All high-flux membranes are equal but some high-flux membranes are less equal than others

Raymond Vanholder¹ and Luciano A. Pedrini²

¹Nephrology Section, Department of Internal Medicine, University Hospital, Gent, Belgium and ²Nephrology and Dialysis Division, Bolognini Hospital, Seriate, Italy

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The progression of renal failure is characterized by the accumulation of a host of compounds [1], which, under normal conditions, are excreted or metabolized by the healthy kidneys. Many of these compounds affect several organ systems, resulting in the uraemic syndrome.

Once this retention has progressed to disabling or life-threatening complications, quality of life and survival can only be maintained by removing retention products by dialysis or transplantation. Over time, it became clear that many of the disabling retention solutes (toxins) are difficult to remove by standard dialysis, as they are either protein bound and/or characterized by a high molecular weight (middle molecules) [2,3].
Removal of such compounds by currently available dialysis strategies can be achieved by increasing dialyzer pore size, i.e. applying high-flux membranes, alone or in combination with convection. Mainly based on secondary analyses of randomized controlled trials or observational experiences, several studies lately pointed to a survival advantage or a decreased morbidity of the latter strategies (summarized in [4]). In the current issue of *Nephrology Dialysis and Transplantation*, Ouseph et al. compare the efficacy to remove low- and high-molecular-weight uraemic retention solutes, such as urea, phosphorus, β2-microglobulin, angiogenin, leptin, complement factor D and immunoglobulin light chains with several different high-flux membranes [5]. Of note, several of these compounds, such as phosphorus, leptin, complement factor D and immunoglobulin light chains have been linked to vascular damage [6,7], as of today the main life-threatening complication of chronic kidney disease [8,9]. In addition, most of these compounds, with the exception of urea, can be qualified as ‘difficult to remove by dialysis’. The main message of the study by Ouseph et al. is that high-flux membranes manufactured from seemingly similar polymers may differ significantly in their removal capacity.

Although it is obvious that the possibilities of up-to-date polymer chemistry allow for the development of large pore membranes with different compositions and characteristics, our current view is to consider all these membranes as the same. This neglects the fact that even small modifications in manufacturing conditions, solvents and other factors will result in different chemical compositions and/or physical characteristics. On top of that, also differences in geometric structure, bundling, etc. play a role. It is known that various high-flux membranes differ in biocompatibility towards leukocytes and complement system, coagulatory properties and/or adsorptive capacity. Hence, although this question has rarely been addressed, it is conceivable that there are also differences in removal capacity.

The study by Ouseph et al. in this issue shows that such differences exist and they are significant. Whether they are important enough to be translated into differences in clinical conditions and outcome remains open for discussion and should be evaluated.

Of note, in a study by Cheung et al., based on the database of the HEMO study, a striking difference in outcome was shown for different strata of β2-microglobulin concentrations, averaged over the entire observation period and irrespective of the type of membrane used [10]. This illustrates how differences in the balance between generation and removal, whatever be their origin, if they result in differences of solute concentration, can effectively impact outcome parameters.

On the other hand, differences in clearance, as observed in the present study, are not necessarily translated into differences in solute concentration, and should be substantial to do so. One phenomenon which refrains this evolution is the complex kinetic behaviour of the difficult to remove compounds, resulting in sometimes impressive rebound phenomena [11,12], especially with highly efficient but relatively short dialysis strategies. In this way, prolonging dialysis may sometimes be as rewarding as increasing pore size and/or convection [13].

The study by Ouseph et al. has been performed applying up-to-date and sophisticated dialysis strategies and evaluation methods. Nevertheless, the study has some drawbacks. First of all, the publication is an amalgamation of two different study arms, which were not run strictly in parallel. Patient cohorts were different, as well as some of the operating conditions such as treatment time, blood flow and ultrafiltration rate. In this context, blood/plasma water clearances, pre- to post-session reduction ratios and Kt/V, while providing an exact measure of instantaneous and mean solute removal of the session for the given operating conditions, may not be reliable tools for a comparison of the different dialyzers among the two study arms. This makes it difficult to extrapolate conclusions from one arm to the other, even if examination of the separate results of the two experimental settings per se may offer useful information.

The only parameter that is independent from the operating conditions and can reliably be used for comparison between study arms is the mass transfer coefficient for urea Ko. Based on this index, the polysulfone (PS) dialyzer Optiflux F200NR is superior to the other tested dialyzers in removing small solutes.

On the other hand, when flux and surface were matched, polyarylethersulfone (PAES) membranes showed greater ability than PS membranes to remove β2-microglobulin and other low-molecular-weight proteins. Evidence in the case of low-molecular-weight proteins other than β2-microglobulin, however, was less compelling due to the only small numerical differences found between membranes and, probably, due to the small number of experiments.

The two high-flux membranes tested in this study are commonly considered to be of similar chemical composition, but differences in polymeric quality and mixture and in manufacturing process may at least result in some important differences, such as the physical structure of the boundary layer (z-potential, mean pore size, shape and density) and the structure and thickness of the sponge support layer [14,15]. Each of these factors may explain the unique properties of a membrane. In addition, the five dialyzers have different capillary diameters and lengths, fibre undulations, surface areas and housings and were sterilized by different techniques.

Many variables at play in this complex evaluation and the relatively few data provided by this study make it hard, if not impossible, to make sound conclusions about whether observed differences in removal are attributable to dialyzer or to membrane characteristics.

What can be generally concluded with regard to middle molecular weight size compounds is that the PS membrane showed greater adsorption capacity, while the PAES membrane could remove a greater amount of these compounds by convection and overall. This finding could be conflicting with the common knowledge on hydraulics, according to which a narrower capillary diameter, resulting in higher internal filtration pressure, should enhance solute transport by convection [15,16]. This was not the case in this study, where higher removal by convection occurred in PAES dialyzers with larger capillary diameter. Probably, one or more additional factors, such as pore size, structure and density and membrane z-potential prevailed in determining this result.
Removal of middle molecular uraemic compounds is highly enhanced by convective therapies, in which filtration pressure, blood and ultrafiltration rates mostly influence membrane permeability to water and solutes [17] by determining formation and thickness of the secondary protein layer on the inner membrane surface. The extent of this process may partially be influenced by the physico-chemical characteristics of the membrane and, in turn, it may deeply modify the in vivo membrane performance [18]. It would be interesting to know if differences between membranes highlighted in this study in high-flux dialysis would be modified or maintained during convective treatments such as haemofiltration or haemodiafiltration performed with high exchange fluid volumes.

In conclusion, the study by Ouseph et al. demonstrates that not all high-flux membranes are identical regarding removal capacity. Rather than comparing these membranes to each other in a kind of competition, this shows that the optimal removal capacity has not yet been reached, and membrane developers should look actively for structural and functional alternatives to further improve removal capacity. The refreshing and stimulating aspect of the publication under discussion is that the authors took the effort to cation under discussion is that the authors took the effort to

Conflict of interest statement. None declared.

(See related article by R. Ouseph et al. Differences in solute removal by two high-flux membranes of nominally similar synthetic polymers. Nephrol Dial Transplant 2008; 23: 1704–1712.)

References


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