist in a significant fraction of HD patients and then necessitates the use of antihypertensive drugs. More worryingly, recent studies conducted in dialysis patients (hemodialysis and peritoneal dialysis) assessing body composition and fluid status by multifrequency bioimpedance methodologies indicate that 40 to 60% of patients have clinically significant fluid overload[3-5]. Finally, it is interesting to note that severe cardiac events represent the main cause of hospitalization in HD patients with an increased frequency of congestive heart failure (pulmonary edema), coronary events and severe arrhythmia.

All these facts converge to indicate that sodium and water imbalance, blood pressure and hemodynamic disorders are still an unmet medical need contributing to CV complications in HD patients. They also suggest that this problem should be managed more precisely, taking into account recent pathophysiologic findings and using more appropriate tools to help reduce dialysis-induced systemic stress (DISS) and improve outcomes in HD patients[6,7]. In this narrative review we take stock of recent advances in this area.

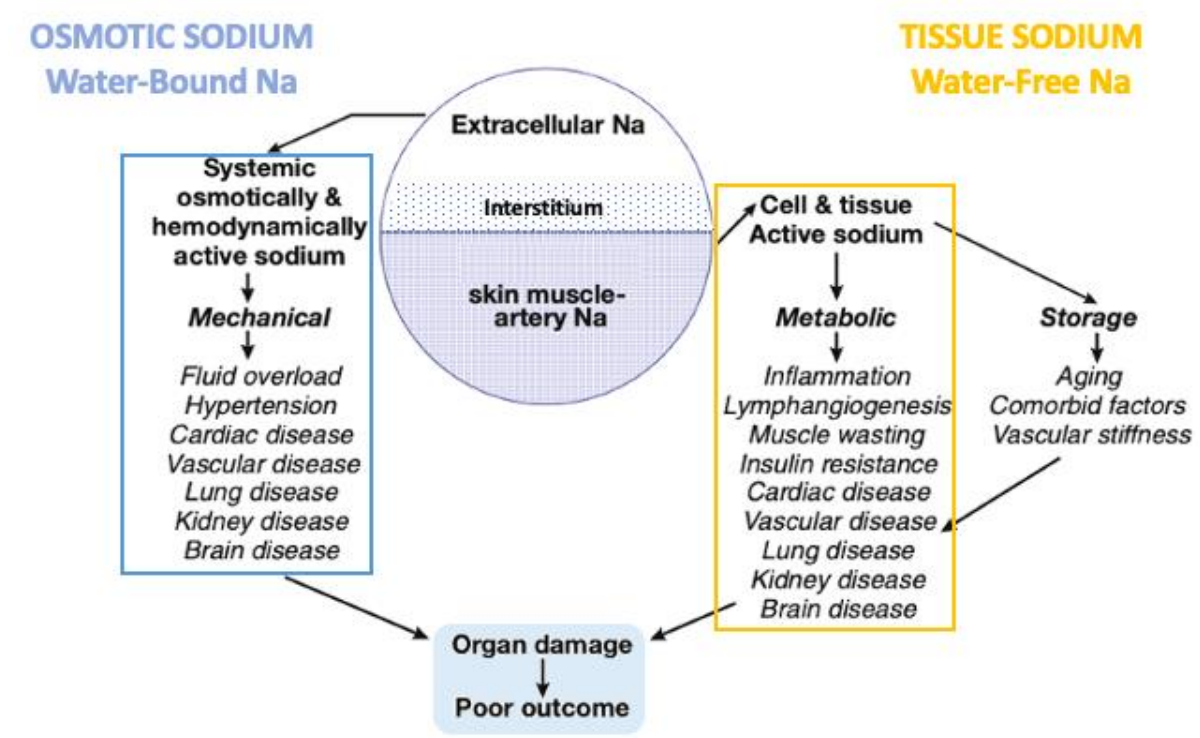
2. New pathophysiologic insights into sodium and water metabolism: Implication of transitioning from a bi-compartmental to a tri-compartmental model.

Since the pioneering work of Guyton and coworkers, it has been established that sodium and water homeostasis responds to a fine regulation capable of maintaining a constant sodium pool while maintaining its distribution almost exclusively in the extracellular sector, regardless of external inputs[8]. This condition is ensured thanks to a fine neurohumoral feedback control system that involves, on the one hand, hemodynamic pressure equilibrium (volume, blood pressure), and on the other hand, renal function which allows the excretion of sodium and water and restore internal homeostasis. Thirst and selective sodium appetence helps to preserve isotonicity of the internal milieu[9]. This model relies on two major components: first, the stability of the sodium pool, responsible for preserving the extracellular volume distributed in two compartments (volemia; interstitium) contributing to preserve hemodynamic status through the osmotic action of salt; second, the kidney function (effector) which ensures the excretion of salt (sodium balance) and water (water volume) as needed. Following the original work of Dahl and coworkers, a very strong link has been established between sodium consumption and high blood pressure[10]. These milestone studies have paved the way for salt-sensitive hypertension. Later, sodium physiology was revisited by Guyton and coworkers who put into perspective the central and preponderant role of the kidneys in controlling sodium balance and blood pressure equilibrium. The two-compartment kidney centric model has been prevalent for many years and enabling physicians to devise therapeutic interventions to control hypertension[8]. Similarly, in patients with advanced CKD and dialysis-dependent patients, it has been well

established that salt accumulation contributes to volume-dependent or salt-sensitive hypertension with its corollary cardiac complications.

Recent work by Titze and coworkers has challenged this two-compartment model by highlighting the existence of a third compartment, the so-called sodium tissue compartment (skin muscle, bone)[11,12]. The suspicion for the existence of this third compartment was suggested by sodium mass balance studies carried out in healthy subjects (cosmonauts) as part of the training program for manned flights to MARS[13,14]. These subjects who were totally isolated in a metabolic apartment were subjected to a fixed stepwise increase of sodium intake diets (6, 9 and 12 g/day) with a precise daily monitoring of the sodium balance. In addition, to precisely measure intakes (food) and losses (stool, urine) allowed the establishment of a precise daily and cumulative sodium mass balance, together with regular monitoring of other individual parameters (weight, hemodynamics, biological, body composition by bioimpedance) that was carried out. Schematically, the authors observed cyclic and nychthemeral fluctuations in sodium mass balance, correlated with aldosterone secretion and cortisol, without significant changes in blood pressure or body weight. In addition, they noted a positive sodium balance over time, suggesting sodium retention as well as an increase in body sodium pool, even though no weight gain was observed. This observation suggested to authors, the existence of a third compartment of sodium 'stored' in tissue as an 'anhydrous form'. The same group, using nuclear magnetic resonance imaging methods to specifically identify sodium 23 (^{23}Na MRI), confirmed later the existence of sodium tissue storage in the skin and muscle[15]. The sodium tissue content could then be quantified, expressed in mmol per g of tissue. This imaging technique helps establish correlations with certain physiological states (aging, sodium intake) or pathological conditions (hypertension, renal failure, diabetes mellitus). Interestingly, sodium stored in tissues and especially the skin is bound to negatively-charged proteoglycans, glycosaminoglycan type (GAG) in the form of a gel that does not contain bound water[14] . The skin content of GAG can be measured after skin biopsy, desiccation, and gel electrophoresis on western blot followed by atomic absorption spectrophotometry. That said, segmental imaging by ^{23}Na MRI remains for the moment the only non-invasive tool to assess tissue sodium content. According to recent work, dermal monocytes phagocytes behave as biosensors capable of detecting tissue hypertonicity related to the accumulation of tissue salt and consequently induce a cascade reaction at a local starting point and systemic action[16,17]. In this context, the tissue sodium responsible for local hypertonicity would have two major actions: on the one hand, the production of a cellular transcriptional factor in response to local osmolar stress, known as nuclear T cell activation factor (NFAT5), also known as TonEBP (tonicity-responsive enhancer-binding protein) and on the other hand, the secretion of a vascular endothelial growth factor (VEGF-C). The latter would stimulate local lymphangiogenesis whose goal would be to locally increase the clearance of local electrolytes via the lymphatic system. It would also stimulate the production of nitric oxide synthase enzyme (eNOS) from the vascular endothelium and thus ensure the release of endothelial nitric oxide (NO) thus contributing to the regulation of blood pressure by systemic vascular vasomodulation. In addition to its hemodynamic action, tissue sodium also appears to be involved in other metabolic actions such as insulin sensitivity, muscle catabolism, inflammation, cancer and even inflammation.

In summary, the physiology of sodium has evolved considerably in recent years. Several essential points deserve to be highlighted: 1. The traditional two-compartment sodium model must be reviewed and completed by a more complex three-compartment model including tissue storage; 2. The kidney-centric sodium regulatory model shall be revisited to include the tissue and skin component; 3. Tissue sodium (skin, muscle) is found in the form of gel-like component (GAG) that actively participates in the overall metabolism of sodium and water in the body; 4. The local action of tissue sodium sensed by the immune system is mediated via an angiogenic action acting on the local lymphatic and systemic endothelial system: 5. Tissue sodium contributes to the regulation of blood pressure independently of its osmotic action and has various systemic metabolic actions; 6. Variations in tissue sodium content as a function of physiological and pathological conditions cannot be overlooked and must be taken into account in new therapeutic strategies. This is schematically summarized in figures 1 and 2.



Canaud B et al, *Kidney Int.* 2019; 95, 296–309
Figure 1: New pathophysiologic pathways of sodium disorders in CKD patients

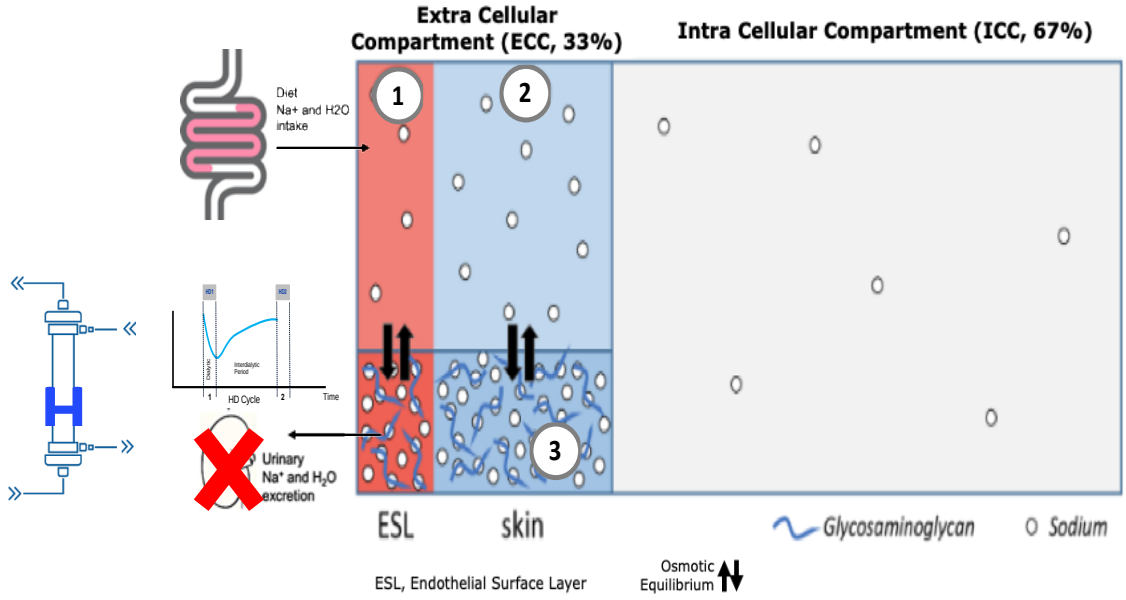


Figure 2: Sodium Homeostasis: Three compartment model and imbalance associated with CKD and HD

3. Management of sodium disorders in hemodialysis and peritoneal dialysis patients

The management of sodium, water, volume and hemodynamic disorders remains a major concern in the treatment of CKD5 dialysis-dependent patients. Restoring homeostasis of sodium and water adequately is still an unmet need to reduce cardiac burden in these patients at high cardiovascular risk[18,19]. Management of these disorders is currently embedded in the 'dry weight' probing approach [20,21]. This clinical approach has proven its effectiveness in numerous studies, but has also shown

its limitations and potential risks[22]. It should be noted that risks have been significantly increased due to the change in clinical practices in hemodialysis (short duration dialysis) as well as the phenotype of dialysis patients treated (elderly, multiple comorbidities). In peritoneal dialysis patients, fluid management depends also on peritoneal membrane performances and residual kidney function. In this specific condition, the use of various osmotic (dextrose-based) and oncotic (icodextrin-based) strength solutions with adapted dwell time and cycles (automated peritoneal dialysis) may help to control fluid volume status[5,23,24]. However, difficulty in controlling fluid volume in peritoneal dialysis patients may be considered as a sign of membrane failure[25]. This aspect is beyond the scope of this review and will not be discussed further. In practice, the management of sodium, water and volume involves two steps: the first which consists in assessing the amplitude of these disorders and their consequences; the second which consists in setting up the most appropriate treatment allowing a safe and tolerable correction. This is schematized in Figure 3.

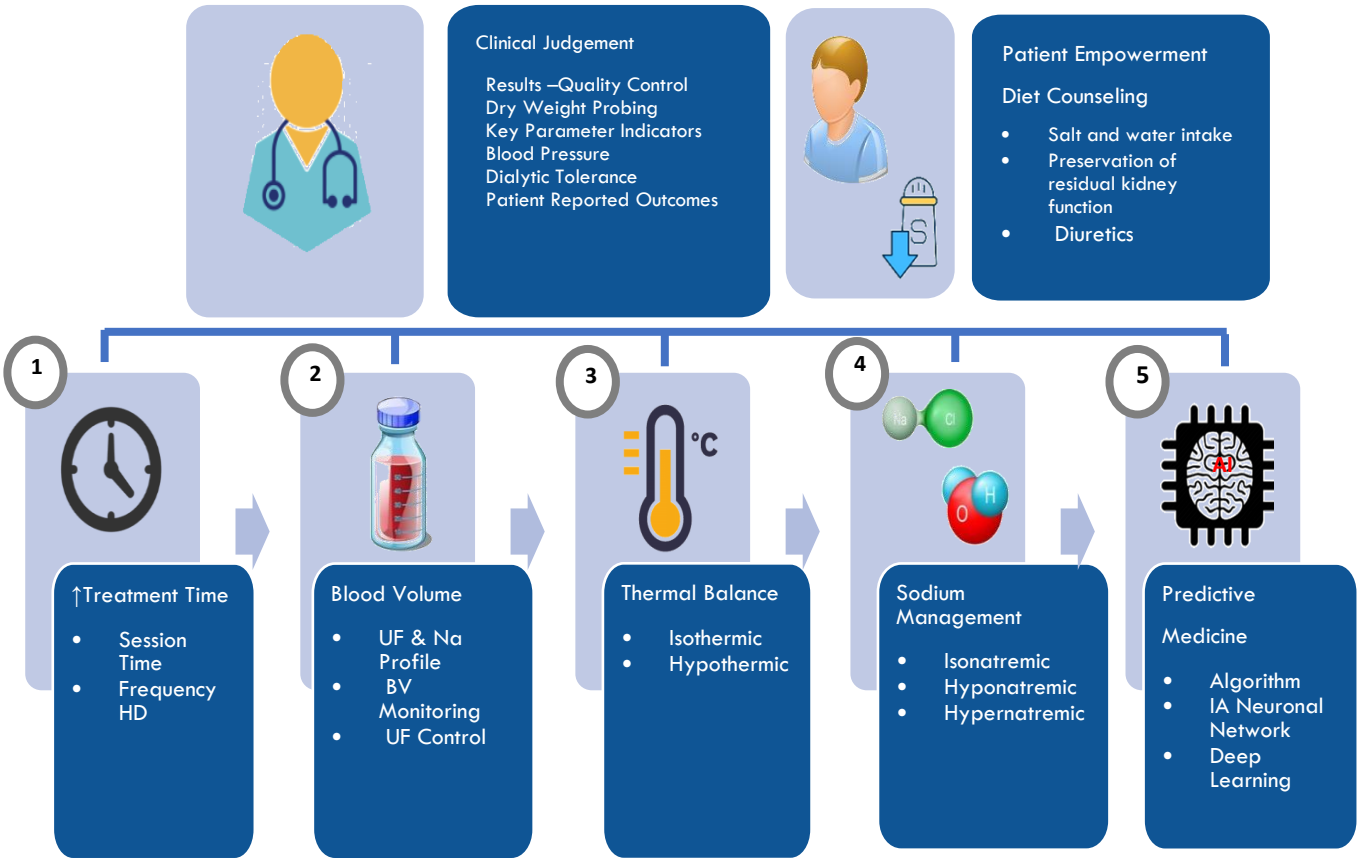


Figure 3: Stepwise approach to restore sodium and water imbalance in HD patients in order to reduce cardiac burden

3.1. Assessment of sodium, water, volume and blood pressure disorders.

The evaluation of sodium and water imbalance is not an easy task in clinical practice in dialysis patients. Most often this is based on a purely clinical approach that aims to set and restore the 'dry weight'. In theory, this is the 'ideal weight' of a patient whose homeostasis of the extracellular volume would have been restored by dialysis and would be in an euvolemic condition. In practice, it is more often the lowest postdialysis weight achieved taking into account clinical tolerance (intradialytic morbidity). It is obvious that this clinical approach remains very subjective, biased by many factors (medical expertise, patient tolerance, logistic and treatment schedule) but also restricting cardiovascular risks to fluid volume overload. In addition, this clinical approach, tends to expose the patient either to excessive correction especially on dialysis days (hypovolemia, intradialytic hypotension) or to insufficient correction (chronic fluid overload, heart disease and hypertension). For this reason, best clinical practices suggest the use of biomarkers and tools to facilitate clinical decision-making and optimize 'dry weight' achievement of dialysis patient[6,7].

1. Clinical evaluation remains necessary but is not sufficient. Clinical management will remain always the overarching process but some support to decision-making is welcome. As previously stated, 'dry weight' is a compromise that stands for postdialysis weight closed to a euvolemic situation, without symptoms (dyspnea, peripheral edema or congestive signs) and keeping in targets blood pressure (pre and postdialysis) with relatively well-tolerated dialysis sessions. At this stage it is important to remember that the 'dry weight' is not constant over time. It must be reassessed and adjusted on a regular basis, taking into account the nutritional status of the patient as well as intercurrent events that may occur. In practice, at a minimum a monthly dry weight reassessment is necessary in a stable patient and a session-by-session reassessment is sometimes necessary in patients who are unstable or developing intercurrent illness.

2. Various non-invasive methods (i.e., instrumental biomarkers) are proposed to assess

fluid volume status, body composition, hemodynamic equilibrium or their cardiac consequences. A brief review is proposed here.

a. *Chest X-ray* remains a simple and useful tool, although less frequently used, to assess lung overload and measure cardiothoracic index (CTI). In milestone studies CTI has been shown highly predictive of outcomes.

b. I*nferior vena cava diameter* (IVCD) and its collapsibility are proposed to monitor intravascular volume and right atrial pressure or central venous pressure in dialysis patients with convincing results. However, its implementation is not easy in a dialysis unit and its predictive value on hemodynamic response is limited.

c. *Relative blood volume changes* (RBVC), reflecting the vascular refilling rate (VRR), measured by an online optical sensor has also been proposed to facilitate volume assessment. In expert hands, this tool provides useful information on the patient's volume status, helps to identify individual critical volume (risk of hypotension), and reduces the incidence of intradialytic events. Despite the indisputable clinical benefits reported by various studies in particular when coupled to a feedback-controlled volume algorithm, its long-term clinical benefits (reduction in morbidity and mortality) in controlled studies remains to be proved.

d. *Multifrequency bioimpedance* (MF-BIS) is commonly recognized as the most convenient and objective method for assessing body composition, total water and fluid status in dialysis patients. Several clinical studies showed that the MF-BIS is an easy-to-use, reliable and reproducible tool for assessing body composition, volume status and relative fluid overload in dialysis patients. In systematic reviews, notified bodies [NICE, UK; CADTH, Canada] have recognized that MF-BIS is currently the most appropriate tool available to support care givers in fluid management of dialysis patients.

e. *More sophisticated* tools have been proposed recently. *Lung ultrasound* (LUS) method is one of the most attractive ones, to assess lung overload (extravascular edema) by measuring thickness of interlobular septa. Thickening of interlobular septa by edema generates beams visualized as B lines (i.e., COMET tails). The simple numbering of these B lines provides an estimate of lung overload and cardiac dysfunction with highly predictive value of morbidity or mortality. *Vascular stiffness* estimated from pulse wave velocity (PWV) measurement provides an indirect way of assessing sodium content with highly predictive value on morbidity. *Sodium MRI* (^{23}Na MRI) was introduced more recently to assess tissue sodium content (skin, muscles). This method remains a clinical research tool that makes it possible to evaluate the specific effect of new therapies or treatment regimens on tissue content.

f. Cardiac assessment is currently used to evaluate the consequences of mid- and long-term effects of volume and pressure levels in dialysis patients. In this context, echocardiography is currently used to assess sodium overload and its cardiac morphological and functional consequences. Different echocardiographic criteria (volume of the atria, ventricular volume, left ventricular mass, thickness of the ventricular septum, ejection fraction, pulmonary arterial pressure) are used for the evaluation and follow-up of dialysis patients. More recently, *cardiac MRI* has been introduced to assess more precisely and objectively cardiac impact of new renal replacement therapy schedules. Cardiac MRI remains still a tool for clinical research.

g. *Cardiac biomarkers* are proposed to assess volume overload and cardiac modifications. Atrial natriuretic peptides (ANP, BNP and NT-proBNP) were the most widely used to assess volume overload. Copeptin (a precursor of vasopressin) has recently been proposed to estimate volume depletion. Markers from the troponin family (troponins I and T) can be used to detect myocardial ischemic insults. Other cardiac or endothelial biomarkers (ADMA, FG23, ROS, NO) seem appealing in volume management and cardiovascular risk stratification. However, it must be noted that these cardiac biomarkers reflect more than just the fluid overload since they encompass tissue remodeling, uremic toxin control, inflammation and oxidative stress mechanisms.

h. Artificial intelligence has recently emerged in this field and opens new and promising prospects in supporting clinical decision making. Recent pilot studies, integrating big data analysis and advanced analytics supported by machine learning, will allow a more personalized and precise control of fluid volume and hemodynamic management (ultrafiltration rate, sodium

dialysate concentration) and likely reduce the incidence of intradialytic morbidity. Further studies are ongoing and should provide more precise answers in near future.

3.2 Therapeutic action plan proposed to reduce cardiac burden in hemodialysis patients

A therapeutic action plan to control sodium, water, volume and hemodynamic disorders in HD patients has several components. Schematically, they are articulated around three axes: The first axe is dietary counseling that consists in educating patients to reduce sodium intakes and resulting fluid intakes with the help of specialized dieticians. The second axis is more theoretical, insofar as it is based on the preservation of residual renal function. This aspect is fundamental but unfortunately will concern a limited number of patients and is very difficult to guarantee in clinic practice. The third axis is more practical since it is related to treatment schedule program and dialysis prescription. For brevity, the first two aspects will not be addressed here, only the dialysis prescription will be developed here. This is schematized in figure 3.

Restoration of sodium, water and hemodynamic homeostasis in hemodialysis patients are based on several elements that are clustered for practical reasons into two categories: primary and secondary means. Among primary means are dialysis prescription relying on weekly treatment time (weekly treatment duration) and dialysate sodium concentration. Other elements can be considered such as the modality of dialysis (hemodialysis vs. hemodiafiltration), the treatment location (center vs. home) or even treatment conditions of (i.e., lying vs. sitting position, consuming snacks or not, dialysate sodium concentration). Among additional options are also some functionalities of dialysis machines that permit to mitigate risk in modulating hemodynamic response to fluid volume depletion due to ultrafiltration. Hemodialysis sessions are part of a multi-systemic stress repeated several times a week that may contribute to morbidity and mortality of dialysis patient.

Weekly dialysis treatment time is a crucial factor that conditions total ultrafiltered volume and ultrafiltration rate per session[26]. Several studies have identified that an hourly ultrafiltration rate greater than 13 ml/kg (or 1000 ml per hour for a 78 kg patient) was associated with an increased risk of mortality of almost 50%. It should be noted that this risk actually starts at 10 ml/kg and increases exponentially with ultrafiltration rate. In this context, the incidence of intradialytic hypotensive (IDH) episodes is increased by 20-50%. Intensity of IDHs (drop >90 mmHg of systolic pressure) is an additional risk factor that increases mortality up to 50-60%. All these facts converge to indicate that too short dialysis exposes patient to high ultrafiltration rate, critical hypovolemia and IDH and results in ischemic insults. For this reason, preservation of volemia should be a focused priority when prescribing a dialysis treatment schedule. Duration of dialysis sessions should be tailored to patient's needs and tolerance to prevent reaching critical hourly ultrafiltration rate of 10 ml/kg. This simple and common-sense approach is unfortunately not often applied or applicable for practical, logistical or simply individual refusal reasons.

The prescription of the sodium concentration of dialysate is another important component in the prescription of dialysis that has been somewhat neglected over time. However, it is a major element that has a dual role: on the one hand, it permits to adjust net sodium loss; on the other hand, it permits to modulate osmotic variations (tonicity) and loss of net free water. The prescription of sodium dialysate responds in the majority of cases, to a fixed prescription (sodium dialysate 138 or 140 mmol/l) to which the patient will adapt and whose plasma sodium concentration at the end of the session will be very close to[27]. The dialysate-plasma sodium gradient (d-pNa) conditions the diffusive sodium fluxes. Three clinical situations can be observed: firstly, the gradient is positive, in this case a diffusive sodium load (sodium gain) is achieved reducing the net mass of sodium removed during the dialysis session; secondly, the gradient is negative, in this case a diffusive sodium removal (sodium depletion) is performed increasing the net mass of sodium removed during the session; thirdly, the gradient is neutral, in this case there is no diffusive sodium transfer (isonatremic dialysis or zero diffusive condition) and the sodium depletion relies only on convective transfers by ultrafiltration. In practice, it is important to emphasize that the mass of sodium subtracted in hemodialysis is essentially achieved by convection (80 to 100%) or ultrafiltration (intradialytic weight loss) while the diffusive part represents only 0 to 30% depending on the dialysate-plasma gradient. As reminder, each liter of ultrafiltrate has 150 mmol and thus subtracts 7-8 g of NaCl [28].

Several functionalities are now incorporated into dialysis machines to help assess the extent of sodium and water overload in HD patients. They permit to modulate hemodynamic response of patients submitted to ultrafiltration and dialysis. In brief, we will only mention few of them here.

Ultrafiltration control has become a standard that is equipped in all modern dialysis machines. It facilitates the management and control of weight loss thus providing undeniable comfort to patients and caregivers, especially with the use of dialyzers with highly permeable membranes.

Ultrafiltration and sodium profiling algorithms are also today widely available and used. Different algorithms are proposed, either addressing ultrafiltration or dialysate sodium concentration alone, or

in combination with ultrafiltration and dialysate sodium concentration adjustment. Without analyzing the advantages or limitations of these algorithms, it is important to emphasize that their combined use is far preferable to facilitate, on the one hand the vascular filling (i.e., positive dialysate-plasma sodium gradient to facilitate vascular refilling rate), and on the other hand to ensure ultrafiltration volume required (i.e., high ultrafiltration rate) to adequately correct the sodium overload of the patient. In all cases, the use of these tools must be constantly supervised by close clinical monitoring and external biomarker tools (i.e., bioimpedance).

Use of relative blood volume changes is a very popular tool that facilitates management of sodium and hemodynamic disorders. Used in manual mode, this tool has several advantages: it allows monitoring of volume variation; it is useful in establishing individual critical volume; it ensures the preservation of effective volume in response to ultrafiltration. Automated volume control (ultrafiltration control) is the most advanced form of this tool. By combining continuous monitoring of volume changes and adjustment of the ultrafiltration rate and/or the sodium profile (conductivity) according to a preset algorithm, it prevents to reach critical hypovolemia. Ultrafiltration control module can preserve volemia and to reduce the incidence of IDH and intradialytic morbidity.

Thermal balance control option is also an interesting tool that makes it possible to handle hemodynamic response when ultrafiltration occurs by means of thermal transfer changes. The major interest of this tool lies in the fact that it becomes possible to modulate the hemodynamic response by acting on the components of heat stress and no longer on sodium or volume exchanges. Since Maggiore's pioneering work, it has been shown with the use of thermal probes and blood temperature monitor (BTM) that standard hemodialysis conducted with a fixed dialysate temperature (37-38 °C), translates into a caloric gain for the patient (hyperthermic dialysis) accompanied by systemic vasodilation and tachycardia. This inadequate hemodynamic response to ultrafiltration-induced hypovolemia was a source of major hemodynamic instability and hypotensive episodes[29]. Since then, the management of the thermal balance in hemodialysis has been integrated into dialysis prescriptions and good clinical practice. Schematically, the clinical prescription of thermal balance in dialysis can respond to three main modalities: hyperthermic dialysis (standard dialysate ≥37-38°C); hypothermic dialysis (dialysate <35°-35.5°C); isothermal dialysis (dialysate 35.5-36.5°C)[30]. This manual prescription, assumes that the core temperature of the dialysis patient is measured at the beginning of the dialysis session. It is easily measured by infrared thermometer, either at the tympanic level or at the frontal level. In this case, the temperature of the dialysate must be fixed on the dialysis machine taking into account the dialysate-patient gradient required to obtain the desired heat balance. It is therefore advisable to set the dialysate temperature 0.5-1°C below that of the patient to maintain an isothermal dialysis. The automatic and individualized management of the thermal balance can be done by means of an integrated thermal balance module (BTM). This is naturally easier and more reliable to ensure a fine modulation of the patient's hemodynamics while avoiding any discomfort that may occur following hypothermic dialysis. Clinical studies on the benefits of controlling heat balance in hemodialysis are quite convincing, both in the short term (reduction of intradialytic morbidity) and in the long term (reduction of systemic hemodynamic stress and associated heart or brain damage).

4. Immediate and short-term perspectives

An automated sodium control module is the latest option for individualizing sodium and water management in HD patients. The sodium module includes biosensors positioned within the dialysate circuit, continuously measuring conductivity on inlet and outlet tubing and transmitting data to the microprocessor of the dialysis machine. A proprietary specific algorithm is then designed to feedback control conductivity of the fresh dialysate according to the set prescription [31]. A schematic representation of the device integrated into the 6008 CAREsystem hemodialysis machines (Fresenius Medical Care, Bad Homburg, Germany) is shown in Figure 4. Several interesting features should be noted: firstly, measurement of conductivity cells from inlet and outlet dialysate circuit guarantee a precise mass balance of electrolytes; secondly, the association of the sodium module and the online ionic clearance provide real time plasma measurement of the plasma sodium concentration; thirdly, the plasma sodium concentration estimate from conductivity is corrected for potassium concentration changes.

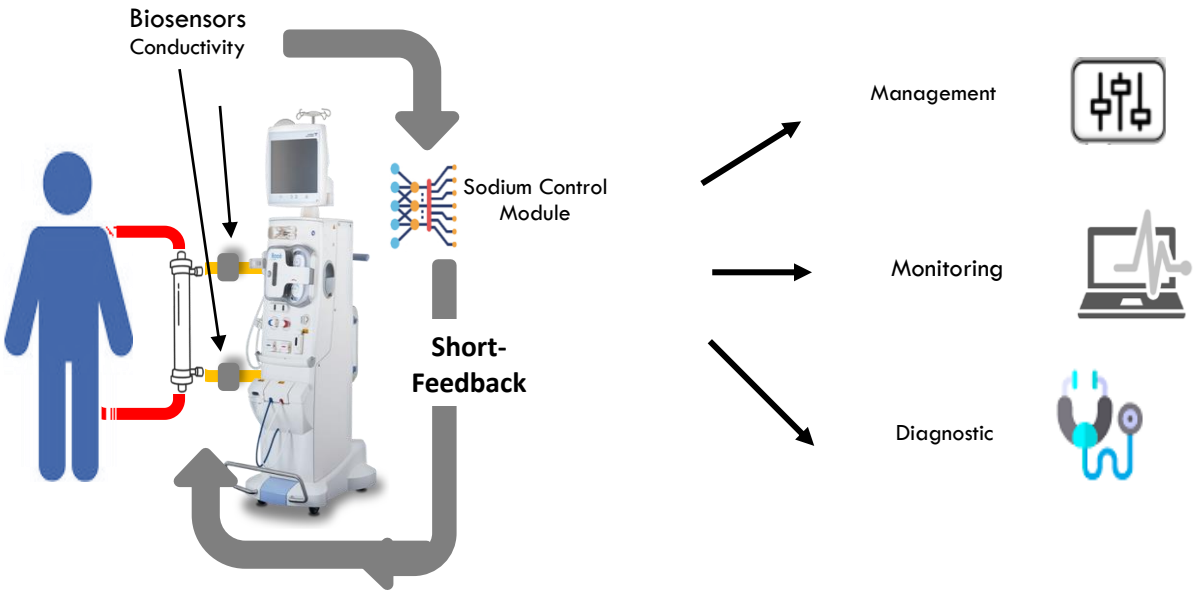


Figure 4: Sodium Control Module, 6008 CARESYSTEM (FMC, Bad Homburg, Germany)

In practice, this sodium control module is a fully automated tool with a user-friendly interface that meets medical prescriptions. When the active mode of prescription is activated, the sodium module may respond to three main modes: isonatremic dialysis, so called zero-diffusive option, in this case the dialysate-plasma gradient is permanently maintained at close to zero[31]; hypertonic dialysis when a positive dialysate-plasma sodium gradient is selected (during dialysis, the patients plasma-sodium level will be increased to a prescribed level); hypotonic dialysis when a negative dialysate-plasma sodium gradient is activated (during dialysis, the patients plasma-sodium level will be lowered to a prescribed level).

The integrated sodium tool works automatically, it doesn't require additional blood-sampling and laboratory testing, and results can be digitally transferred when the 6008 is connected to a hospital information system. Therefore, it does not increase the workload of the dialysis staff. Moreover, it can be operated on every 6008-dialysis machine, in every treatment, thereby contributing to equity in care.

Recent clinical studies have validated the safety and accuracy of the sodium control module but also the value of the clinical information provided by the module[32,33]. Used in isonatremic condition or zero-diffusive sodium option, the variation of the plasma sodium concentration achieved at the end of dialysis is less than 0.53 mmol/l on average compared to the control group. In addition to this active sodium and water management, the sodium control module offers other interesting features such as the evaluation of the total mass of sodium removed per session, an estimate of plasma sodium concentration and also it facilitates management of patients at risk such as patients presenting with hyponatremia. Further clinical studies are ongoing to evaluate the clinical benefits of this tool in HD patients either on short-term (intradialytic morbidity) or long-term (cardiovascular morbidity and mortality).

Remote and connected tools (iHealth) offer a new opportunity to monitor dialysis patients on an outpatient basis during interdialytic periods, especially at home and during activity. Responding to these needs, many non-intrusive and non-obstructive wearable devices, independent or paired with cellular phones have been developed[34]. They now allow the monitoring of vital parameters (blood pressure, heart rate, oxygen saturation, respiratory rate) or even other functions (physical activity, caloric consumption, sleep duration, sleep apnea syndrome). The reliability and clinical value of these devices needs to be proven by controlled studies. If the promises and results are there, iHealth tools will provide addition information to medical decision-making support. For the monitoring of blood pressure and rhythmic disorders, these new devices will surely provide incomparable help in personalized hemodynamic management of HD patients.

Artificial intelligence and advanced analytics will also help to manage big data generated by all these medical devices. Preliminary reports indicate interest of artificial intelligence and digital systems to support medical decision in various fields: monitoring and management of fragile patients; quality control of treatment adequacy; risk stratification; predictive medicine. A pilot study suggests that individualized fluid and hemodynamic management assisted by artificial intelligence and

advanced analysis tools may reduce intradialytic morbidity[35].

5. Conclusions

The optimized management of sodium and water disorders in HD patients is a priority that tends to be forgotten by the nephrological community for multiple reasons. However, it is an essential component of the dialysis adequacy targets panel that largely conditions cardiovascular complications.

Essentially, sodium should be considered as one of the main uremic cardiotoxin that has higher toxicity compared to the majority of organic uremic toxins identified to date. In addition, recent pathophysiological findings suggest that salt toxicity beyond its osmotic activity and mechanical consequences (hemodynamic, hypertension) has a tissue sodium component with metabolic actions. In the future, management and restoration of sodium homeostasis in HD patients must include all dimensions of sodium disorders.

New tools for monitoring sodium and water disorders are needed to fine tune this management and to judge the response to therapeutic strategy. Some have been mentioned, we will only recall the crucial role of multifrequency bioimpedance, lung ultrasound and non-obstructive connected wearable devices to assess hemodynamic status of outpatients.

New therapeutic options must be applied to ensure an effective and safe restoration of sodium and water homeostasis. In this context, the automated sodium control module may offer particularly attractive prospects. Sodium control module, possibly combined with other technical options (ultrafiltration control, thermal balance), or even therapeutic modifications (longer or more frequent dialysis) makes it possible to foresee a reduction in cardiovascular morbidity and mortality of HD patients.

In conclusion, it seems necessary today to change our clinical perspectives in terms of management of sodium, volume and hemodynamic disorders in HD patients. It is necessary to move on a 'sodium first' approach considering that volume and hemodynamic disorders are only consequences of sodium and water imbalance. This is briefly schematized on figure 5.

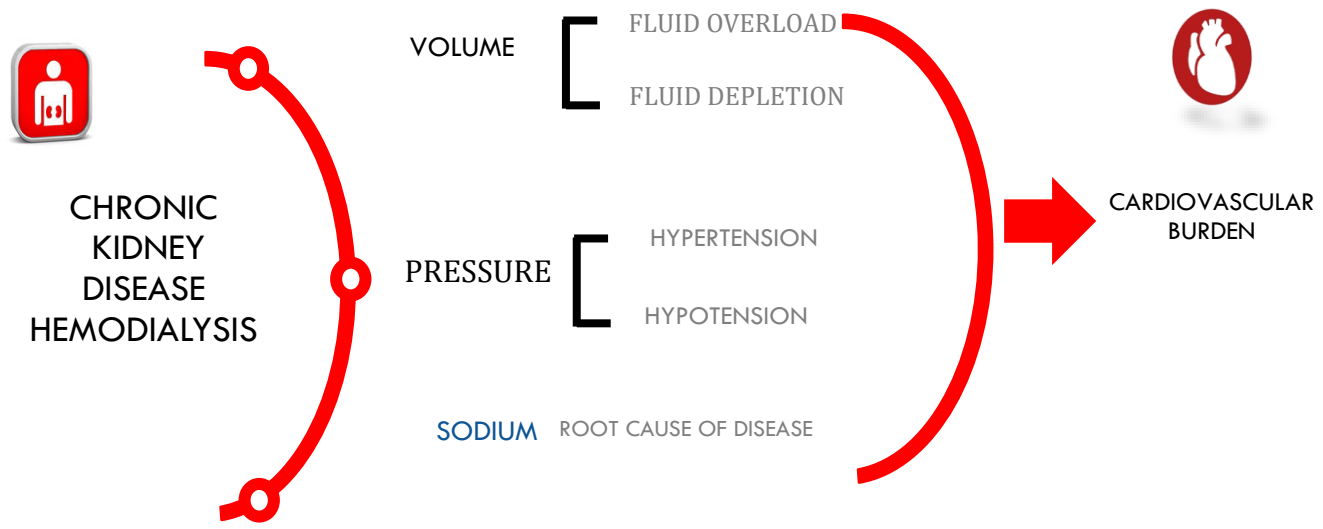


Figure 5: Sodium first approach proposed to tackle cardiovascular burden in CKD HD patients

References

1. Canaud B, Kooman J, Selby NM, et al. Sodium and water handling during hemodialysis: new pathophysiologic insights and management approaches for improving outcomes in end-stage kidney disease. *Kidney Int* 2019;95:296-309.
2. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis.* 1998;32:S112-S9.
3. Zoccali C, Moissl U, Chazot C, et al. Chronic Fluid Overload and Mortality in ESRD. *J Am Soc Nephrol* 2017;28:2491-7.
4. Van Biesen W, Verger C, Heaf J, et al. Evolution Over Time of Volume Status and PD-Related Practice Patterns in an Incident Peritoneal Dialysis Cohort. *Clin J Am Soc Nephrol* 2019;14:882-93.
5. Van Biesen W, Williams JD, Covic AC, et al. Fluid status in peritoneal dialysis patients: the European Body Composition Monitoring (EuroBCM) study cohort. *PLoS One* 2011;6:e17148.
6. Canaud B, Chazot C, Koomans J, Collins A. Fluid and hemodynamic management in hemodialysis patients: challenges and opportunities. *J Bras Nefrol* 2019;41:550-9.
7. Pinter J, Chazot C, Stuard S, Moissl U, Canaud B. Sodium, volume and pressure control in haemodialysis patients for improved cardiovascular outcomes. *Nephrol Dial Transplant* 2020;35:ii23-ii30.
8. Guyton AC. Blood pressure control--special role of the kidneys and body fluids. *Science* 1991;252:1813-6.
9. Frame AA, Wainford RD. Renal sodium handling and sodium sensitivity. *Kidney Res Clin* Pract 2017;36:117-31.
10. Bashyam H. Lewis Dahl and the genetics of salt-induced hypertension. *J Exp Med* 2007;204:1507.
11. Titze J. Sodium balance is not just a renal affair. *Curr Opin Nephrol Hypertens* 2014;23:101-5.
12. Titze J. A different view on sodium balance. *Curr Opin Nephrol Hypertens* 2015;24:14-20.
13. Rakova N, Juttner K, Dahlmann A, et al. Long-term space flight simulation reveals infradian rhythmicity in human Na(+) balance. *Cell Metab* 2013;17:125-31.
14. Rakova N, Kitada K, Lerchl K, et al. Increased salt consumption induces body water conservation and decreases fluid intake. *J Clin Invest* 2017;127:1932-43.
15. Schneider MP, Raff U, Kopp C, et al. Skin Sodium Concentration Correlates with Left Ventricular Hypertrophy in CKD. *J Am Soc Nephrol* 2017;28:1867-76.
16. Titze J, Shakibaei M, Schafflhuber M, et al. Glycosaminoglycan polymerization may enable osmotically inactive Na+ storage in the skin. *Am J Physiol Heart Circ Physiol* 2004;287:H203-8. .
17. Polychronopoulou E, Braconnier P, Burnier M. New Insights on the Role of Sodium in the Physiological Regulation of Blood Pressure and Development of Hypertension. *Front Cardiovasc Med* 2019;6:136.
18. Agarwal R, Alborzi P, Satyan S, Light RP. Dry-weight reduction in hypertensive hemodialysis patients (DRIP): a randomized, controlled trial. *Hypertension* 2009;53:500-7.
19. Agarwal R, Weir MR. Dry-weight: a concept revisited in an effort to avoid medication-directed approaches for blood pressure control in hemodialysis patients. *Clin J Am Soc Nephrol* 2010;5:1255-60.
20. Chazot C, Charra B, Vo Van C, et al. The Janus-faced aspect of 'dry weight'. *Nephrol Dial Transplant* 1999;14:121-4.
21. Charra B, Laurent G, Chazot C, et al. Clinical assessment of dry weight. *Nephrol Dial Transplant* 1996;11 Suppl 2:16-9.
22. Odudu A, McIntyre C. Volume is not the only key to hypertension control in dialysis patients. *Nephron Clin Pract* 2012;120:c173-7.
23. Vrtovsnik F, Verger C, Van Biesen W, et al. The impact of volume overload on technique failure in incident peritoneal dialysis patients. *Clin Kidney J* 2021;14:570-7.
24. Verger C, Ronco C, Van Biesen W, et al. Association of Prescription With Body Composition and Patient Outcomes in Incident Peritoneal Dialysis Patients. *Front Med* (Lausanne) 2021;8:737165.
25. Teitelbaum I. Ultrafiltration failure in peritoneal dialysis: a pathophysiologic approach. *Blood Purif* 2015;39:70-3.
26. Flythe JE, Brookhart MA. Fluid management: the challenge of defining standards of care. *Clin J Am Soc Nephrol* 2014;9:2033-5.
27. Santos SF, Peixoto AJ. Revisiting the dialysate sodium prescription as a tool for better blood pressure and interdialytic weight gain management in hemodialysis patients. *Clin J Am Soc Nephrol* 2008;3:522-30.
28. Mann H, Stiller S. Sodium modeling. *Kidney Int Suppl* 2000;76:S79-88.
29. Maggiore Q, Pizzarelli F, Santoro A, et al. The effects of control of thermal balance on vascular stability in hemodialysis patients: results of the European randomized clinical trial. *Am J Kidney Dis* 2002;40:280-90.
30. Schneditz D, Ronco C, Levin N. Temperature control by the blood temperature monitor. *Semin Dial* 2003;16:477-82.

31. Kuhlmann U, Maierhofer A, Canaud B, Hoyer J, Gross M. Zero Diffusive Sodium Balance in Hemodialysis Provided by an Algorithm-Based Electrolyte Balancing Controller: A Proof of Principle Clinical Study. *Artif Organs* 2019;43:150-8.
32. Ságová M, Wojke R, Maierhofer A, Gross M, Canaud B, Gauly A. Automated individualization of dialysate sodium concentration reduces intradialytic plasma sodium changes in hemodialysis. *Artif Organs* 2019;43:1002-13.
33. Ponce P, Pinto B, Wojke R, Maierhofer AP, Gauly A. Evaluation of intradialytic sodium shifts during sodium controlled hemodialysis. Int J Artif Organs 2020;43:620-4.
34. Kollias A, Ntineri A, Kyriakoulis KG, Stambolliu E, Stergiou GS. Validation of the iHealth ambulatory blood pressure monitor in adults according to the American National Standards Institute/Association for the Advancement of Medical Instrumentation/International Organization for Standardization standard. *Blood Press Monit* 2018;23:115-6.
35. Barbieri C, Cattinelli I, Neri L, et al. Development of an Artificial Intelligence Model to Guide the Management of Blood Pressure, Fluid Volume, and Dialysis Dose in End-Stage Kidney Disease Patients: Proof of Concept and First Clinical Assessment. *Kidney Dis* (Basel) 2019;5:28-33.