Nephrol Dial Transplant (2018) 33: iii22–iii27
doi: 10.1093/ndt/gfy228

ndt
Nephrology Dialysis Transplantation

REVIEW

Membrane innovation: closer to native kidneys

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ABSTRACT

Modern methods in analytical biochemistry have established that uraemia is associated with the retention of proteins, both in their native state and post-translationally modified, over a wide range of molecular weights up to 60 kDa. Evidence is accumulating that these higher molecular weight retention solutes are important uraemic toxins, and therapies such as online haemodiafiltration (HDF), which enhance their removal, are associated with improved outcomes. However, HDF has limitations regarding cost, clinical implementation and the need for an external source of sterile substitution solution to maintain fluid balance. New membranes that have a solute removal profile more closely approaching that of the glomerular filtration barrier when used for conventional haemodialysis, while at the same time not allowing the passage of clinically significant amounts of beneficial proteins, are needed to address these limitations. Tighter control of the molecular characteristics of the polymers used for membrane fabrication, along with the introduction of additives and improvements in the manufacturing process, has led to membranes with a tighter pore size distribution that allows the use of an increased absolute pore size without leaking substantial amounts of albumin. At the same time, the wall thickness and internal diameter of membrane fibres have been decreased, enhancing convective transport within the dialyser without the need for an external source of substitution solution. These new expanded range membranes provide a solute removal profile more like that of the native kidney than currently available membranes when used in conventional haemodialysis.

Keywords: clearance, haemodialysis, membrane, solute removal

INTRODUCTION

Early in the use of dialysis as a therapy for end-stage renal disease (ESRD), it became evident that not all the morbidity associated with ESRD could be attributed to the retention of small water-soluble substances such as urea. Outcomes with haemodialysis were poor despite increases in urea removal and outcomes for patients treated with peritoneal dialysis were as good as those with haemodialysis despite peritoneal dialysis patients having higher blood urea concentrations. The latter finding was attributed to the greater solute permeability of the peritoneal membrane compared with that of the low-flux cellulose membranes used for haemodialysis. Together, these observations gave rise to the hypothesis that at least some of the morbidity and mortality associated with ESRD was due to the retention of substances with molecular weights in the 500–5000 Da range, so-called 'middle molecules' [1]. Support for the middle-molecule hypothesis came from studies using size exclusion and ion exchange chromatography, which showed the presence in uraemic plasma of peptides with molecular weights of 1000–2000 Da that were absent in normal plasma [2]. However, there was little evidence to link those substances to clinical outcomes and, as a result, there was limited enthusiasm for developing more permeable membranes to remove them, particularly given the difficulty in maintaining fluid balance during haemodialysis with more permeable membranes.

In the mid-to-late 1980s, identification of the 11.8 kDa protein, β_2-microglobulin, as the principal component of the amyloid deposits associated with severe arthropathy in long-term haemodialysis patients [3], provided clear evidence for the existence of higher molecular weight uraemic toxins and stimulated renewed interest in membranes capable of their removal. Subsequently, advances in analytical biochemistry have allowed the identification of a wide range of middle molecules with molecular weights up to 40 kDa, many of which have been linked to various aspects of uraemic toxicity [4–8]. Evidence for the existence and toxicity of solutes approaching 60 kDa in size continues to accumulate and it is increasingly clear that new strategies, including membranes with performance characteristics more closely aligned with those of the native kidneys, will be needed for their removal. This article summarizes the performance of current dialysis membranes and illustrates how recent advances in membrane technology have resulted in solute removal characteristics closer to that of native kidneys.

PERFORMANCE CHARACTERISTICS OF CURRENT MEMBRANES

Conventionally, current dialysis membranes are divided into two broad categories, low flux and high flux, based on their

Table 1. Classification of haemodialysis membranes

Category	Ultrafiltration coefficient[a] (mL/h/mmHg/m^2)	β_2-microglobulin		Albumin		Reference
		Clearance[b] (mL/min)	Sieving coefficient[a]	Loss into dialysate[c] (g)	Sieving coefficient[a]	
Low flux	<12	<10	–	0	0	[9]
High flux	14–40	20–80	<0.7–0.8	<0.5	<0.01	[9]
Medium cut-off	40–60	>80	0.99	2–4	<0.01	[10]
Protein-leaking	>40	>80	0.9–1.0	2–6	0.01–0.03	[11]
High cut-off	40–60	–	1.0	9–23	<0.2	[12, 13]

[a]*In vitro*.
[b]For conventional haemodialysis with a blood flow rate of 300–400 mL/min. Includes contributions from diffusion, convection and adsorption.
[c]For 4 h of conventional haemodialysis.

β_2-microglobulin clearance and sieving coefficient [9] (Table 1). Water permeability, as indicated by the ultrafiltration coefficient, was used in some past classifications but is no longer a clinically relevant measure of performance since a dialysis machine that can control ultrafiltration is required for the use of all high-flux membranes. That simple classification of membranes as either low flux or high flux is now being challenged by the development of new, more permeable membranes variously described as medium cut-off [10, 14], protein-leaking [11], high cut-off [12] and other less well-defined terms such as super-flux and super high-flux. Just how these new membranes are to be classified remains to be established, as discussed below.

Initial observational studies suggested that the use of high-flux membranes was associated with improvements in morbidity and mortality and led to two large randomized controlled trials (RCTs), the Hemodialysis (HEMO) Study [15] and the Membrane Permeability Outcome (MPO) Study [16], designed to determine if the use of high-flux membranes would improve survival in ESRD patients. Neither study showed a significant survival benefit for high-flux membranes, except in *post hoc* analysis for subgroups of patients.

In the aftermath of the HEMO and MPO studies, it was speculated that the removal of middle-molecule-sized uraemic toxins by haemodialysis with high-flux membranes was simply inadequate to obtain a survival benefit. Solute removal by haemodialysis occurs primarily by diffusion, which decreases rapidly with increasing molecular size [17]. In contrast, solute removal by convection is less sensitive to increases in solute size [17]. Thus the introduction of haemodiafiltration (HDF), which combines diffusive and convective solute removal, was a way of increasing the removal of middle-molecule-sized solutes beyond what was possible with high-flux haemodialysis.

Several observational cohort studies found an association between the use of HDF and survival [18, 19] and led to three RCTs designed to test the ability of online post-dilution HDF to improve all-cause mortality in ESRD patients compared with low-flux [20] or high-flux [21, 22] haemodialysis. The results of those three studies were mixed, with only one finding that patients treated with HDF had a significantly lower risk of all-cause and infection-related mortality than patients treated with high-flux HD [22]. Interpretation of the study results has been complicated, however, by questions about the adequacy of the convection volume—a surrogate for the removal of middle-molecule-sized uraemic toxins—used in each study. *Post hoc* analysis showed that higher convection volumes were associated with better survival in each study and secondary analyses of individual patient data pooled from the three RCTs, plus a fourth [23], found that HDF was associated with a significant reduction in the relative risk of mortality for patients in the highest tertile of convection volume [24, 25]. Overall, the results of the RCTs support a role for the superior removal of middle-molecule-sized uraemic toxins provided by HDF in improving patient survival when a high convection volume is delivered.

While the use of online HDF with high convection volumes to increase the removal of middle-molecule-sized uraemic toxins appears to be beneficial, it has drawbacks. Specialized and costly equipment is required to perform HDF, it is not always possible to achieve the high convection volumes needed to achieve a benefit [26], dialysis fluid (water and concentrate) consumption can be increased by up to 40% if the total dialysis fluid flow rate is increased to maintain the dialysis fluid flow through the dialyser and the diffusive clearance of small solutes and there are potential risks associated with the online preparation and infusion of large volumes of sterile non-pyrogenic substitution solution. The development of new membranes with permeability versus molecular size profiles more like that of the native kidney that could be used for haemodialysis, without the external convection added in online HDF, would be one means of addressing these potential disadvantages.

CHALLENGES TO THE DEVELOPMENT OF MEMBRANES THAT MORE CLOSELY MIMIC THE NATIVE KIDNEY

Beyond the science of fabricating membranes with an enhanced permeability profile that more closely mimics that of the native kidney is the challenge of doing so without increasing the loss of beneficial proteins. Of particular concern is the loss of albumin, given the role albumin plays in determining the colloid pressure of plasma and the association between hypoalbuminaemia and poor clinical outcomes [27]. Serum albumin concentration is determined by its rate of synthesis and catabolism, its distribution between body compartments and external losses such as into the dialysate.

Inflammation is associated with a reduction in albumin synthesis, possibly arising from downregulation of albumin mRNA in the liver [28] or an increase in fractional catabolic rate [29]. In ESRD patients, inflammation can lead to a stable decline in

serum albumin concentration [29]. However, in the absence of inflammation, ESRD patients respond normally to some level of albumin loss by increasing the rate of synthesis and maintaining a serum albumin concentration at the low end of the normal range [30, 31]. Thus the presence or absence of inflammation should be considered in assessing any changes in serum albumin concentration that occur with membranes allowing increased loss of albumin into the dialysate.

Very little albumin is lost into the dialysate with conventional haemodialysis. Losses with post-dilution HDF are greater, with amounts in the range of 0.5–4.2 g per treatment being reported for the most commonly used dialysers [32, 33]. The four RCTs comparing HDF to conventional haemodialysis were performed using comparable dialysers. In those studies, serum albumin concentrations in the HDF-treated groups did not differ [20, 22, 23] or were only slightly lower [21] than those in the groups treated with conventional haemodialysis, suggesting that this level of albumin loss does not pose a risk. In extreme cases, much higher levels of albumin loss have been reported [34, 35]. For example, Kaplan *et al.* [34] measured average albumin losses of 20–30 g/week in patients treated with reused dialysers where the permeability of the polysulphone membranes was increased by exposure to bleach between successive treatments. Those patients showed a significant increase in serum albumin concentration when reuse with bleach was discontinued. Similarly, patients treated with protein-leaking membranes producing an average albumin loss of 23 g/week showed a significant decrease in serum albumin that reversed when use of the protein-leaking membrane was discontinued [35]. Thus the available data suggest that in the absence of inflammation, the use of dialysers allowing a weekly loss of $\leq$12 g poses little risk to patients, whereas routine use of dialysers containing membranes that produce a loss of albumin of $\geq$20 g/week should be undertaken with considerable caution.

MEMBRANE CLASSIFICATION

While the use of β_2-microglobulin clearance and sieving coefficient to differentiate between low-flux and high-flux membranes is widely accepted, there is no consensus on how to classify the new, more permeable membranes. Because the new membranes are intended to provide enhanced removal of middle-molecule-sized uraemic toxins, a classification based on the removal of those solutes would seem to be most appropriate. Three categories of high-flux membranes can be envisioned: (i) standard high-flux membranes corresponding to those currently in widespread use; (ii) expanded range membranes able to remove higher molecular weight middle molecules than standard high-flux membranes through a combination of diffusion and convection, without recourse to an external source of substitution fluid and with clinically insignificant albumin loss; and (iii) protein-leaking membranes also able to remove an expanded range of higher molecular weight middle molecules without infusion of external substitution fluid, but with significant albumin loss.

Differentiating between the three categories of high-flux membrane will require the establishment of some new performance criteria. β_2-microglobulin clearance can be used to discriminate between low-flux and high-flux membranes but is not useful for separating standard high-flux membranes from expanded range and protein-leaking membranes. The boundary between those latter two classes of membrane and standard high-flux membranes could be defined in terms of the clearance and sieving coefficients of additional higher molecular weight proteins, such as YKL-40 (40 kDa) [8] or pentraxin 3 (45 kDa) [6]. Finally, albumin loss into the dialysate could be used to discriminate between expanded range membranes and protein-leaking membranes. As discussed previously, current data suggest that the level of albumin loss that separates expanded range membranes from protein-leaking membranes could be set at an average of $\leq$4 g/treatment for thrice-weekly therapy, with an absolute upper limit for expanded range membranes of 6.7 g/treatment.

APPROACHES TO THE DEVELOPMENT OF NEW MEMBRANES

The goal of mimicking the transport characteristics of the native kidney has guided the development of haemodialysis membranes for decades and the glomerular filtration barrier (GFB), with its intricate structural and functional properties, has served as a model for membrane developers. Replicating the sieving profile of the GFB to effectively remove toxins while retaining essential large proteins has been considered the holy grail of dialysis membrane technology.

Various experimental approaches have been used to expand our understanding of glomerular solute permeability and retention. Inert polysaccharide tracer molecules, which are not reabsorbed or metabolized in the renal tubules, have been used to explore the sieving characteristics and selectivity of the GFB. Sieving curves obtained from filtration studies with dextrans and Ficoll in rats reveal that the GFB is characterized by uniformly sized pores that provide a sharp separation of middle-molecular-weight proteins and larger proteins such as albumin. Öberg and Rippe [36] suggested a two-pore model to describe the permeability of the glomerular capillary wall, with the predominant small pores having a radius of 36.6 Å. Although the GFB is thought to act as a dynamic barrier that exhibits both size-based and electrostatic interactions with solutes [37], in practice a membrane with pores that are uniform in size and regular in shape is likely to be a more achievable design goal for the development of new dialysis membranes.

Conventional approaches to large-scale manufacturing of dialysis membranes, such as phase inversion techniques, which involve precipitation of polymers from solutions after extrusion of the solution through a spinneret, generally result in membranes with a random pore structure and a polydisperse distribution of pore sizes. A population of non-uniform pores results in inadequate retention of solutes larger than the desired cut-off of the membrane. Thus to avoid substantial loss of those solutes, membranes have been designed with a mean pore size significantly smaller than the size of the target molecules, resulting in inadequate removal of those substances.

Substantial efforts have been made in recent years to develop membranes with both a narrow pore-size distribution and a high porosity. Tighter control of the molecular characteristics

of the polymers used for the membrane, introduction of additives such as polyelectrolytes, polyampholytes and inorganic ions during membrane formation [38–41] and optimized control of downstream processes such as thermal treatments during drying or sterilization have led to a significant increase in the uniformity of pore sizes [13]. The decreased variance in pore dimensions has allowed the fabrication of novel membranes with an increased absolute pore size without, at the same time, leaking substantial amounts of vital proteins such as albumin.

Polydisperse solute rejection curves from dialysis membranes and from the rat glomerulus, obtained using macromolecular polysaccharides having a broad molecular weight distribution, demonstrate that the permeability profile of novel medium cut-off dialysis membranes is close to that of the natural kidney [10, 42] (Figure 1). The tight pore size distribution and consequent steeper sieving curve yields a membrane with a high retention onset—the molecular weight at which the sieving coefficient is 0.9—in the range of 10 kDa and a cut-off—the molecular weight at which the sieving coefficient is 0.1—close to but lower than that of albumin. As a result, a higher permeability for large middle molecules up to a molecular weight of 45 kDa can be achieved compared with that obtained with conventional high-flux membranes, while simultaneously maintaining low passage of albumin.

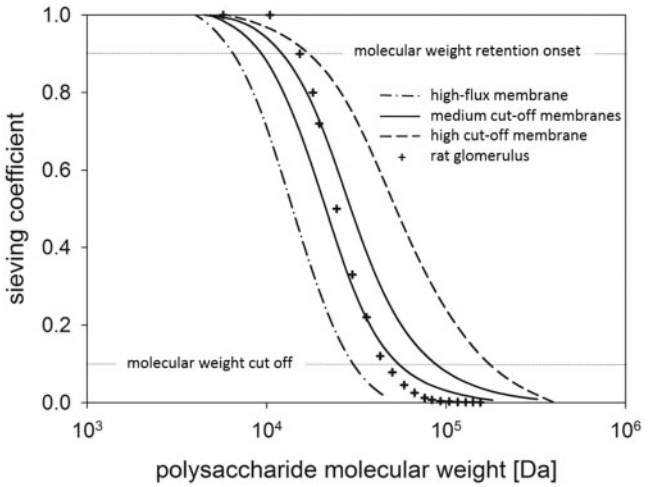

FIGURE 1: Sieving profile of high-flux, medium cut-off and high cut-off dialysis membranes as determined by dextran filtration in comparison to sieving data for Ficoll from rat glomerulus [10, 42].

Besides tailoring sieving profiles, membrane scientists and engineers have been working to reduce the diameter and wall thickness of hollow fibres to reduce the length of the diffusion path and maximize diffusive solute transport. Since large molecules have low diffusion coefficients, their efficient removal requires a contribution from convective flow across the membrane wall. Even in the absence of net ultrafiltration, convective mass transport is inherently present in haemodialysis treatments due to the principle of internal filtration, also known as Starling flow, which is caused by the axial hydrostatic and oncotic pressure gradients along the blood and dialysate flow paths of a dialyser. In the proximal portion of a dialyser, the pressure in the fibre lumen is higher than on the dialysate side of the fibre, resulting in flow from the blood into the dialysate, whereas in the distal portion of the dialyser, fluid is progressively reabsorbed from the dialysate because of the reversal of the pressure conditions associated with countercurrent flow.

At given blood and dialysate flow rates, transmembrane convective transport is primarily dependent on the membrane pressure modulus, which is a measure of the ratio of axial resistance to radial resistance [43]. The axial resistance determines the pressure drop along the blood flow path and is proportional to the length of the hollow fibre and inversely proportional to the fourth power of the inner diameter of the fibre. The radial resistance describes the resistance of the membrane. Accordingly, alterations in the diameter and length of the hollow fibres and in membrane hydraulic permeability significantly affect the rate of internal filtration [44–46]. The effect of capillary internal diameter on the rate of internal filtration and

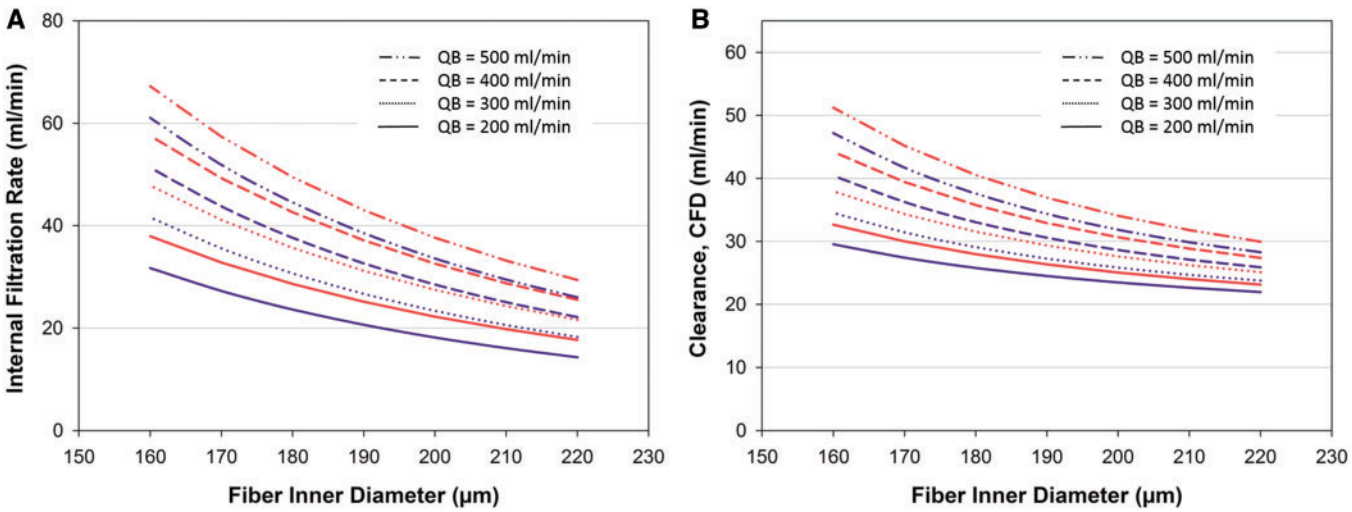

FIGURE 2: Effect of **(A)** fibre inner diameter on internal filtration rate and **(B)** clearance of complement factor D (24 kDa) at different blood flow rates studied computationally by employing a two-dimensional transport model [47] [net ultrafiltration: 0 mL/min; dialysate flow rate: 500 mL/min (blue lines), 800 mL/min (red lines); effective fibre length: 23.6 cm; membrane surface area: 1.7 m^2; fibre packing density: 56.1%; ultrafiltration coefficient: 48 mL/h/mmHg; sieving coefficient for complement factor D: 0.52].

the clearance of complement factor D (24 kDa) as an indicator of middle molecule removal is shown in Figure 2 [47].

The increasing risk of haemolysis associated with increasing blood flow resistance and pressure gradient limits the extent of the reduction in fibre diameter. New membrane designs harness the effect of a high fibre length:diameter ratio with the aim of enhancing convective transport rates by increasing proximal filtration and distal backfiltration and thus the removal of large molecules. Direct quantification of internal filtration based on nuclear imaging techniques has revealed that maximum internal filtration rates of >50 mL/min can be achieved with new dialysis membrane designs by adjustments of hydraulic membrane permeability and fibre geometry [48].

Increasing the removal of middle molecules by increasing diffusion and convection must be balanced against the transport of pyrogenic bacterial products from the dialysate to the blood [49]. The materials used in contemporary membranes retain endotoxins and other bacterial products by adsorption, which offers a size-independent retention mechanism in addition to the size exclusion mechanism of the membrane. The importance of adsorption as a barrier against endotoxin transfer is evident from the observation that membranes with similar chemical composition but different pore sizes show no difference in permeability to endotoxins and other cytokine-inducing substances [50].

FUTURE PROSPECTS

The fundamental goal of membrane engineers remains unchanged: more effective removal of uraemic toxins during dialysis by membranes with an improved separation profile. To that end, advances in nanotechnology may pave the way to the manufacture of more selective membranes on a large scale that exhibit unimodal pore sizes, very thin membrane thicknesses and high porosities [51, 52]. Double-layer, mixed-matrix membranes, which combine dialysis and adsorption, have shown promising results with respect to removal of protein-bound uraemic toxins, which are only poorly cleared with conventional dialysis membranes [53]. Finally, bioartificial kidneys that combine synthetic membranes with renal epithelial cells may open the door to the biggest breakthroughs. These approaches would add functionalities, which are not provided with the use of today's biopassive membrane devices, including active transport functions, but also metabolic and endocrine functions. Humes *et al.* [54] used human primary proximal tubule epithelial cells cultured on polysulphone hollow-fibre membranes in patients with acute kidney injury, while Chevtchik *et al.* [55] devised a living membrane in which microporous polyethersulphone hollow-fibre membranes supported a tight monolayer of immortalized human renal proximal tubular epithelial cells. While they remain at an early stage of development, these possibilities demonstrate the range of approaches being adopted to develop innovative membrane technologies that can lead to further improvements in patient outcomes.

ACKNOWLEDGEMENTS

This article is published as part of a Supplement to *NDT* on 'Translating Innovation to Clinical Outcomes', financially supported by Baxter Healthcare Corporation.

CONFLICT OF INTEREST STATEMENT

None declared. M.S. is a full-time employee of Baxter International Inc. R.A.W. reports personal fees from Baxter Healthcare Inc., outside the submitted work.

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Received: 31.3.2018; Editorial decision: 19.6.2018