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Theoretical Aspects of Renal Replacement Therapy

Solute fluxes in different treatment modalities

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Abstract The principles governing solute flux or transport in different artificial kidney treatment modalities are reviewed. Solute clearance profiles were calculated for identical artificial kidney membranes during haemodialysis, haemofiltration and haemodiafiltration. It was shown that the clearance of small solutes depends largely on the dialysate flow rate and is similar when using either haemodialysis or haemodiafiltration. In contrast, clearance of middle molecules, especially low-molecular-weight proteins, depends largely on convective transport induced by high ultrafiltration rates and is maximized when using either haemofiltration or haemodiafiltration. Optimal fluxes for both small solutes and middle molecules can be achieved by using postdilution haemodiafiltration.

Recent work has shown that use of the reduction in plasma concentration, even after normalization for changes in extracellular volume during therapy, is not an exact measure of β_2-microglobulin (and other low-molecular-weight proteins) clearance. It is proposed that β_2-microglobulin clearance be reported in future studies instead of the normalized reduction in β_2-microglobulin plasma concentration. Additional studies are necessary to determine the effects of postdialysis rebound on the calculated clearance for β_2-microglobulin and other high-molecular-mass uraemic toxins.

Introduction

The adequacy of chronic dialysis therapy depends on the amount of uraemic solutes removed from the patient. Low removal of small solutes, such as urea, leads to inadequate therapy and therefore decreased patient survival [1]. The amount of small-solute removal that is optimal is likely to be patient dependent, but the minimum level beyond which patient survival does not improve remains difficult to define [2–4]. Analysis of the Case Mix Adequacy Study from the United States Renal Data Systems has also shown that the type of membrane used during haemodialysis also impacts on patient survival [5]. Whether this is due to membrane biocompatibility [5] or enhanced removal of middle molecules [6] has not been resolved. While small-solute and middle-molecule removal are clearly not the only factors that affect chronic haemodialysis patient survival, they are two important parameters that can be quantified and altered easily by the nephrologist.

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Solute flux

Solute flux across membranes

Two different mechanisms for solute flux or transport are possible across artificial kidney membranes. Diffusive solute transport occurs when there is a difference in solute concentration across the membrane, and the direction of solute movement is from high to low solute concentration. Diffusive solute transport is rapid for small solutes but decreases with increasing molecular size. The rate of solute diffusion across membranes depends upon their thickness and porosity, and the development of high-flux membranes (containing larger pore sizes) has allowed enhanced transmembrane diffusion of middle molecules, including low-molecular-weight proteins. Ultimately, however, it is difficult to achieve significant rates of middle-molecule removal across high-flux membranes by diffusion alone (see below).

Solute transport across artificial kidney membranes can also occur by convection or solvent drag. Here, hydraulic- and osmotic-pressure differences across the membrane are the driving forces for transmembrane fluid movement. This flux of fluid carries or drags solutes, and the solute flux is proportional to the rate of fluid movement across the membrane. The proportionality constant between the rate of solute movement and fluid movement across the membrane is called the sieving coefficient. The sieving coefficient is often considered to be constant for each solute–membrane combination, but it can vary depending on the rate of fluid flux across the membrane. This process is called convective solute transport or convection, and generally permits increased transmembrane transport rates for middle molecules. While it is often stated that convective solute transport is independent of molecular size,

this is not strictly true. Convective solute transport across high-flux artificial kidney membranes is independent of molecular size for small solutes and many middle molecules, but decreases with increasing molecular size for low-molecular-weight proteins. Exactly where within the middle molecular size range the sieving coefficient begins to decrease is dependent on the membrane [7,8].

Mathematical models of solute flux

A mathematical description of combined diffusive and convective solute flux across artificial kidney membranes was first described by Villarroel *et al.* [9], an adaptation of that described previously across biological membranes [10]. The governing equation for membrane transport can be integrated along the length of the artificial kidney to predict total solute flux under given flow conditions [11]; however, the integrations must usually be calculated numerically by a computer. When experimental data are analysed, the dependence of ultrafiltration on solute clearance is often assumed to be linear and is described by the following equation

$$K_d = K_{d0} + TrQ_f, \tag{1}$$

where K_d denotes the clearance at the studied ultrafiltration rate (Q_f), K_{d0} denotes the clearance at zero ultrafiltration rate and Tr denotes a proportionality factor called the transmittance coefficient. The transmittance coefficient is a function of the flow conditions and membrane properties but can be considered a constant under many conditions. Granger *et al.* [12] first derived simple expressions for the transmittance coefficient by considering ultrafiltration (or convective solute transport) and diffusive solute transport to occur sequentially rather than simultaneously. Based on certain experimental data, these investigators suggested that the following expression best represented the increase in solute clearance with increasing ultrafiltration rate

$$Tr = S\,(1 - K_{d0}/Q_{bi}), \tag{2}$$

where S denotes the solute sieving coefficient and Q_{bi} denotes the input or arterial blood flow rate to the dialyser. This equation was recently rediscovered by Waniewski *et al.* [13] who expressed the sieving coefficient in terms of fundamental membrane-transport parameters; however, their expression for S is not constant. A more simple formula was proposed by Sargent and Gotch [14] and Weryński [15] for solutes whose sieving coefficient was equal to one

$$Tr = 1 - K_{d0}/Q_{bi}. \tag{3}$$

This expression can be considered to be a limiting case of equation (2). An expression for the transmittance coefficient that is universal for all solutes and is a quadratic function of the ultrafiltration rate has recently been proposed by Jaffrin [16]. This approach is interesting but requires further validation.

Equations (1)–(3) have been used for the past two decades to evaluate the effect of ultrafiltration on solute clearance. Indeed, two groups of investigators [17,18] used these equations as the basis for their analysis of the effect of ultrafiltration on solute clearance during the First Symposium on Hemodiafiltration in 1981. Therefore, these equations are used here to illustrate solute flux in different treatment modalities.

Solute flux in different treatment modalities

Solute clearance profiles for different treatment modalities were calculated using the above equations and a pore model of membrane transport. The pore model of membrane transport was chosen to illustrate that the same artificial kidney membrane can be used in various ways to produce different solute clearance profiles. The effect of membrane characteristics is considered briefly below. For each treatment modality, the diffusive permeability or mass transfer coefficient (P) and the solute reflection coefficient (σ) were calculated as a function of molecular size using the following equations derived by Mason *et al.* [19]

$$P/D = (1-\lambda)^{7/2}/(1 - 0.3956\lambda + 1.0616\lambda^2) \tag{4}$$

$$1 - \sigma = (1-\lambda/3)\,(1-\lambda)^2\,[2-(1-\lambda)^2]/(1 - \lambda/3 + 2\lambda^2/3), \tag{5}$$

where D denotes the solute diffusivity in free solution and was assumed to vary inversely with λ, the ratio of solute radius to pore radius. The value of K_{d0} was calculated under given blood and dialysate flow-rate conditions from the equation derived by Michaels [20], and the sieving coefficient was estimated to be $1-\sigma$. Note that the following calculations assume that blood is a homogeneous fluid and neglect the complexities resulting from the presence of red blood cells. These latter effects can significantly alter the clearance of certain solutes, such as urea [21]; therefore, these calculations are only approximate for small solutes. It should be noted that the presence of red blood cells was neglected for all treatment modalities; this should still allow valid comparisons.

Solute clearance profiles during haemodialysis using dialysers containing low-flux and high-flux membranes are shown in Figure 1. The low-flux membrane was assumed to be isoporous with a pore radius of 20 Å, and the high-flux membrane was assumed to be isoporous with a pore radius of 40 Å. Note that the membrane surface area of the low- and high-flux dialysers was chosen so they have approximately equivalent clearances for small solutes. There are significant differences in solute clearance profiles for these dialysers in the middle molecular size range. Indeed, clearance for β_2-microglobulin is approximately one order of magnitude greater for the high-flux than for the low-flux dialyser. Nevertheless, when using diffusion as the primary mode of transport, middle-molecule removal is necessarily limited.

During the late 1960s, haemofiltration [22] was introduced to enhance middle-molecule removal during artificial kidney therapy. During haemofiltration, there is no flow of dialysate and solute removal occurs primarily by convection. The rate of solute removal is

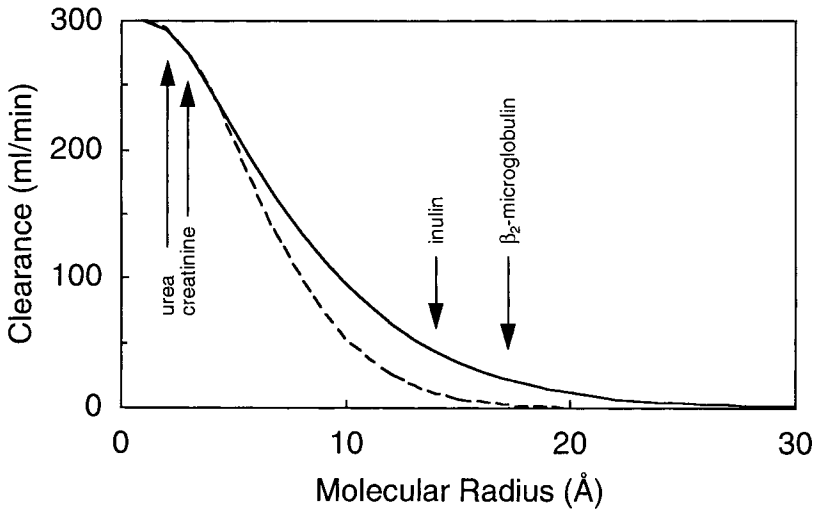

Fig. 1. Solute clearance profiles during haemodialysis when using dialysers containing low-flux (dashed line) or high-flux (solid line) membranes. These profiles were calculated for hypothetical isoporous membranes with pore radii of 20 and 40 Å for the low-flux and high-flux membranes, respectively, as described in the text. The blood flow rate was assumed to be 300 ml/min, the dialysate flow rate was assumed to be 800 ml/min, and the ultrafiltration rate was assumed to be 10 ml/min. The approximate molecular size of certain marker molecules is indicated.

proportional to the ultrafiltration rate, which during haemofiltration is substantially greater than that during haemodialysis and exceeds the fluid-removal requirements for the patient. Therefore, a substitution fluid must be infused either before (predilution) or after (postdilution) the artificial kidney. Figure 2 shows solute clearance profiles for postdilution haemofiltration compared with that for high-flux haemodialysis. During postdilution haemofiltration, clearance rates for middle molecules, such as β_2-microglobulin, are approximately 3-fold those obtained using high-flux haemodialysis. Note, however, that the removal of small solutes, such as urea, is substantially less for postdilution haemofiltration than for high-flux haemodialysis.

In the late 1970s, several groups proposed combining the two processes of haemodialysis and haemofiltration into a new process called haemodiafiltration, and this modality was studied most extensively by investigators in Giessen [23]. This modality combines the advantages of haemodialysis and haemofiltration and permits optimal removal of both small solutes and middle molecules. As with haemofiltration, the ultrafiltration rate during haemodiafiltration is greater than that necessary for patient fluid removal; therefore, the infusion of a substitution fluid is necessary. Figure 3

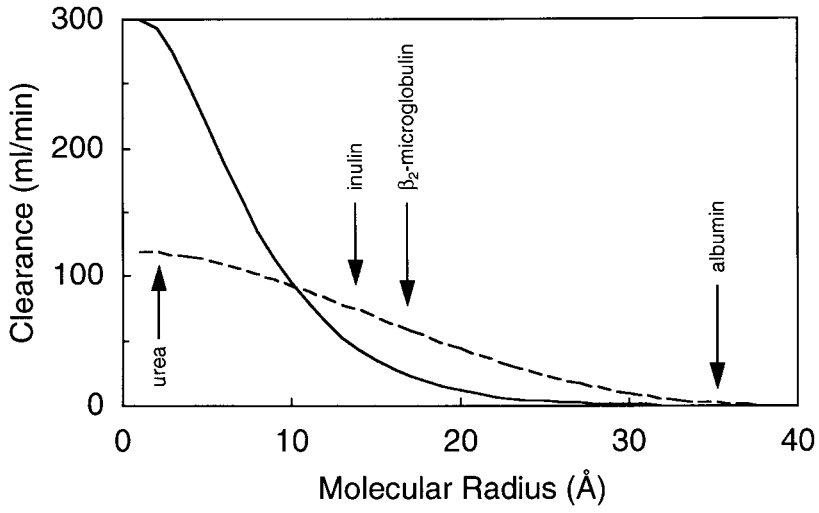

Fig. 2. Solute clearance profiles during haemodialysis (solid line) compared with that for postdilution haemofiltration (dashed line) when using the same high-flux membrane with a pore radius of 40 Å. These profiles were calculated as described in the text. The blood flow rate was assumed to be 300 ml/min for both haemodialysis and haemofiltration. During haemodialysis, the dialysate flow rate was assumed to be 800 ml/min and the ultrafiltration rate was assumed to be 10 ml/min. During haemofiltration, the ultrafiltration rate was assumed to be 120 ml/min. The approximate molecular size of certain marker molecules is indicated.

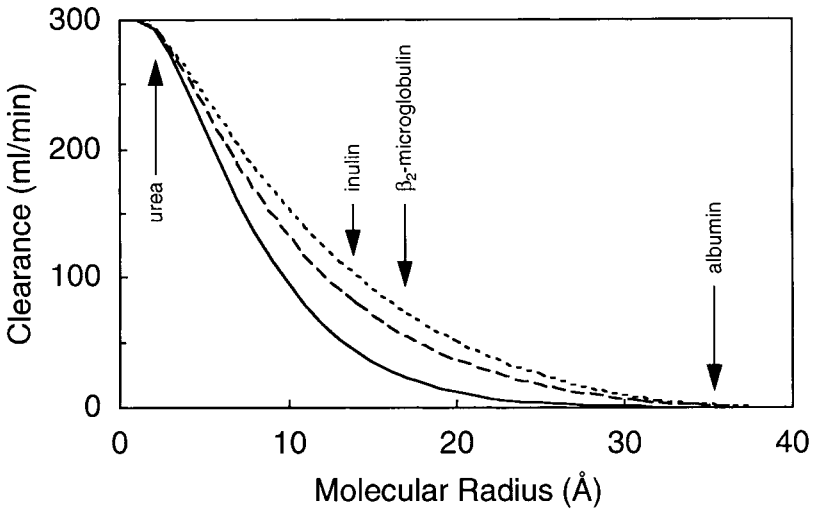

Fig. 3. Solute clearance profiles during haemodialysis (solid line) compared with those for postdilution haemodiafiltration with ultrafiltration rates of 80 (dashed line) and 120 (dotted line) ml/min when using the same high-flux membrane with a pore radius of 40 Å. These profiles were calculated as described in the text. The blood flow rate was assumed to be 300 ml/min and the dialysate flow rate was assumed to be 800 ml/min for haemodialysis and 800 ml/min minus the ultrafiltration rate for haemodiafiltration. During haemodialysis, the ultrafiltration rate was assumed to be 10 ml/min. The approximate molecular size of certain marker molecules is indicated.

compares solute clearance profiles for high-flux haemodialysis with postdilution haemodiafiltration at two different ultrafiltration rates. Clearance of small solutes, such as urea, during haemodiafiltration is similar to that during high-flux haemodialysis, but the clearance of middle molecules is substantially greater during haemodiafiltration. Furthermore, the clearance of middle molecules during haemodiafiltration increases with increasing ultrafiltration rate. For molecules the size of β_2-microglobulin, the clearance is almost 4-fold more during postdilution haemodiafiltration at an ultrafiltration rate of 120 ml/min than that occurring during high-flux haemodialysis.

With the development of new technology for producing large volumes of fluid on-line, there is increasing interest in the use of predilution rather than postdilution for infusing substitution fluid [24,25]. With this new technology, high substitution fluid rates are now practical and permit the achievement of very high ultrafiltration rates in the predilution mode. Figure 4 compares solute clearance profiles during predilution haemofiltration with that achieved during postdilution haemodiafiltration and high-flux haemodialysis. Predilution haemofiltration permits even greater clearances of middle molecules than postdilution haemodiafiltration; however, urea clearance, while increased substantially from that for postdilution haemofiltration (compare with Figure 2), remains lower than that achieved during postdilution haemodiafiltration.

Predilution haemodiafiltration has also recently been evaluated both theoretically and experimentally by Ahrenholz *et al.* [26]. These investigators showed theoretically that predilution haemodiafiltration does not provide more small-solute clearance than during postdilution haemodiafiltration. Since predilution dilutes the concentration of all solutes in the bloodstream, predilution will decrease the concentration difference across the membrane and therefore decrease the rate of solute diffusion. Furthermore, there are no significant advantages for predilution compared with postdilution regarding middle-molecule clearance. Indeed, the experimental observations of Ahrenholz *et al.* show only small differences in urea and β_2-microglobulin clearance when comparing predilution and postdilution haemodiafiltration [26]. Therefore, the use of large quantities of substitution fluid in predilution haemodiafiltration are apparently not warranted, at least not to increase solute clearance.

The above discussion has been theoretical only and may not completely reflect what occurs during clinical haemodiafiltration at high ultrafiltration rates. One of the first comparisons between haemodialysis, haemodiafiltration and haemofiltration using modern high-flux membranes was published by Floege *et al.* [27], who reported both urea Kt/V and the reduction in β_2-microglobulin plasma concentration, a measure of β_2-microglobulin clearance (see below), when using four different artificial kidney membranes. As predicted theoretically above these investigators reported that urea Kt/V for postdilution haemofiltration was substantially less than that for either haemodialysis or postdilution haemodiafiltration. These investigators reported that the reduction in plasma β_2-microglobulin concentration was greater when using postdilution haemofiltration than during haemodiafiltration and haemodialysis. While this observation contradicts the above predictions, it should be noted that the ultrafiltration rate employed during haemofiltration was almost 50% greater than that employed during haemodiafiltration. These investigators also showed that the reduction in the β_2-microglobulin plasma concentration, but not urea Kt/V, differed depending on the membrane; therefore, middle-molecule clearance rates

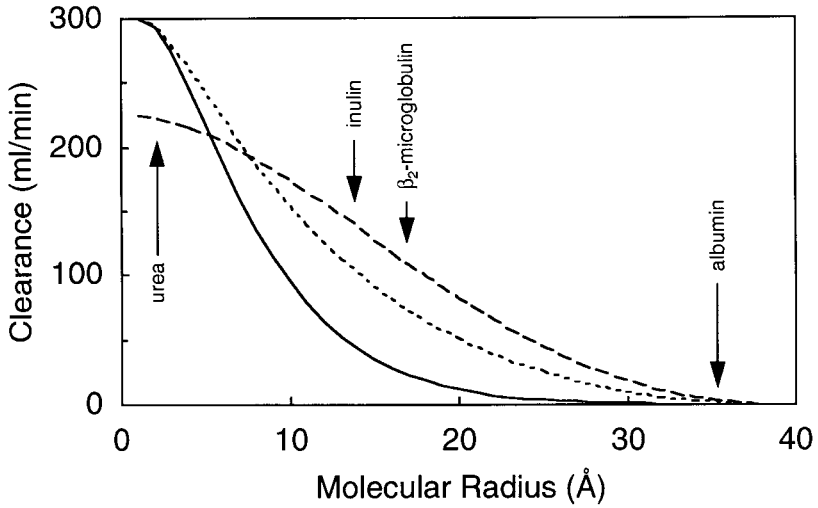

Fig. 4. Solute clearance profiles during haemodialysis (solid line) compared with that for postdilution haemodiafiltration at an ultrafiltration rate of 120 ml/min (dotted line) and that for predilution haemofiltration at an ultrafiltration rate of 450 ml/min (dashed line) when using the same high-flux membrane with a pore radius of 40 Å. These profiles were calculated as described in the text. The blood flow rate was assumed to be 300 ml/min for all modalities. The dialysate flow rate was assumed to be 800 ml/min for haemodialysis and 800 ml/min minus the ultrafiltration rate for haemodiafiltration. During haemodialysis, the ultrafiltration rate was assumed to be 10 ml/min. The approximate molecular size of certain marker molecules is indicated.

when using different treatment modalities depend on the properties of the membrane.

The work of Kim [28] reported certain experimental results that contrast with the above theoretical predictions. This investigator showed that the reduction in marker protein plasma concentration first increased with increasing ultrafiltration rate (as expected) until a plateau was reached, but then a further decrease occurred (unexpected), particularly for β_2-microglobulin. Note also that the increase in clearance of high-molecular-weight proteins, such as albumin, was substantially greater than that predicted by theoretical models. These data suggest that substantial losses of plasma proteins, including albumin, can occur when using certain membranes during postdilution haemodiafiltration at high ultrafiltration rates.

In summary, the above analysis predicts that clearances for small solutes and middle molecules depend on the treatment modality employed, even when using the same artificial kidney membrane. In particular, the clearance of small solutes depends largely on the dialysate flow rate and is similar when using either haemodialysis or haemodiafiltration. Clearance of middle molecules depends primarily on convective transport induced by high ultrafiltration rates and is maximized when using either haemofiltration or haemodiafiltration. Optimal fluxes for both small solutes and middle molecules can be achieved by using postdilution haemodiafiltration.

Evaluation of middle molecule clearance

Two concerns have recently been identified when evaluating solute clearances during treatment modalities in which significant removal of middle molecules, such as β_2-microglobulin, occurs. The first is whether the reduction in plasma concentration of middle molecules during therapy, even after correcting or normalizing the postdialysis concentration for changes in solute volume of distribution, is an exact measure of clearance. The second concern questions whether middle-molecule removal is limited by physiological barriers within the patient. If the latter is true, the solute-clearance profiles calculated above for different treatment modalities may not be realized from the patient.

Even when there is no significant removal of β_2-microglobulin during therapy, such as when using low-flux dialysers, its plasma concentration can change during therapy by either generation within the patient or by a decrease in solute distribution volume as a result of fluid removal. In 1987, Bergström and Wehle [29] showed that the increase in the plasma concentration of β_2-microglobulin during haemodialysis using a low-flux cuprophane membrane was largely due to extracellular volume contraction and not to β_2-microglobulin generation. The results from this study led other investigators to use the postdialysis-to-predialysis concentration ratio or the reduction in β_2-microglobulin concentration normalized for extracellular volume contraction as a measure of β_2-microglobulin clearance.

We have recently shown that the postdialysis-to-predialysis concentration ratio for β_2-microglobulin normalized for extracellular volume contraction, depends not only on β_2-microglobulin clearance, but also on treatment time and the size of the patient [30]. In particular, the normalized reduction in plasma concentration depends primarily on the parameter β_2-m K_dT/V (β_2-microglobulin clearance multiplied by treatment time divided by the volume of distribution for β_2-microglobulin at the end of therapy). This

relationship is analogous to the relationship between the urea reduction ratio and urea Kt/V. Furthermore, we showed that the normalized postdialysis-to-predialysis concentration ratio also depends on the rate of fluid removal from the patient.

We therefore proposed that evaluation of β_2-microglobulin clearance from the artificial kidney would be more accurate if it was calculated directly [30]. If it is assumed that β_2-microglobulin is distributed equally in the extracellular volume, that there is no intradialytic generation of β_2-microglobulin, that physiological (both renal and nonrenal) clearance of β_2-microglobulin is negligible and that fluid is removed entirely from the extracellular compartment, it was then shown that β_2-microglobulin clearance (β_2-m K_d) can be calculated using the following formula

$$\beta_2\text{-m } K_d = Q_f\,(1-\ln[C(T)/C(0)]/\ln[1+Q_fT/V(T)]), \quad (6)$$

where $C(0)$ and $C(T)$ denote the predialysis and postdialysis plasma concentrations of β_2-microglobulin, Q_f denotes the average ultrafiltration rate throughout the entire treatment session of length T, and V denotes extracellular fluid volume. The latter can be estimated to be one-third of total body water estimated either by anthropometric formulas [31] or by the distribution volume of urea determined during urea kinetic modelling. Clearance determined by this equation yields an average value for the entire treatment and includes removal by diffusive, convective and adsorptive mechanisms.

Table 1 shows how the normalized postdialysis-to-predialysis β_2-microglobulin concentration ratio can error in estimating β_2-microglobulin clearance from the patient. Table 1 lists three patients treated differently but having the same normalized concentration ratio. Two primary concerns are illustrated. First, it is possible for the normalized concentration ratio to be identical even when β_2-microglobulin clearance is different (compare patient 1 with patient 2). For a given normalized concentration ratio, the clearance is directly proportional to patient size (via the solute distribution volume). By comparing patient 1 with patient 3, it can be seen that the clearance of β_2-microglobulin also depends on the rate of fluid removal from the patient. Clearly, the normalized postdialysis-to-predialysis concentration ratio, or equivalently, the normalized percent reduction in plasma concentration, cannot be used by itself to evaluate β_2-microglobulin clearance from the patient.

Table 1. The relationship between the normalized postdialysis-to-predialysis concentration ratio ($C(T)/C(O)$) and clearance (K_d) for β_2-microglobulin (β_2-m) during a 210-min treatment

Patient	$C(T)/C(O)$	Normalized $C(T)/C(O)$	V (l)	Q_f (ml/min)	β_2-m K_d (ml/min)
1	0.373	0.3	13	15	68.2
2	0.418	0.3	8	15	54.4
3	0.300	0.3	13	0	74.5

V denotes the volume of extracellular fluids and Q_f denotes the average ultrafiltration rate during therapy.

We have also evaluated the accuracy of β_2-microglobulin clearance calculated using equation (6) when compared with that calculated using the arterial and venous concentration difference of β_2-microglobulin directly across the dialyser [30]. For low-flux dialysers, β_2-microglobulin clearance, calculated using equation (6), was not different from that determined directly across the dialyser. For high-flux dialysers, β_2-microglobulin clearance, determined using equation (6), was significantly greater than that determined directly across the dialyser. These observations suggested that other phenomena affect β_2-microglobulin clearance from the patient when using high-flux dialysers.

A plausible explanation for the disparity between the clearance of β_2-microglobulin calculated from predialysis and postdialysis plasma concentrations and that determined directly across high-flux dialysers is unequal distribution of β_2-microglobulin within the extracellular compartment. If β_2-microglobulin is not distributed equally within the extracellular compartment, one would expect significant rebound of the β_2-microglobulin plasma concentration after completion of therapy. Indeed, it has been reported that significant postdialysis rebound of β_2-microglobulin occurs [32,33]. Whether postdialysis rebound is caused by shedding of β_2-microglobulin from cell surfaces [32] or by slow transfer of β_2-microglobulin between the interstitial and plasma compartments [33] remains unclear.

Recently, we described postdialysis rebound kinetics for both urea and β_2-microglobulin after both low-flux and high-flux haemodialysis [34]. Blood urea concentration decreased during haemodialysis; however, its concentration rebounded for the next 30–60 min. The kinetics of urea rebound were similar for both low- and high-flux dialysers. When using a low-flux dialyser, β_2-microglobulin concentration increased during haemodialysis due to the decrease in circulating blood volume [35]; however, plasma concentrations of β_2-microglobulin decreased after therapy. When using a high-flux dialyser, β_2-microglobulin concentration decreased during therapy but its plasma concentration rebounded significantly. Indeed, the plasma reduction in β_2-microglobulin concentration was 27% when calculated using the immediate postdialysis concentration but only 14% when calculated using the postdialysis concentration 60 min after therapy. Others have recently reported that postdialysis rebound of β_2-microglobulin is greater following haemodiafiltration than during high-flux haemodialysis therapy [36]. These studies demonstrate that further work is necessary to accurately evaluate β_2-microglobulin clearance from predialysis and postdialysis plasma concentrations when using therapies that permit large removal of middle molecules.

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