

Improving Solute Clearances by Hemodialysis

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Abstract

The adequacy of hemodialysis is now assessed by measuring the removal of the single-solute urea. The urea clearance provided by contemporary dialysis is a large fraction of the blood flow through the dialyzer and therefore cannot be increased much further. Other solutes however likely contribute more than urea to the residual uremic illness suffered by hemodialysis patients. We here review methods which could be employed to increase the clearance of nonurea solutes. We will separately consider the clearances of free low-molecular-mass solutes, free larger solutes, and protein-bound solutes. New clinical studies will be required to test the extent to which increasing the clearance on nonurea solutes with these various characteristics can improve patients' health.

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Introduction

We presume that an important part of the residual illness in patients maintained on hemodialysis is due to incomplete removal of uremic solutes [1–4]. The variety of such solutes is enormous [2–5]. Yet, we now assess the adequacy of treatment by removal of the single-solute urea. This review will describe potential means to improve the clearance of nonurea solutes using mechanical devices. We will not discuss peritoneal dialysis and will deal only in passing with solute properties which prevent increases in their clearance from achieving proportional reductions in their plasma levels. We will discuss only organic solutes and not phosphate, bicarbonate, and other inorganic ions. We will separately consider the clearances of free low-molecular-mass solutes, free larger solutes, and protein-bound solutes. In so doing, we follow the classification originally proposed by the European Uremic Toxin Work Group (EUTox), founded in 1999 to address solute retention and removal in chronic kidney disease [2, 5, 6]. We should note however that solute mass and protein binding are continuously variable qualities, and the characterization of solutes as either “small” or “large” and “bound” or “not bound” may limit consideration of the effect of various maneuvers on their removal from the body.

Free Low-Molecular-Mass Uremic Solutes

The EUTox classification designated solutes with mass less than 500 Da as low-molecular mass. Urea has served as the prototype for free, low-molecular-mass uremic solutes which are also simply called “small.” The use of urea to assess dialysis adequacy has directed the design of dialyzers and dialysis machines. With conventional hemodialysis, a large portion of the urea is cleared from the blood during a single pass through the dialyzer. The urea clearance is thus limited by the extracorporeal blood flow and cannot be increased much further by increasing the dialyzer membrane capacity or dialysate flow [7, 8].

Two factors are responsible for the high dialytic clearance of urea. First, the urea clearance can approach the extracorporeal blood flow because urea moves rapidly out of red blood cells as well as the plasma during the passage of the blood through the dialyzer [9, 10]. It is the only uremic solute which has so far been shown to do this. Rapid movement of urea is made possible by the presence on red cell membranes of the urea transporter UT-B [11]. Other uremic solutes also accumulate in red cells. The concentration of creatinine in red cells is for instance about the same as that in the plasma. Equilibration between the plasma and red cell creatinine concentrations however takes several minutes, and little creatinine is therefore removed from red cells during the less than 30 s required for blood passage through a modern dialyzer [12]. The concentrations of guanidine, methylguanidine, and methylamine are even higher in red cells than in the plasma [10, 13]. Their higher concentration in cells may reflect high pKa values causing accumulation in red cell water which, like other cell water, is acidic compared to the plasma. As dialysis is now performed, guanidine and methylguanidine are not removed from red cells while monomethylamine is actually taken up by red cells during blood passage through the dialyzer [10, 13]. Red cell uptake of monomethylamine may reflect an increase in red cell pH relative to the plasma in the dialyzer along with facilitated diffusion of this very small solute across red cell membranes [13]. Theoretically, the clearance of all these solutes could be increased if they could be induced to exit red cells within the dialyzer. However, no means to accomplish this have been proposed. Of note, the calculated volumes of distribution for guanidine, methylguanidine, and methylamine within the body are greater than the body water volume [13, 14]. This suggests that their concentrations in body cells other than red cells are also higher than their concentrations in the plasma. Their removal from the body during dialysis, though not their clear-

ance, could theoretically be increased if the hypothesized gradient between cell water and plasma could be reduced during dialysis.

The second factor responsible for the high clearance of urea is its low mass. Our current reliance on urea removal as a marker of dialysis adequacy has caused us to ignore how effectively we remove solutes which are somewhat larger but still usually classified as “small.” Small solutes diffuse from the blood to dialysate at rates proportional to their diffusivity in water. The diffusivity of small solutes in water cannot be predicted precisely but appears to decline in approximate proportion with the inverse of the square root of solute mass [15]. The capacity of a dialyzer for diffusive clearance of a given small solute can be represented by a mass transfer area coefficient KoA for that solute. It should be noted that the meaning of KoA has changed with time. It originally represented the permeability of the membrane material per unit area (Ko) multiplied by the membrane area (A) and was used to calculate clearances in an ideal system in which solutions on both sides of the membrane were perfectly mixed [16]. KoA values are now usually back-calculated from measured clearance values and are influenced by structural features of the dialyzer which determine solute diffusion in the blood and plasma compartments as well as by the membrane material and area. Calculated KoA values for small solutes do however decline approximately as we would predict based on the assumption that solute diffusivity declines in proportion with the inverse of the square root of solute mass [15]. The mass of urea is 60 Da. We would thus expect to find that a dialyzer which had KoA for urea of 1,000 mL/min would have a KoA of 500 mL/min for a solute with a molecular mass of 240 Da (four times that of urea) and a KoA of 333 mL/min for a solute with a molecular mass of 540 Da (nine times that of urea). With lower KoA values, larger solutes have lower dialytic clearances than urea even if urea could not move out of red cells as the blood passes through the dialyzer.

As noted above, we now have no means to induce non-urea solutes to exit red cells as the blood passes through the dialyzer. We can however by increasing KoA values and dialysate flows increase the clearance of small solutes which are larger than urea closer to the maximum imposed by the extracorporeal plasma flow. It is important to recognize that the clinical effects of such increases in KoA and dialysate flow have not been adequately assessed. The Hemodialysis (HEMO) Study is widely considered to have shown that increasing the clearances of small solutes would provide little clinical benefit [17]. However, the large separation in Kt/V_{urea} between the

“standard” and “high-dose” groups in HEMO was achieved largely by increases in treatment time and extracorporeal blood flow with almost no increase in dialyzer KoA and little increase in dialysate flow. The “high-dose” treatment would thus not have been expected to have greatly increased the clearance of “small” solutes larger than urea. Increasing dialyzer size and dialysate flows could thus increase their clearances and lowered their plasma levels as shown in Table 1. The extent to which plasma levels can be reduced by increasing dialytic clearances is highly dependent on a solute’s volume of distribution as further shown in Table 1.

Increasing the clearances of small nonurea solutes has not been studied because we know so little of solute toxicities. Here, we encounter a persistent problem in dialysis research which is reminiscent of the conundrum which gave the novel “Catch 22” its title. We cannot prove that solutes are toxic without lowering their levels, and we do not develop means to lower their levels without proof that they are toxic. However, KoA values could be increased with current membrane materials simply by increasing membrane surface areas. The hope that dialysis can be miniaturized for ambulatory treatment has stimulated the development of membrane materials which have higher diffusive permeability per unit area [19]. Such materials could make it easier to bring the clearance of small solutes which are not removed from red cells closer to the maximum imposed by the extracorporeal plasma flow.

Larger Solutes (“Middle Molecules”)

In the EUTOX classification, solutes with mass between 500 and 45,000 Da are designated “middle molecules.” [5] Use of this term has changed over time. The first dialysis membranes were impermeable to solutes with molecular mass much above 400 Da. Dialysis with these membranes reversed uremic coma and kept patients alive for years. Researchers hypothesized however that removal of larger solutes would improve health. It was initially suggested that toxic solutes and in particular those responsible for uremic neuropathy had molecular masses in the range between approximately 300 and 2,000 Da. Solute in this size range were designated “middle molecules” though no specific toxic solutes were identified [20, 21]. The hypothesis that only solutes within this narrow range contributed to residual illness in hemodialysis patients was gradually abandoned. The term “middle molecules” however remained in use and gradually came to designate solutes with mass between an arbitrary

Table 1. The potential effect of increasing KoA on the clearance of solutes larger than urea

| | Standard dose, high flux | High dose, high flux | Increase, KoA |
|------------------------------|--------------------------|----------------------|---------------|
| <i>Dialysis prescription</i> | | | |
| Time, min | 191 | 218 | 218 |
| Q_b , mL/min | 311 | 376 | 376 |
| Q_d , mL/min | 639 | 708 | 708 |
| <i>Urea</i> | | | |
| KoA, mL/min | 600 | 600 | 1,200 |
| Kd, mL/min | 252 | 281 | 342 |
| Relative APC | – | 0.89 | 0.83 |
| Relative TAC | – | 0.85 | 0.75 |
| <i>Free solute mass 240</i> | | | |
| KoA, mL/min | 300 | 300 | 600 |
| Kd, mL/min | 188 | 201 | 280 |
| Relative APC if Vd 36 L | – | 0.90 | 0.76 |
| Relative TAC if Vd 36 L | – | 0.86 | 0.67 |
| Relative APC if Vd 14 L | – | 0.96 | 0.91 |
| Relative TAC if Vd 14 L | – | 0.92 | 0.85 |
| <i>Free solute mass 540</i> | | | |
| KoA, mL/min | 200 | 200 | 400 |
| Kd, mL/min | 149 | 157 | 234 |
| Relative APC if Vd 36 L | – | 0.90 | 0.71 |
| Relative TAC if Vd 36 L | – | 0.86 | 0.62 |
| Relative APC if Vd 14 L | – | 0.95 | 0.87 |
| Relative TAC if Vd 14 L | – | 0.91 | 0.78 |
| <i>Free solute mass 960</i> | | | |
| KoA, mL/min | 150 | 150 | 300 |
| Kd, mL/min | 125 | 129 | 201 |
| Relative APC if Vd 36 L | – | 0.90 | 0.68 |
| Relative TAC if Vd 36 L | – | 0.87 | 0.59 |
| Relative APC if Vd 14 L | – | 0.94 | 0.83 |
| Relative TAC if Vd 14 L | – | 0.90 | 0.73 |

Concentrations relative to those with standard-dose, high-flux dialysis were modeled based on the average time; Q_b and Q_d values reported in the HEMO study using a published model and an initial in vivo KoA_{urea} of 600 mL/min [17, 18]. KoA is assumed to decrease proportionally to the square root of solute mass. Increases largely in time and Q_b to achieve “high-dose” dialysis as was done in the HEMO study are predicted to reduce solute levels only modestly across the size range from urea’s 60–960 Da. Increasing KoA could however theoretically further reduce the concentrations of larger solutes, depending on their presumed volumes of distribution. Time, session length on thrice weekly hemodialysis; Q_b , blood flow; Q_d , dialysate flow; Kd, dialytic clearance; APC, average peak concentration; TAC, time-averaged concentration.

ly selected minimum value and an increasingly higher maximum value.

It would perhaps be better if the term “middle molecules” were abandoned. We could then more clearly de-

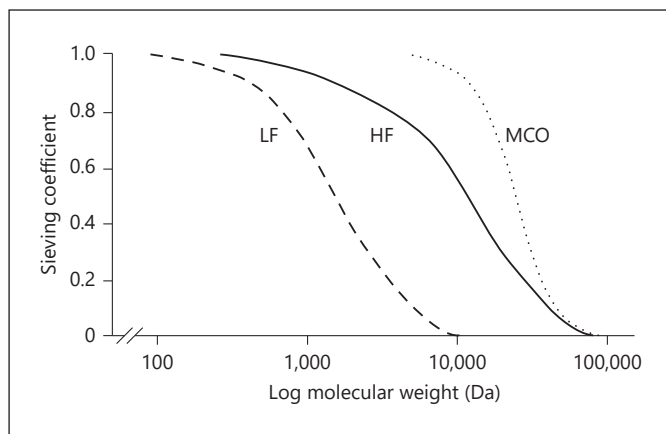


Fig. 1. Sieving curves for LF, HF, and MCO dialysis membranes. The sieving coefficient represents the fraction of a solute that would accompany water with the membrane employed for filtration. The curves depicted are only representative as a variety of membranes have been employed in dialyzers classified as low flux and high flux. Adapted with permission from ref. [24]. MCO, medium-cutoff; LF, low-flux; HF, high-flux.

scribe the dependence of dialytic clearance on solute mass over the whole range from around 30 Da to more than 40,000 Da occupied by uremic solutes. Increasing solute mass reduces dialytic clearance in two ways [22]. First, as noted in the discussion of low-molecular-mass solutes, increasing mass slows the rate at which solutes diffuse in the blood, the fluid channels through the dialysis membrane, and the dialysate. Second, increasing mass eventually keeps solutes from entering the fluid channels in the membrane through which they must pass to get from the blood to the dialysate side of the membrane. Modern membrane materials differ widely in the extent to which they exclude solutes of increasing mass, as depicted in Figure 1 [22, 23]. Increasing the clearance of a solute of a particular mass thus requires selection of an appropriate membrane material.

In 1985, a series of reports established that accumulation of β_2 microglobulin (β_2 M) caused amyloidosis in dialysis patients [25–27]. This finding was a major stimulus to the use of membranes permeable to larger solutes. β_2 M with a molecular mass of 12,000 Da was adopted as the prototypical large solute just as urea with a molecular mass of 60 Da had been adopted as the prototypical free, low-molecular-mass solute. With urea and β_2 M chosen to represent “small” and “large” solutes, little effort was subsequently made to increase the clearance of free solutes with intermediate mass. This intermediate mass range however includes most known individual uremic solutes

along with a wide variety of peptides and possibly also fragments of DNA and RNA [2, 3, 28–30].

Over the lower end of the mass range between urea and β_2 M, modern membranes provide solute clearance largely by diffusion. Manufacturer’s dialyzer datasheets confirm that solutes up to the mass of vitamin B₁₂ at 1,355 Da are cleared at rates that can be predicted based on the assumption that clearance is diffusive and that *KoA* declined in inverse proportion to the square root of solute mass as shown in online supplementary Table 1 (see www.karger.com/doi/10.1159/000524512 for all online suppl. material). To the extent that this is correct, it should be possible to increase clearances of solutes up to this mass and possibly beyond simply by increasing dialyzer size as described in Table 1. These theoretical predictions of course require clinical testing. It should be noted that *KoA* values measured in vivo are only a fraction of manufacturer’s *KoA* values measured using aqueous solutions. The relation of *KoA* in vivo to *KoA* in vitro has been shown to be approximately stable over the mass range 60–180 Da but could be different above this range [9].

As solute mass increases closer to that of β_2 M, rapid passage of the blood through the dialyzer does not allow sufficient time for large solutes to be cleared by diffusion even if the dialysis membrane is permeable to them. Increasing solute clearances depends on promoting convection within the dialyzer as well as using membranes which are permeable to large solutes [22, 23]. Convective clearances within the dialyzer results from ultrafiltration near the higher pressure “arterial” ends of the dialyzer’s hollow fibers, where solute concentrations are high and back filtration near their lower pressure “venous” ends where solute concentrations are lower. Clearance in this setting can no longer be accurately modeled by back-calculating theoretical *KoA* values from measured clearances and blood and dialysate flow rates. The combination of new membrane materials and fiber designs has however allowed clearances of solutes with the mass of myoglobin (17 kDa) and complement factor D (24 kDa) to reach rates above 50 mL/min and 25 mL/min, respectively [31].

The question of whether increasing clearances of solutes with the mass of β_2 M and above affords clinical benefit remains unsettled. The HEMO study failed to show clear benefit from increasing β_2 M clearance to an average of 34 mL/min with “high-flux” dialyzers as compared to the few mL/min achieved with “low-flux” dialyzers was beneficial [17]. The dialysis community however responded to this failure differently than to HEMO’s failure to show benefit with increased removal of urea. While

“high-flux” dialysis failed to show benefit in HEMO, dialysis practice guidelines have recommended its use [32]. Observational studies indicate that it has reduced the incidence of amyloidosis [33]. Major efforts have subsequently been made to increase the clearance of solutes in the mass range of β_2 M above the level achieved in HEMO.

The chief means so far tested to further increase the clearance of large solutes has been hemodiafiltration. In hemodiafiltration, convective clearance is increased by increasing the pressure within the dialyzer fibers, and fluid is administered to replace the volume lost. Increasing β_2 M clearances to approximately 80 mL/min by hemodiafiltration has so far failed to clearly improve outcomes in patients enrolled in clinical trials [34]. Proponents of the technique note that patients who have achieved the highest ultrafiltration volumes have appeared to benefit [35, 36]. A randomized trial is now being conducted to more rigorously test the benefit of high-volume ultrafiltration [37].

Additional efforts to increase the clearance of large solutes are also ongoing. β_2 M and other low-molecular-mass proteins have been cleared by passing the blood over sorbent columns [38]. Currently, such protein sorbent columns are being considered largely for treatment of sepsis and associated acute kidney insufficiency [39]. Convective clearance of large solutes has also been increased by manipulating blood and dialysate pressures within the dialyzer [40, 41]. Increasing internal convection has been particularly important in the design of dialyzers which provide increased clearance of low-molecular-mass proteins which are larger than β_2 M. New dialyzers can clear such solutes by using “medium-cutoff” membranes which are permeable to solutes with molecular mass up to 50 kDa combined with fiber dimensions which promote internal convection [22, 23, 31].

Our ability to increase clearances of β_2 M and even larger solutes brings us back to a fundamental pathophysiological problem. Plasma levels may not fall in proportion to the increase in solute clearances, particularly when treatment is intermittent [42]. In the HEMO study, increasing the average β_2 M clearance by more than fivefold reduced the average plasma level by only 20% [43]. This apparent discrepancy may be attributable to two factors [44]. First, a low but continually operating nonrenal clearance accomplishes a large portion of β_2 M removal. Second, β_2 M movement from the interstitium to the plasma is restricted, and plasma β_2 M levels rebound following rapid removal from the plasma during intermittent dialysis or hemodiafiltration. It seems likely that these factors also limit the extent to which high renal replacement

clearances can lower levels of large solutes other than β_2 M. It is notable that increasing the clearances of solutes with molecular mass greater than 20 kDa using “medium-cutoff” membranes has generally failed to lower their plasma levels [45–47]. These findings should stimulate further investigation of the largely unknown mechanisms by which low-molecular-mass proteins are cleared outside the kidney at a low rate. We might be able to increase this nonrenal clearance in patients whose kidneys have failed.

Protein-Bound Solutes

The protein-bound solutes are small molecules that bind to plasma proteins, with known examples binding largely to albumin [48–50]. Conventional dialysis clears them poorly because only the free portion of the solute contributes to the concentration gradient driving their diffusion from the plasma to the dialysate [51]. The degree to which protein binding reduces clearance depends on the dialyzer size and dialysate flow as well as the extent of protein binding. However, with a conventional three times weekly dialysis prescription, we can predict that the clearance of a solute which is 50% bound will be about two-thirds of the clearance of an unbound solute of the same size. Clearances decline much further with greater protein binding. Thus, a solute which is 90% protein-bound will have a clearance less than one-fifth that of an unbound solute; a solute which is 95% bound will have a clearance which is less than one-tenth that of an unbound solute. The bound solutes which have been most extensively studied are 90–95% bound in dialysis patients. There has been much less clinical study of increasing the clearance of these solutes than of increasing the clearance of large solutes. Looking back, it appears that this may have been because no single-bound solute was shown to have a specific ill effect like the amyloidosis caused by accumulation of β_2 M.

The clearance of bound solutes can be increased by increasing the free fraction of the solute as the blood passes through the dialyzer. One attractive means to accomplish this is addition of displacing agents to the blood entering the dialyzer [52]. Madero et al. [53] recently showed that infusion of ibuprofen could significantly increase the clearance of the bound solutes indoxyl sulfate and p-cresol sulfate during single-dialysis treatments. Successful chronic treatment will require identification of displacing agents which can be repeatedly administered in sufficient concentrations without ill effect. Alternative agents have

been considered but not yet shown to satisfy this requirement [54, 55].

Imposing physical-chemical changes could also increase the free fractions of bound solutes as the blood passes through the dialyzer. The free fraction of many bound solutes can be increased by lowering the blood pH [56]. Clinical testing has been restricted to preventing a rise in the blood pH during hemodialysis treatment rather than lowering the blood pH [57]. This had only a limited effect on the clearance of protein-bound uremic solutes and whether reduction of the blood pH below physiologic levels would have a greater effect remains to be tested. Another potential means to increase the free fraction of bound solutes is to increase the ionic strength of the blood as it flows through the dialyzer [58]. As with changes in pH, large changes in ionic strength may be required to increase the free fractions of bound solutes, and the extent to which such changes can be safely imposed remains uncertain. It has also been suggested that the clearance of bound solutes can be increased by the imposition of electrical fields, possibly in conjunction with the use of new composite membrane materials [59, 60].

Sorbents provide an alternate means to remove uremic solutes which bind to plasma proteins. Early workers attempted to clear uremic solutes by direct passage of the blood over activated carbon [61]. Contact of the blood with carbon however caused platelet consumption and other complications [62, 63]. These complications were largely avoided by coating carbon granules with cellulose acetate or other materials. Hemoperfusion using coated carbon cartridges has since been used largely to remove poisons. Cartridges remain available, but evidence for efficacy is lacking, and their use has declined where hemodialysis is available [63].

Hemoperfusion over coated sorbent granules provided limited clearance because solutes which diffuse through the coating cannot readily permeate the interior of the granules [64]. Several strategies have been envisioned to improve plasma solutes' access to sorbents [65]. The first is to create sorbents which allow direct hemoperfusion by taking up solutes of interest without adversely affecting other blood constituents. Modern materials science provides a variety of means to create such sorbents [66–69]. Clinical testing however has been limited, and ability to enhance the removal of protein-bound uremic solutes has not been demonstrated [68, 69].

A second strategy for sorbent removal of bound solutes is to separate the plasma from the cellular components of the blood using a membrane with a molecular cutoff of 250–300 kDa. The plasma stream created by this

“plasma fractionation” can then be passed over sorbents to remove bound solutes. This strategy was developed largely for the treatment of liver failure, and its effect was measured by removal of bilirubin and bile acids [70]. Limited trials showed that it could increase the clearance of protein-bound solutes from patients with end-stage renal failure [71, 72]. Testing in end-stage renal failure was however complicated by coagulation abnormalities and therefore abandoned [73].

A third strategy for sorbent removal of bound solutes in hemodialysis is to add a sorbent to the dialysate compartment. This has the effect of reducing the solute concentration in the dialysate compartment toward zero and thereby increasing the concentration gradient across the dialysis membrane [74]. Because the free solute concentration of a highly bound solute in the plasma remains low, a high capacity membrane is required to achieve high clearances of bound solutes with sorbent addition to the dialysate compartment [51]. Indeed, adding a sorbent to the dialysate compartment has the same effect on bound solute clearances as greatly increasing the dialysate flow [74]. Pilot clinical studies have shown that the bound solute clearances achieved with conventional hemodialysis can be increased significantly by increasing dialyzer membrane capacity together with dialysate flow [75, 76].

An obvious candidate sorbent for addition to the dialysate compartment is albumin. Solute bound to albumin in a patient's plasma would pass through the dialysis membrane and be absorbed onto albumin in the dialysate compartment. Two designs for “albumin dialysis” have been considered. In “single-pass albumin dialysis,” the patient is dialyzed against an albumin solution which is discarded after passage over the dialysis membrane. In “sorbent-recirculating dialysis,” the patient is dialyzed against an albumin solution which is itself then dialyzed against standard dialysate in a second dialyzer to remove unbound solutes and electrolytes and then passed through sorbent cartridges to remove bound solutes before being recirculated to dialyze the patient. Like plasma fractionation, albumin dialysis has been developed as a short-term treatment for liver failure [70]. Questionable efficacy and great expense have discouraged consideration of its use as renal replacement therapy.

Other sorbents can also be added to the dialysate compartment to increase the diffusive clearance of protein-bound solutes. This has so far been tested only *in vitro* with activated carbon being the sorbent most frequently used. Various configurations for addition of activated carbon to the dialysate stream have been envisioned, as illustrated in Figure 2. Perhaps, the simplest design is for

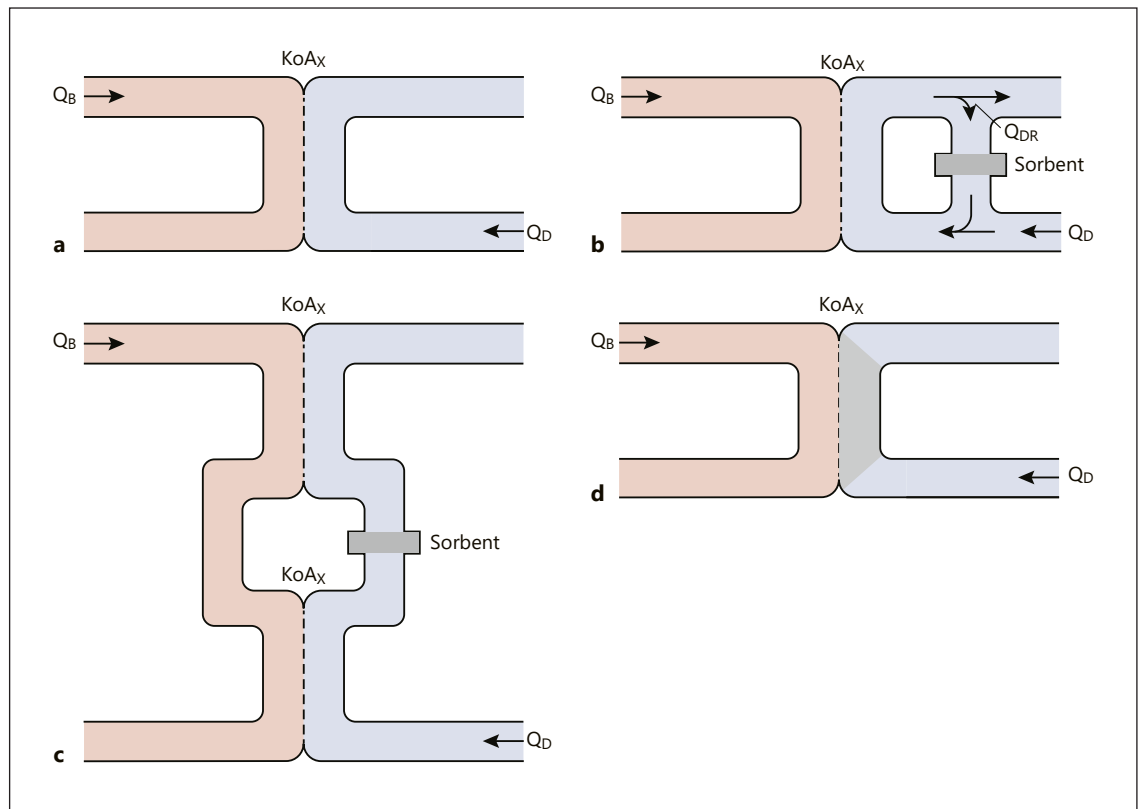


Fig. 2. Potential configurations for sorbent addition to the dialysate compartment to improve the clearance of protein-bound solutes. **a** In standard hemodialysis without any sorbent, the blood (pink shaded) flows at a rate Q_B past a semipermeable membrane (dashed line) with size K_oA_x for solute x with dialysate (blue shaded), flowing at a rate Q_D in the opposite direction on the other side of the membrane. Uremic solutes (not shown) diffuse from the blood into the dialysate which goes down the drain. Different configurations for addition of a sorbent to lower the concentrations of bound solutes in the dialytic compartment have been considered.

b Part of the dialysate stream now is diverted and flows at a rate Q_{DR} over a sorbent (gray shaded area) before being reintroduced into the stream of fresh dialysate entering the system at a flow rate of Q_D . The effective dialysate flow for a given solute is determined by the extent to which the sorbent takes up that solute. **c** Blood passes through two dialyzers in series, and a sorbent cartridge is inserted in the dialysate stream between the two dialyzers. **d** Sorbent material (gray shaded area) is fixed along the dialysate path within a dialyzer (reproduced with permission from Lee et al. [84]).

addition of a sorbent to the dialysate stream [74]. This is equivalent to “albumin dialysis” with the use of a sorbent other than albumin. Alternate designs would fix the sorbent in different positions in the dialysate stream. As is the case with plasma separation, sorbent addition to the dialysate stream has been considered more extensively for the treatment of liver failure than kidney failure [77]. In one design, part of the dialysate stream would be passed over a sorbent and then added to the fresh dialysate being pumped past the dialysis membrane (Fig. 2b). The effect would be to greatly increase the effective dialysate flow for solutes taken up by the sorbent and increase their clearances by keeping their concentrations low in the dialysate compartment. This design might have particular application in home hemodialysis in which low dialysate flows

are commonly prescribed to limit the cost and complexity of in-home dialysate production [78]. Another design would be to insert a sorbent cartridge in the dialysate path of two dialyzers used in series (Fig. 2c). This configuration has the advantage that it could be tested using standard dialyzers and dialysis machines. Perhaps, the optimal configuration for sorbent addition to the dialysate compartment would be to fix sorbent in the dialysate compartment along the length of a dialyzer (Fig. 2d). Of note, sorbent fixation to the dialysis membrane was tested early during the development of hemodialysis; however, its effect on bound solute clearances was not evaluated [79–81]. The recent development of a mixed matrix hemodialysis membrane in which activated carbon is incorporated in to the membrane material represents a techni-

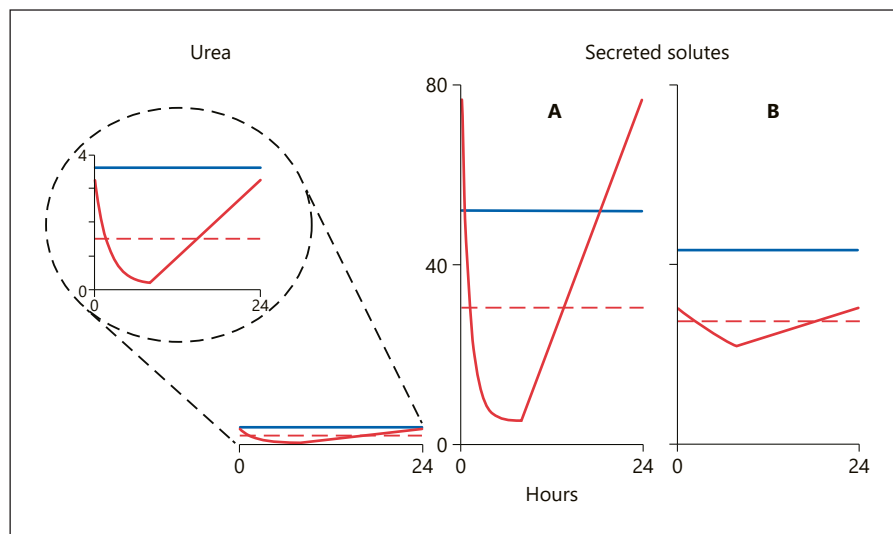


Fig. 3. Predicted plasma solute levels with continuous dialysis using a wearable dialyzer (blue lines) compared to 8 h of nocturnal dialysis providing 10-fold higher solute clearances (red lines, with time-averaged concentrations as dashed lines). Levels are depicted over the course of 24 h for urea and two solutes which are normally cleared by tubular secretion. Solute A is not protein-bound and normally cleared at 540 mL/min by the kidneys with a volume of distribution of 14 L. Solute B is normally 98% bound and has a kidney clearance of 23 mL/min and a volume of distribution of 13 L in terms of its total plasma levels. The figure is scaled so that plasma free levels would be 1.0 for each solute in humans with normal kidney function. The continuously operating wearable dialyzer provides a urea clearance of 17 mL/min equal to that of the device described by Gura et al. [102]. Dialytic clearances of the secreted solutes are adjusted downward relative to urea to 10 mL/min for the unbound solute and 1.3 mL/min for the bound solute

based on dialytic clearances of phenylacetylglutamine and p-cresol sulfate observed by Sirich et al. [103]. The figure shows first that plasma levels of solutes normally cleared by secretion are poorly controlled by dialysis whether provided continuously or intermittently. Levels of urea are maintained within 4-fold normal by both treatments and must be plotted on an expanded scale for their diurnal variation to be apparent, while levels of the secreted solutes remain more than 20-fold normal. Compared to continuous dialysis, a higher clearance during nocturnal treatment can control average solute levels but will allow wide diurnal variation in the levels of those solutes for which the dialytic clearance is high relative to their volume of distribution. The control of a solute's plasma level with continuous dialysis compared to intermittent dialysis is highly dependent on the solute's volume(s) of distribution and compartmental behavior (reproduced with permission from Lee et al. [84]).

cal advance along these lines [82]. The performance of mixed matrix membranes could potentially be enhanced by an “outside-in” design, with dialysate flowing through hollow fibers, while the blood flows outside the fibers [83].

While activated carbon has been the sorbent most commonly considered for addition to the dialysate stream, other materials could provide special benefits or greater safety [66, 85–87]. Addition of lipids to the dialysate was initially evaluated as a means to improve removal of drugs which bind to both lipids and plasma proteins [88, 89]. Addition of lipid to the dialysate could potentially increase the clearance of as yet unknown uremic toxins that bind to circulating lipids more than to proteins. It has also recently been suggested that liposomes could be added to the dialysate to absorb uremic solutes and thereby increase their dialytic clearance [86].

What Next

We have means, as described above, to increase the clearances of various types of solutes. We have not however identified those solutes which are most toxic and therefore most important to remove. This lack of information is a major impediment to progress. If we knew which solutes were toxic, we could refine our proposed methods for solute clearance. Sorbents which remove specific solutes from the blood or dialysate, displacing agents which release specific solutes from binding proteins and active membrane materials which selectively pass or chemically degrade specific solutes could be devised. Solute behaviors are not adequately characterized under our current classification scheme may require additional consideration, including solutes that bind to plasma lipids.

“Metabolomic” studies employing untargeted mass spectrometry have provided a new means to identify toxic uremic solutes. This analytic method has increased the number of known uremic solutes to more than 250, and additional solutes continue to be identified [3, 90–93]. Large scale studies will be required however to associate levels of individual solutes with clinical and physiological endpoints. An alternate means to identify toxic solutes is to try to increase the clearance and lower the levels of whole groups of solutes. Positive clinical effects could both improve current treatment and direct our search for specific toxins. As described above, free solutes in the mass range between urea and β_2M have been largely neglected. We have relatively simple means to increase their clearance but have not evaluated the clinical effect of doing so. Several means to improve the removal of protein-bound solutes have been developed; however, their effect on patients' health has not been tested. A clinical trial of adding activated carbon to the dialysate stream using the configurations depicted in Figure 2b or c might speed progress in this area. Such a trial could be performed with only modest modifications to existing dialysis equipment, and a positive result would spur development of more effective means to clear bound solutes. The only group of solutes so far targeted in clinical trials has been solutes in the mass range of β_2M and larger. Results so far have not been strongly positive, but an ongoing trial will provide further information.

We must also face the question of how solute levels respond to changes in their extracorporeal clearances. The failure of β_2M levels to fall in proportion to increases in the extracorporeal β_2M clearance has been noted above. At present, increasing treatment time is the only means we have to overcome the limitation to solute removal imposed by slow intercompartmental equilibration. Other studies suggest that plasma levels of the commonly studied bound solute p-cresol sulfate are unaffected by large changes in its time-averaged dialytic clearance [94–97]. This phenomenon remains unexplained but could reflect changes in solute production combined with nonrenal clearance and/or a complex compartmental distribution. A question currently attracting interest is the value of residual native kidney function relative to dialysis [98, 99]. The ratio of residual to dialytic clearance for individual solutes is highly variable [44, 100]. Better knowledge of the extent to which residual function allows dialysis to be curtailed could help identify the solutes which are most toxic. Another important question is the value of providing continuous clearance with a wearable or implantable dialyzer [19, 101]. The value of continuous as opposed to

intermittent clearance can depend on a solute's dialytic clearance relative to its volume of distribution within the body as depicted in Figure 3. Finally, it is possible the dialysis treatment contributes to illness by removing valuable solutes. Discussion of this concern is currently focused on the removal of albumin by new dialyzers with “medium-cutoff membranes.” However the possibility that conventional dialysis injures patients by excessive removal of valuable smaller solutes has not been conclusively excluded.

Conclusion

We need more knowledge not only of solute toxicity but also of solute generation and disposition within the body to improve our methods for solute removal.

Conflict of Interest Statement

T.W. Meyer reports having consultancy agreements with and receiving honoraria from Baxter, serving on the editorial boards for JASN and Kidney International, and receiving research funding from Outset Medical. T.L. Sirich reports having consultancy agreements with Baxter. The remaining author has nothing to disclose.

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Author Contributions

S. Lee, T.L. Sirich, and T.W. Meyer wrote the original draft and reviewed and edited the manuscript.

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