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Optimizing haemodialysate composition

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Abstract

Survival and quality of life of dialysis patients are strictly dependent on the quality of the haemodialysis (HD) treatment. In this respect, dialysate composition, including water purity, plays a crucial role. A major aim of HD is to normalize predialysis plasma electrolyte and mineral concentrations, while minimizing wide swings in the patient's intradialytic plasma concentrations. Adequate sodium (Na) and water removal is critical for preventing intra- and interdialytic hypotension and pulmonary edema. Avoiding both hyper- and hypokalaemia prevents life-threatening cardiac arrhythmias. Optimal calcium (Ca) and magnesium (Mg) dialysate concentrations may protect the cardiovascular system and the bones, preventing extraskeletal calcifications, severe secondary hyperparathyroidism and adynamic bone disease. Adequate bicarbonate concentration [HCO_3^-] maintains a stable pH in the body fluids for appropriate protein and membrane functioning and also protects the bones. An adequate dialysate glucose concentration prevents severe hyperglycaemia and life-threating hypoglycaemia, which can lead to severe cardiovascular complications and a worsening of diabetic comorbidities.

Key words: chronic kidney disease, chronic renal insufficiency, haemodiafiltration, haemodialysis, secondary hyperparathyroidism

Introduction

The dialysate composition is a key element for an effective and safe haemodialysis (HD) since it influences the exchanges of electrolytes between blood and dialysate, restores body electrolyte concentrations and acid–base equilibrium and strongly affects intradialytic cardiovascular stability.

The optimal dialysate should normalize predialysis plasma electrolyte and mineral concentrations, minimize wide swings in plasma concentrations of several substances and guarantee adequate toxin and phosphate removal. This aim is facilitated by longer or more frequent HD, which reduces the electrolyte and chemical gradients between blood and dialysate. Unfortunately, this approach cannot be implemented easily because of organizational and economic problems and its impact on patient quality of life.

Sodium

Sodium balance

Sodium (Na) crosses the dialysis membrane by diffusion and convection. The fraction of Na transported by these two mechanisms is not the same, and this is a key aspect in defining intradialytic Na kinetics and selecting the proper dialysate sodium concentration [Na].

A major aim of intermittent HD is to normalize total body water by means of ultrafiltration. In clinically stable patients, the amount of water and Na that accumulates during the interdialytic period must be removed at each HD session to obtain zero balance. Although reaching the normal clinical dry body weight of the patient may normalize the extracellular volume, the amount of water and salt introduced in each individual

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patient is not uniform, leading to a variety of increases in extracellular volume and sodium concentrations. Therefore, considering that the interdialytic Na load and the Na/water ratio vary from one patient to another, and even in the same patient, the amount of Na removal should be individualized by adjusting the dialysate [Na] during each dialysis [1]. Therefore, this approach is unsuitable for routine clinical application, and several attempts have been made to sort out these difficulties.

High dialysate [Na] has been suggested to compensate for excessive Na losses due to ultrafiltration and can prevent cardiovascular instability, as a result of increased osmotic refilling of water from the cells to the intravascular compartment, which counteracts the effects of intravascular emptying secondary to ultrafiltration. However, this may cause insufficient net Na removal, favouring the development of refractory hypertension, intradialytic hypertension, increased thirst, overhydration and risk of pulmonary edema [2].

Conversely, a low dialysate [Na] causes a loss of Na by diffusion and a decrease in plasma osmolarity that may lead to cellular overhydration due to an osmotic fluid shift from the extracellular to the intracellular compartment, which contributes significantly to the so-called 'disequilibrium syndrome'. Moreover, a negative Na balance causes intradialytic cardiovascular instability with hypotension due to insufficient refilling of the intravascular compartment from the intracellular space and 'disequilibrium' symptoms such as fatigue, muscle cramps, headache and orthostatic hypotension. Paradoxically, it can cause hypertensive crises, driven by the activation of the renin–angiotensin system [1].

It is important to know that when there is no ultrafiltration and the dialysate Na activity corresponds to plasma Na activity multiplied by a Donnan factor of 0.967, the net intradialytic Na removal is zero ('isonatric dialysate').

Sodium and conductivity kinetic models

The best approach to select the appropriate dialysate [Na] has been the development of the Na kinetic model. The attainment of a neutral Na balance during HD requires constant values of the product of total body water per plasma water [Na] to be maintained at the end of HD. However, it is preferable to maintain constant values of both total body water and plasma [Na] to avoid fluctuations of plasma water [Na]. While achieving the removal of total body water, as reported above, is simply reaching the previous dry body weight, the achievement of the same value of plasma [Na] at the end of each HD session is affected by several variables, such as convective and diffusive Na flux, length of the HD session and Na dialysance. Kinetic mathematical models consider all these factors in determining the net Na flux and predicting plasma water [Na] at the end of HD. The variable volume single-pool Na kinetic model allows the targeted end-dialysis plasma water [Na] to be obtained [3]. Nevertheless, this is also not suitable for routine clinical application, because the real-time determination of initial plasma water [Na] and 'effective' Na dialysance is difficult.

Considering the linear correlation between [Na] and conductivity of saline solutions and the basic theory [4, 5] for ionic dialysance determination, conductivity values can be used instead of [Na] values. The conductivity kinetic model is more easily applicable in everyday clinical practice, because no blood samples or laboratory test is needed to determine plasma water conductivity and ionic dialysance used, instead of plasma water [Na] and Na dialysance, respectively.

Sodium profiling

An Na profiling programme simplifies the Na kinetic model approach. The session starts with a higher dialysate [Na] to reduce the decline in blood volume during ultrafiltration, followed by a lower dialysate [Na] in the final part of the session. This restores the patient's normal plasma [Na] at the end of HD [6]. Unfortunately, the Na balance is not usually calculated, leading to a frequent positive Na balance [7].

Observational data

Interestingly, dialysate [Na] varies widely across the countries of the Dialysis Outcomes and Practice Patterns Study (DOPPS); moreover, no survival benefits were found when using a lower dialysate [Na]. Similarly, matching low plasma [Na] with low dialysate [Na] was not related to any survival benefit. Conversely, every 2 mEq higher dialysate [Na] coincided with an increase in interdialytic weight gain of 0.12 kg. However, this was not associated with a higher risk of mortality or hospitalizations [8].

Recently, Dahlmann *et al.* [9] showed that Na magnetic resonance imaging (sodium-MRI) can detect the amount of Na stored in the skin and the muscle and its removal during HD. Interestingly, older HD patients showed increased Na and water in the skin and the muscle compared with age-matched controls. This coincided with low levels of vascular endothelial growth factor-C (VEGF-C). The lower the VEGF-C levels, the higher the skin Na content after HD. The new concept of skin and muscle Na storage is interesting and could have relevant clinical implications in the near future, although these stores are separate from the osmotic relationships of Na.

In conclusion, in order to obtain an Na zero balance in relation to the amount of water and Na accumulated during the interdialytic period, a rate of ultrafiltration equal to the interdialytic increase in body weight should be applied and the dialysate [Na] individualized. This can best be performed only using a conductivity kinetic model. In any case, the Donnan factor and the gradient between patient plasma water and dialysate [Na] must be considered in selecting the appropriate dialysate [Na].

Potassium

Kinetics of potassium in haemodialysis

In patients on HD, dietary potassium (K) intake and metabolic acidosis are the main contributors of life-threating K overload and high plasma K concentration [K].

As for all the electrolytes, the intermittent nature of HD leads to fluctuations in plasma [K], with frequent high predialysis plasma [K] and low intra- and/or postdialysis plasma [K] values. HD removes K from the intracellular, but even more from the extracellular compartment [10]. Indeed, the major part of the K pool (98%) is in the intracellular compartment, and only 2% of total K is found in the extracellular fluids. The difference in K content is mainly determined by the Na-K ATPase pump activity, but several factors contribute to K flux between the two compartments (acid–base balance, hormonal factors, plasma osmolality, drugs, etc.), some of which are influenced by HD treatment.

After HD, plasma K concentration rebounds to restore the balance between the two compartments. This shift may increase the intradialytic cellular membrane polarization and trigger arrhythmias [11].

Standard HD removes K mainly by diffusion (85%) and marginally by convection (15%) [12]. Thus, the choice of

dialysate [K] is critical for maintaining K homeostasis, since K removal is strictly dependent on the gradient between predialysis plasma and dialysate [K] (together with K dialysance and HD time).

Observational data

Several studies have shown that both hypo- and hyperkalaemia significantly increase the intradialytic risk for cardiac arrhythmias [13–17].

The arrhythmogenic effect of low plasma [K] is amplified by a rapid correction of metabolic acidosis, the use of a low dialysate [Ca] and a high ultrafiltration rate [18, 19].

The importance of recognizing the high risk for life-threating outcomes due to high predialysis plasma [K] is also supported by an increased incidence of sudden death on the first days of the week (at the end of the long interdialytic interval) [20, 21] when plasma [K] is usually higher. Kovesdy *et al.* showed that, in patients with high predialysis plasma [K], the use of a higher dialysate [K] was significantly associated with increased mortality [13]. Moreover, the use of a higher dialysate [K] in patients with predialysis plasma [K] >5 mEq/L was not associated with a significant trend towards a reduction in sudden death and all-cause mortality. In addition, there was no clear relationship between sudden death (and all-cause mortality) and low dialysate [K] in patients with predialysis plasma [K] <5 mEq/L.

Fixed versus variable K dialysate

When using a fixed dialysate [K], standard HD causes a rapid fall in plasma [K] during the first hour, followed by a slower [K] decrease. Redaelli *et al.* [22] hypothesized that, during the first hour of HD, there is an increased passive diffusion of K through the cell membranes, due to a chemical gradient leading to a negative polarization of the cell membranes.

A dialysate [K] profiling, with a graded decrease in the dialysate [K] during the course of the HD session, was proposed to obtain a smooth K removal [23]. Ideally, the plasma-to-dialysate [K] gradient should be kept constant at around 1.5 mEq/L to achieve a good correction of high plasma [K] while avoiding K depletion. Importantly, the dialysate [K] modelling was found effective in reducing the frequency of intradialytic premature ventricular beats [23–25]. According to a secondary analysis of the Hemodialysis Study (HEMO), potassium kinetics during HD can be described using a pseudo-one-compartment model [26].

Optimal potassium dialysate prescription

Ideally, dialysate [K] should remove the interdialytic K load without causing K depletion and to avoid rapid plasma [K] changes. However, the interdialytic K load cannot be easily quantified, also considering the confounding effects of metabolic acidosis, oral bicarbonate supplements and K binders. These binders are very helpful in controlling plasma [K] in the interdialytic period, since HD patients have a gastrointestinal K excretion that is almost the double that of healthy subjects [27, 28] and accounts for nearly 35% of total K excretion [29]. Very recently, two new K binders have been proposed to facilitate this approach [30, 31].

Considering that, in HD patients, the lowest overall mortality is observed at a predialysis plasma [K] between 4.6 and 5.3 mEq/L [14], the ideal predialysis plasma [K] should be ~5 mEq/L. The total amount of K that should be removed by HD to maintain a normal K body pool is still unknown.

The mean age of HD patients is progressively increasing. One of the main problems of this patient population is malnutrition, due to inadequate caloric and protein intake. We can thus assume that, in the elderly, K dietary intake is also relatively low. In these subjects, standard HD may then cause an excessive K removal, with consequent muscle mass impairment. Thanks to a profiled dialysate [K], the HD should instead redistribute K between the intra- and extracellular compartments. In this respect, moderate and incremental muscle exercises have been recommended to avoid the risk of high plasma [K] due to muscle cell cytolysis. Physical exercise, even during HD, should be associated with a comprehensive clinical management, enhancing the nutritional status but without requiring a too restrictive diet.

Due to the progressive ageing of HD patients, dialysate [K] modulation has become an issue of extreme clinical relevance. In general, a dialysate [K] of <2 mEq/L should be avoided.

Calcium

Overall, Ca balance in HD patients is the result of Ca absorption from the gut, Ca excretion by residual renal function and Ca balance during HD.

The optimal dialysate [Ca] should take into consideration contrasting needs: favour the cardiovascular stability during HD; avoid cardiac arrhythmias; maintain normal bone turnover and mineralization, in order to avoid severe secondary hyperparathyroidism (SHPT), bone pain and fractures; and prevent cardiovascular and soft tissue calcifications.

Before the availability of active vitamin D therapy, HD patients were often in a negative Ca balance due to an impaired intestinal Ca absorption [32]. A dialysate [Ca] of 1.5–1.75 mmol/L was selected, which was higher than plasma [Ca] [33]. However, the ingestion of large amounts of Ca can lead to Ca overload, because its passive transintestinal transfer is normal [34]. With the use of calcitriol in a large proportion of patients, HD patients absorb a significant proportion of the Ca ingested from the diet and also from Ca-based phosphate binders.

Today, chronic Ca overload is considered one of the main factors contributing to the high rate of vascular and valvular calcifications in HD patients. The achievement of a net zero Ca mass balance over the HD cycle is thus required to remove the total Ca absorbed between HD, but this is very difficult to be evaluated clinically. During HD, Ca shifts from the plasma to the bones, and vice versa, can take place, as well as possible deposition of Ca (and phosphate) in the soft tissues, including vessels and cardiac valves, making the evaluation of the Ca mass balance very complex.

A debate is going on about the optimal dialysate [Ca] [35, 36], either favouring the use of a low dialysate [Ca], mainly to avoid the long-term risk of vascular and valvular calcifications, or against low dialysate [Ca], being associated with hypotension and cardiac arrhythmias during HD and long-term risk of SHPT.

Even a neutral Ca balance may be harmful in patients with high-turnover bone disease, in whom bone reabsorption could prevail over bone formation, leading to Ca deposition in soft tissues. Obviously, before reducing the dialysate [Ca], reasons for a positive Ca balance, including excessive Ca intake or high doses of vitamin D, should be corrected [35]. The control of SHPT in patients treated with low dialysate [Ca] (1.25 mmol/L) may require higher doses of calcitriol or paricalcitol than when treated with higher dialysate [Ca]. In the presence of adynamic bone disease and low serum parathyroid hormone (PTH) levels, a low dialysate [Ca] has been shown to increase circulating PTH and bone-specific alkaline phosphatase [37, 38]. In patients with long daily or

nocturnal HD sessions, a low dialysate [Ca] may lead to excessive bone mineral loss; a relatively high dialysate [Ca] may be necessary to prevent osteopenia [39].

High dialysate [Ca], together with high bicarbonate, may even further improve the haemodynamic pattern during HD session.

In patients with SHPT, a dialysate [Ca] of 1.75 mmol/L resulted in a better control of parathyroid over-function and high-turnover bone disease than a lower dialysate [Ca]. In comparison with drugs that increase serum Ca and/or P (like vitamin D), the introduction of cinacalcet, which decreases not only serum PTH but also serum Ca and phosphate [40], requires lower dialysate [Ca]. This avoids the patient receiving a large amount of Ca, due to a large increase in the gradient between the dialysate and plasma [Ca], which may cause Ca deposition in soft tissues, favoured by the rapid correction of the metabolic acidosis. On the other hand, in patients treated with cinacalcet, a high dialysate [Ca] may allow the control of serum PTH levels with lower doses of the calcimimetic and prevent severe hypo-[Ca]. These contrasting needs should be carefully taken into consideration in selecting an adequate dialysate [Ca], but lower dialysate [Ca] should be preferable in many instances, eventually in association with active vitamin D or analogue use.

Although the control of SHPT is more effective with a high dialysate [Ca] (1.75 mmol/L), the over-suppression of PTH should be avoided due to the risk of adynamic bone disease and to prevent high plasma [Ca] and soft tissue calcifications. This is particularly true for patients receiving oral Ca, both as supplements or phosphate binders, and active vitamin D, which may enhance intestinal Ca absorption. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NFK-KDOQI) guidelines recommend a dialysate [Ca] of 1.25 mmol/L as a compromise between optimization of bone health and reduction in cardiovascular risk [41]. Gotch *et al.* [42] suggested that all patients should receive a 1.0 mmol/L dialysate [Ca] and developed a formula to justify this conclusion. Recently, Di Filippo *et al.* [43] described a single-pool kinetic model using a 'nominal' 1.5 mmol/L label dialysate [Ca]. In patients with predialysis [Ca] in the normal range, an 'ionized' dialysate [Ca] of 1.26 mmol/L ('nominal' total [Ca] of 1.50 mmol/L, the difference being related to the modification in the conductivity in order to have a personalized dialysate [Na] for the different patients) did not cause higher plasma water [Ca]. Given that the predicted and measured final plasma water [Ca] were similar, it avoided the extracellular buffering of increased plasma water [Ca] induced by the diffusive gradient. On the contrary, high plasma [Ca] and extracellular buffering were the rule when using an ionized dialysate [Ca] of 1.50 mmol/L ('nominal' total [Ca] of 1.75 mmol/L). Considering that Ca deposits in the soft tissues are hardly removed, a dialysate [Ca] of 1.75 mmol/L is not recommended.

Accordingly, the DOPPS data showed that the use of a high dialysate Ca (1.75 mmol/L) has declined over time. Indeed, the patients dialysed with a dialysate [Ca] of 1.75 mmol/L who are taking a Ca-based phosphate binder have a significantly higher risk of cardiovascular or sudden death [44].

On the other hand, the use of a low dialysate [Ca] as well as high serum dialysate [Ca] gradients has been associated with an increased risk of sudden cardiac arrest [45].

In conclusion, an 'ionized' dialysate [Ca] of 1.25 mmol/L should be an appropriate choice for the majority of the patients.

Magnesium

Magnesium (Mg) plasma concentration is increasingly recognized as being associated with vascular ageing, especially in diabetic patients. Free Mg represents only 1% of the total body contents, ranging between 0.62 and 1.02 mmol/L, where 60% of this circulates as the biologically active free cation, while the remaining 40% is protein bound or complexed as salts.

The selection of dialysate Mg concentration [Mg] is very challenging for the nephrologists, and the problem is further complicated by the availability of Mg carbonate as a phosphate binder. Dialysate [Mg] is a major determinant of Mg balance in HD patients, as it crosses the HD membranes easily. The amount of Mg eliminated depends on ultrafiltration and the gradient between plasma and dialysate-diffusible [Mg] [46]. Considering the sieving coefficient, usually only a dialysate [Mg] of <0.5 mmol/L will result in a diffusive elimination of Mg [47, 48]. However, a magnesium-free dialysate is poorly tolerated because of leg cramps [47].

In a large observational study, the baseline prescribed dialysate [Mg] showed only a weak correlation with plasma [Mg], suggesting that other factors, including Mg food intake, supplements such as antacids and phosphate binders, and possibly laxatives, may also play an important role [49].

Kyriazis *et al.* [50] investigated the effect of different dialysate [Mg] and [Ca] on blood pressure during HD. The combined use of a dialysate [Ca] of 1.25 mmol/L and [Mg] of 0.25 mmol/L caused a significant drop in mean arterial pressure, due to a drop in cardiac index not compensated by an increase in total peripheral resistance. Conversely, the combination of the same dialysate [Ca] with a higher dialysate [Mg] (0.75 mmol/L) prevented a fall in blood pressure [49]. Intermediate values of dialysate [Mg] had intermediate effects (50). Despite these observations, a high dialysate [Mg] has no favourable effects on the intradialytic cardiovascular stability or cardiac performances [49].

Plasma [Mg] levels up to 2 mmol/L are frequent in HD patients and are usually asymptomatic. However, ionized and intracellular [Mg] could be more representative of the active Mg state [51].

Plasma [Mg] may have an important regulatory role in PTH secretion [52]. The maintenance of normal-high [Mg] could be useful in the control of SHPT, activating the calcium-sensing receptors (CaSR) and optimizing the molecular actions on vitamin D receptors (VDR), fibroblast growth factor 23 (FGF23) and Klotho. However, it is still unclear whether Mg supplementation may improve bone health in CKD patients. In a recent cohort study of 142 069 HD patients in Japan, an increase in serum phosphate levels over 1 year was associated with a higher risk of cardiovascular mortality in patients with low serum [Mg] levels (<2.7 mg/dL), as well as in those with intermediate serum levels (2.7 to 3.0 mg/dL). However, no significant risk was observed in patients with [Mg] levels ≥3.1 mg/dL. Among patients with serum phosphate levels ≥6.0 mg/dL, the cardiovascular mortality risk significantly decreased with increasing serum [Mg] levels [53].

At present the dialysate [Mg] should be 1 mg/dL.

Bicarbonate

The maintenance of a stable pH is essential in the body fluids since changes in hydrogen ions [H^+] alter almost all protein and membrane functions [54–58].

The daily acid production that is to be neutralized can be calculated as 0.77 mmol/g of catabolized proteins [59]. The kidney plays an important role in maintaining the acid–base balance by excreting non-volatile acids and regenerating $HCO3^-$.

HD cannot remove a large amount of [H^+] because of their low blood concentration. The [H^+] produced is buffered by plasma HCO_3^- and other body buffers; during HD, the process of [H^+] removal is mainly achieved by the flux of alkaline equivalents

from the dialysate into the blood, which replaces the buffers used in the buffering process.

Because plasma HCO_3^- is the most important buffer in the body, the choice of bicarbonate as a dialysate buffer was a logical choice in the old days of HD [60, 61]. At that time, the preparation of bicarbonate dialysate was a complicated procedure because of the precipitation of calcium and magnesium carbonate and bacterial contamination [60, 61].

To obviate these problems, Na acetate was introduced in the dialysate in the 1960s [62] as a substitute for HCO_3^-. However, at high HD efficiency, acetate accumulates in the plasma and worsens cardiovascular instability [63] and tolerance to HD (nausea, headache and fatigue) [64].

In the early 1980s, new HD techniques overcame the technical limitations of acetate HD, and bicarbonate HD was widely reintroduced. Dialysate HCO_3^- corrects the base deficit by the diffusive transfer of bicarbonate from the dialysate to the blood. The acid–base balance is achieved when the bicarbonate gain compensates the inter-HD [H^+] production plus the HD removal of organic anions and bicarbonates. Many factors, including blood and dialysate flows, dialyser type and surface area, dialysate HCO_3^- concentration [HCO_3^-] and ultrafiltration rate, may affect acidosis correction. During bicarbonate HD, the HCO_3^- gradient between the dialysate and the plasma water and the HD efficiency determine how much HCO_3^- is transferred into the blood; the apparent HCO_3^- distribution space (40–50% of the total body weight) determines post-HD plasma [HCO_3^-].

Achieving normal plasma [HCO_3^-] levels during the interdialytic period with intermittent HD is virtually impossible; plasma [HCO_3^-] should be maintained as much as possible within a physiological range. The HCO_3^- flux during HD rapidly increases plasma [HCO_3^-]; then, HCO_3^- is slowly consumed by endogenous acid production during the interdialytic interval [65].

The catabolic effect of acidosis contributes to the frequent abnormal protein metabolism and malnutrition of HD patients [66]. Acidosis has also been identified as a mortality risk factor in HD patients [67]. Finally, the bone buffering associated with chronic acidosis could aggravate osteodystrophy [68].

On the other hand, acidosis over-correction (i.e. postdialysis plasma [HCO_3^-] >28 mmol/L) should be avoided, especially in patients with compromised left-ventricular function. Indeed, alkalosis increases Ca binding to protein and may reduce ionized [Ca] and impair cardiac muscle contraction and arterial pressure preservation [69].

Furthermore, pH >7.40 increases the affinity of haemoglobin for oxygen and may cause hypoxaemia, which further impairs cardiac function. Finally, the decrease in plasma [K] during HD is further enhanced by alkalosis, through the shift of K from the extracellular to the intracellular space, possibly leading to severe cardiac arrhythmias [70].

Much evidence shows that low predialysis plasma [HCO_3^-] is an independent risk factor for morbidity and mortality [71–74]. However, the cut-off level at which the risk significantly increases varies from study to study. According to the DOPPS data [74], a plasma [HCO_3^-] of >23 mmol/L was not associated with increased mortality; this is in contrast with a previous analysis of participants in the first phase of the DOPPS study (72) and with a US cohort of HD patients [67].

Finally, there is wide variability in predialysis plasma [HCO_3^-], and the level achieved is related inversely to protein catabolic rate [71, 75]. The increasing age of HD patients, and an associated decrease in endogenous acid production because of a spontaneous, lower protein intake, could explain the gradual increase in predialysis plasma [HCO_3^-] without changes in dialysate [HCO_3^-] [76].

Ideally, the optimal predialysis and postdialysis plasma [HCO_3^-] should not be <24 mmol/L and not >28 mmol/L. Assuming a postdialysis plasma [HCO_3^-] of 28 mmol/L, for a bicarbonate distribution volume of 40% of body weight and a mean protein intake of about 1 g/kg/day, there will be a decrease in a plasma [HCO_3^-] of about 4 mmol/L in the interdialytic period, with a predialysis plasma [HCO_3^-] of about 24 mmol/L at the following session.

Most patients receiving HD are dialysed with a dialysate containing a final [HCO_3^-] of ≥35 mmol/L and have a postdialysis plasma [HCO_3^-] of 28–30 mmol/L [67] and a pre-HD plasma [HCO_3^-] of 19–22 mmol/L after the long interval between HD [71, 72, 76].

The optimal pre- and postdialysis plasma [HCO_3^-] cannot be attained using a standard procedure for all patients: the base requirement varies from patient to patient, according to protein intake and fixed acid production, the volume of bicarbonate distribution and HD ultrafiltration rate. In theory, with a modern proportioning system, the dialysate [HCO_3^-] can be varied over a wide range, allowing for individualization of the dialysate [HCO_3^-] to obtain an end HD plasma [HCO_3^-] of about 28 mmol/L.

A recent cohort study [74] suggested that higher dialysate [HCO_3^-] increases the hazard risk for all-cause mortality, regardless of the predialysis plasma [HCO_3^-]. These results call into question the safety of high dialysate [HCO_3^-] (>38 mmol/L), as recommended by the 2000 NKF-KDOQI guidelines [77]. The risk of aggressively increasing predialysis plasma [HCO_3^-] may also include accelerating Ca phosphate precipitation in the tissues [78].

In patients with predialysis acidosis (plasma [HCO_3^-] <19–20 mmol/L), it is necessary to evaluate the protein catabolic rate and the interdialytic weight gain [79]. An appropriate blood sample handling is also warranted, since processing delays can falsely lower [HCO_3^-] [80]. In these patients, interdialytic oral Na bicarbonate administration is preferable [81] to the increase in dialysate [HCO_3^-], because it does not expose patients to the risk of higher postdialysis plasma [HCO_3^-].

In HD patients with predialysis [HCO_3^-] values >27 mmol/L, it is necessary to exclude a coexisting acute metabolic alkalosis (excessive alkali administration, vomiting, nasogastric drainage, high-volume ileostomy drainage, etc.) and eventually treat these acute disorders [81]. A dialysate [HCO_3^-] of >35 mmol/L is not desirable in these patients. In the absence of acute events, the most probable cause of predialysis alkalosis is severe malnutrition and low endogenous acid production [81].

In summary, the ideal pre- and postdialysis plasma [HCO_3^-] should range between 24 and 28 mmol/L, although as reported above, most patients have a pre-HD plasma [HCO_3^-] of 19–22 mmol/L after the long interval between HD sessions. The dialysate [HCO_3^-] (or better, the total base concentration) should not exceed 35 mmol/L.

Glucose

Years ago, concentrations of glucose up to 1800 mg/dL were used to generate an osmotic pressure that allowed the removal of water and Na in excess by ultrafiltration and prevented haemolysis in the extracorporeal circulation with large blood volume [82]. In later years, ultrafiltration was obtained through the transmembrane pressure, and the dialysate glucose concentration was drastically reduced. Many HD centres used a glucose-free dialysate to avoid hypertriglyceridaemia and the potential risk of increased bacterial growth in the dialysate [83]. However, this approach exposed patients to hypoglycaemia, especially in diabetics treated with insulin or oral antidiabetic agents [84–89]. As in metabolic alkalosis, insulin favours the shift of K from the

extracellular to the intracellular space. Thus, hypoglycaemia determines a less effective shift of K from plasma to the cells and caused a greater loss of amino acids in the dialysate [84]. Consequently, a higher K removal should be expected when selecting a glucose-free dialysate [90]. Today, HD solutions are glucose-free, isoglycaemic (100 mg/dL) or moderately hyperglycaemic (200 mg/dL) [91]. It is unclear whether dialysate glucose concentrations of 100–200 mg/dL may have a deleterious effect on triglyceride metabolism [92, 93]. There are also some concerns with using glucose dialysate concentrations of 200 mg/dL because hyperglycaemia may be a proinflammatory stimulus [94–96].

The Food and Drug Administration (FDA) currently approves of a dialysate containing 100 mg/dL of glucose.

Dialysate concentrations in alternative dialysis techniques

Long nocturnal haemodialysis

Long nocturnal HD is an interesting dialysis technique for those patients who prefer to be free of dialysis during the day and in the meantime have a better control of fluid retention and related complications, such as several parameters such as phosphate and anaemia.

This technique usually lasts 8–10 h, allowing more time for the mechanism of diffusion compared with standard HD, thus facilitating plasma [Na] to be reached at the end of dialysis very close to the dialysate [Na]. In this setting, a dialysate [Na] higher than plasma water [Na] should be avoided, because Na removal by convection is limited in relation to the large effect of diffusion.

The longer time required for the mechanism of diffusion applies to all electrolytes, including K, with the risk of hypokalaemia at the end of dialysis.

Daily short haemodialysis

Daily short HD causes the opposite problem. Na is mainly removed by convection, and the time for diffusion to equilibrate Na between plasma water [Na] and dialysate [Na] is too short. This is true for all electrolytes, and the problem is very delicate. A too low dialysate [K] in order to enhance K removal should be avoided because a high [K] gradient between the plasma water and the dialysate could facilitate cardiac arrhythmias. When a high dialysate [Na] is used for improving intradialytic cardiovascular stability, the removal of Na by convection should take into consideration the amount of Na that the patient is receiving by diffusion, in order to avoid the risk of Na and water retention and their related complications.

Less frequent haemodialysis

In patients receiving twice a week HD, the increase in interdialytic body weight is the factor affecting the amount of Na to be removed by convection. The dialysate [Na] should be selected accordingly, also considering the plasma water [Na].

The same holds true for once a week HD. This dialysis technique is suitable only to very selected and motivated patients, who also follow a very low protein diet (0.3–0.4 g/kg/ideal body weight with keto-analogue supplements) [97, 98]. Considering that, in these highly motivated patients, the sodium intake is usually very low, the selected dialysate [Na] should often be close to 132–130 mEq/L to avoid Na retention by diffusion and the related complications.

Being that the ultrafiltration is usually very low due to the high compliance of these patients, the removal of calcium (Ca) by convection is also very low. Thus, in order to remove the amount of Ca eventually accumulated by the patient during the interdialytic period, the dialysate Ca concentration [Ca] could be lower than in standard HD, avoiding in any case a negative calcium balance.

Online haemodiafiltration

This HD technique uses a large amount of reinfusion fluids (about 20 L in the predilution modality) [99] and is gaining growing popularity considering the large amount of convection that the technique is able to provide. When coupled with high-flux membranes, online haemodiafiltration is able to remove middle molecules, including beta$_2$ microglobulin, which is associated with higher mortality in HD patients [100]. Compared with standard HD, the dialysate composition does not need particular adjustment. Conversely, the reinfusion fluid composition should take into consideration the sieving effect, causing a small retention of cations and a higher removal of anions. To avoid Na retention, the reinfusate [Na] should be about 8 mEq/L lower than the dialysate [Na]. This technique may improve intradialytic cardiovascular stability, possibly due to the colder reinfusate and a less negative Na balance [101].

Future developments

The dialysate can be used as a vehicle for the administration of various compounds. Phosphate-enriched dialysate has been used for short-term phosphate supplementation in certain patients [102]. Some years ago, L-carnitine was administered via dialysate to maintain tissue carnitine levels [103]. A new iron supplement, ferric pyrophosphate citrate (Triferic®) has recently been approved by the FDA as an iron replacement product to be

Table 1. Summary of the correct dialysate solute concentrations

Solute	Correct choice
Sodium (Na)	To obtain an Na zero balance in relation to the amount of water and Na accumulated during the interdialytic period, a rate of ultrafiltration equal to the interdialytic increase in body weight should be applied and the dialysate [Na] needs to be individualized. The Donnan factor and the gradient between patient plasma water and dialysate [Na] must be considered.
Potassium (K)	HD should remove the inter-HD K load, obtaining an ideal pre-HD plasma [K] of ~5 mEq/L at the successive HD session. In general, a dialysate [K] of <2 mEq/L should be avoided.
Calcium (Ca)	An 'ionized' dialysate [Ca] of 1.25 mmol/L (nominally 1.5 mmol/L) should be appropriate for the majority of the patients.
Magnesium (Mg)	Considering the sieving coefficient, usually only a dialysate [Mg] of <1 mg/dL will result in a diffusive elimination of Mg; the dialysate [Mg] should be 1 mg/dL.
Bicarbonate (HCO_3)	The base requirement varies from patient to patient, according to protein intake and fixed acid production, the volume of bicarbonate distribution and HD ultrafiltration rate. The ideal pre- and post-HD plasma [HCO_3] should range between 24 and 28 mmol/L. The dialysate [HCO_3^-] (or better, the total base concentration) should not exceed 35 mmol/L.
Glucose	Isoglycaemic HD solution (100 mg/dL).

Table 2. Possible adverse effects secondary to the prescription of the wrong haemodialysate; the table shows, for each component of the haemodialysate, the major possible short-term and long-term adverse reactions secondary to an excessively low (left column) or to an excessively high dialysate concentration (right column).

Adverse reactions due to an excessively LOW concentration		*Adverse reactions due to an excessively HIGH concentration*
– Intradialytic cardiovascular instability – Disequilibrium symptoms (fatigue, muscle cramps, headache, etc.)	Na^+	– Refractory hypertension – Intradialytic hypertension – Increased thirst sense – Pulmonary edema
– Arrhytmogenic effect amplified by a rapid correction of metabolic acidosis, low dialysate calcium concentration, high ultrafiltration rate, abrupt kalemia decrease	K^+	– Risk of insufficient potassium removal with secondary hyperkalemia in the interdialytic period – Increased mortality
– Hypotension and cardiac arrhythmias during hemodialysis and long-term risk of secondary hyperparathyroidism – Increased risk of sudden cardiac arrest – Increased circulating parathyroid hormone levels (PTH) in the presence of adynamic bone disease and low serum PTH levels – Risk of excessive bone mineral loss in patients with long daily or nocturnal hemodialysis sessions	Ca^{++}	– Long-term risk of vascular and valvular calcifications – Significantly higher risk of cardiovascular and sudden death in patients who are taking a calcium-based phosphate binder – Risk of over suppression of parathyroid hormone and adynamic bone disease, with high plasma [Ca] and soft-tissue calcifications
– Leg cramps – Significant drop in mean arterial pressure in the association of dialysate calcium concentration of 1.25 mmol/L and magnesium concentration of 0.25 mmol/L	Mg^{++}	– Signs and symptoms of hypermagnesemia (hyporeflexia, weakness up to paralysis that can involve the diaphragm, bradycardia, hypotension, cardiac arrest, inhibition of parathyroid hormone secretion with secondary hypocalcemia)
– Acidosis with secondary abnormal protein metabolism and malnutrition – Osteodystrophy	HCO_3^-	– Increased calcium binding to proteins, reduction of ionized calcium, and impaired cardiac muscle contraction and arterial pressure preservation – Hypoxemia, with further impaired cardiac function – Increased potassium removal – Accelerated tissue calcium phosphate precipitation
– Risk of hypoglycemia – Greater loss of aminoacids in the dialysate – Higher potassium removal secondary to alkalosis	*Glucose*	– Impaired triglyceride metabolism – Risk of pro-inflammatory stimulus secondary to hyperglycemia

added to the dialysate for the maintenance of haemoglobin in patients receiving chronic HD. It is a soluble iron salt with a molecular weight of 1313 Da. When added to the $HCO3^-$ concentrate, it diffuses across the dialyser membrane to donate iron directly to transferrin. Ferric pyrophosphate citrate can be administered at each HD treatment and maintains stable haemoglobin levels without increasing iron stores [104].

Conclusions

Table 1 and Table 2 summarize the main aims and pro and contra of the various components of the dialysate. An adequate Na and water removal is critical for assuring the control of body fluids, avoiding the risk of pulmonary edema and hypertension and reducing the risk of intra- and extradialysis hypotension and cramps. Minimizing wide swings in plasma [K] is of paramount importance for preventing the risk of life-threatening hyper- and hypokalaemia, possibly leading to severe cardiac arrhythmias. With regard to Ca and Mg (and phosphorus), the most important aim is to guarantee the protection of the cardiovascular system and bones while avoiding extraskeletal calcifications, controlling SHPT and reducing the risk of adynamic bone disease. Bicarbonate concentration should also protect bones and maintain a stable pH in the body fluids, which is crucial for almost all protein and membrane functions. A physiological dialysate glucose concentration is important, particularly in diabetic patients, to avoid the potential, severe complications of both hyper- and hypoglycaemia.

Conflicts of interest statement

None declared.

(See related articles by Perez-Gomez *et al*. Haemodialysate: long neglected, difficult to optimize, may modify hard outcomes. *Clin Kidney J* (2015) 8: 576–579.)

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