Water and solute transport in peritoneal dialysis: models and clinical applications

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Keywords: aquaporin; distributed model; glycoscalyx; peritoneal transport; three-pore model

Introduction

The physiology of water and solute transport across the peritoneal membrane during peritoneal dialysis (PD) has been widely studied during the last 30 years. The peritoneum can be viewed as a semi-permeable, heterogeneous membrane containing three major components: a monolayer of mesothelial cells; an interstitial tissue containing fibroblasts, macrophages and a conjunctival matrix; and a network of capillaries. It is now commonly accepted that the endothelium lining the peritoneal capillaries represents the main barrier to water and solute transport during PD [1]. Diffusion is the main mode of transport for small solutes (e.g. urea, creatinine, etc. from blood to the dialysate and glucose in the opposite direction) whereas higher molecular weight solutes (e.g. albumin, immunoglobulins, etc.) are transported by convection and water flow is driven by osmosis [1]. Only the perfused membrane in contact with the dialysate participates in solute and fluid transport. Therefore, the effective peritoneal surface area available for transport depends on the number of capillaries that have been recruited or dilated by the dialysis procedure itself. Deterioration of transport properties and loss of ultrafiltration (UF) are the main reasons for technical failure in PD, explaining the necessity for models aiming at a better understanding of the transport mechanisms across the peritoneal membrane.

In this issue, Michael Flessner [2] and Bengt Rippe [3] debate the nature of and utility of the models used to predict water and solute transport across the peritoneum as well as the potential importance of the endothelial glycoscalyx in these processes. The debate is completed by an original study from the group of Raymond Krediet [4], which details the determinants of water transport during PD in relation with the evolution of the osmotic gradient during the dwell.

The three-pore model

The most widely used model for the transport of water and solutes across the peritoneal membrane is the ‘three-pore model’ (TPM) based on computer simulations [5]. This model postulates that the major transport barrier of the peritoneum is the capillary endothelium, which contains three distinct types of pores. The ‘small pores’ (radius 40–50 Å) correspond to the clefts, or gaps, located between endothelial cells. They account for ~95% of the hydraulic...
conductance ($L_pS$), i.e. the vast majority of the total pore surface area available for the diffusion of small solutes. The ‘large pores’ (radius 250 Å), thought to correspond to the venular interendothelial gaps, account for 5% of $L_pS$. These pores are involved in the transport of macromolecules, and although they represent only 0.01% of the total number of pores, they also mediate a part of the UF via convection of plasma from blood to the peritoneal cavity. The water-specific, ‘ultrasmall pores’ are located in the endothelial cells and account only for 1–2% of the hydraulic conductance. However, because they reject solutes but facilitate the transport of water, the ultrasmall pores are extremely important during crystalloid osmosis. Indeed, they have been predicted to mediate up to half of UF during a dwell with hypertonic glucose [5,6]. The identification of the archetypal water channel, aquaporin-1 (AQP1), and its subsequent localization in the peritoneal capillaries and post-capillary venules [7] provided a molecular counterpart to the ultrasmall pore. The importance of the ultrasmall pores was demonstrated by Ni et al., who used AQP1 knockout mice to show that ∼50% of the total UF occurs through AQP1 [8], confirming the initial computerized assumptions of Rippe. It must be noted that, during PD, a fluid reabsorption (or back-filtration) also occurs through the lymphatic vessels and the interstitial tissue. This phenomenon counteracts the transcapillary UF, making net UF the result of the two opposing fluid processes. Altogether, the main water and solute transport of the peritoneal membrane can therefore be defined by the effective peritoneal surface area, the intrinsic peritoneal permeability (i.e. the resistance of the peritoneal interstitial tissue to the size-selective process of solutes diffusion) and the AQP1 function.

Membrane versus distributed models

In the present debate, Flessner suggests that ‘membrane models’ such as the TPM (or the Pyle-Popovich model), in which the peritoneal membrane is considered as a single membrane between the blood and the dialysate, may have significant limitations in predicting transport in complicated PD or in research settings [2]. Flessner does acknowledge the practical side of the TPM and the fact that it provides a correct estimation of solute and water transport in normal clinical settings. However, he suggests that such membrane models fail to distinguish between structural changes, including fibrosis, inflammation or angiogenesis, that are associated with PD. Furthermore, the TPM does not include lymphatics or the interstitial space, and thus it fails to account for the fluid reabsorption driven by the positive hydrostatic pressure within the cavity. The capillary model has no tissue surrounding it, whereas the presence of interstitium and matrix may significantly alter the membrane transport properties. Finally, the TPM does not take into account the exponential decrease in the osmotic pressure from the cavity to the peritoneal tissue, so that the profound capillaries (deeper than 500 μm to 1 mm to the peritoneal surface) are only exposed to a fraction of the actual osmotic pressure in the dialysate and are probably contributing less to UF [9].

Flessner proposes that the limitations of the TPM may be circumvented by the use of the ‘distributed model’ that is based on a two-dimensional simulation that integrates the microvasculature with the surrounding cells and interstitium within the peritoneal membrane [2]. This model is less practical for clinical purposes, but more appropriate for integrating parameters such as the local density of blood vessels, or the contribution of the interstitium, to the single endothelial permeability.

Facing these arguments, Rippe argues that the TPM adequately predicts solute and fluid transport and UF for a variety of dialysates containing glucose and alternate osmotic agents, which is not the case for the distribution model [3]. Important predictions of the TPM, related to the ultrasmall pores in the endothelium, have been confirmed in mice lacking AQP1. In particular, these studies confirmed UF under conditions of crystalloid (glucose) versus colloid (icodextrin) osmosis and the role of ultrasmall pores in sodium sieving [8].

Another feature of the TPM is the inclusion of large pores for macromolecules larger than albumin that are unaffected by the oncotic or colloid osmotic pressures. Thus, the large pore transport is dictated only by the hydrostatic pressure gradient and/or the number of large pores available for transport, both increasing with inflammation. Support for the large pore hypothesis was provided by studies in eNOS knockout mice, showing that the lack of endothelial NO production during acute peritonitis was associated with a significant reduction in albumin loss [10].

The importance of lymphatics is also debated, since the TPM predicts the reabsorption of isosmotic fluid from the cavity through the small pores with only minor contribution of the lymphatics. Finally, Rippe argues that the direct measurement of the drained peritoneal volume, on which the TPM is based, avoids the complexity associated with the use of a macromolecular marker that is continuously cleared from the peritoneal cavity into adjacent tissues.

How to reconcile these positions? Flessner and Rippe, like many investigators in the field, recognize the importance of structural changes—fibrosis, vasculopathy and neo-vascularization—in mediating UF failure in PD [2,3]. To take these changes into account, Rippe and Venturoli have recently proposed an extended version of the TPM, which includes the capillary wall and a serial barrier consisting of fibres in the interstitium [11]. This serial membrane-fibre matrix model could indeed explain the pathophysiology of UF failure and the uncoupling of solute transport (PS to glucose), which gradually increases with time on PD, from the peritoneal UF coefficient ($L_pS$) that remains largely unchanged [12]. Further experiments taking advantage of genetically modified mouse models should provide a direct counterpart of these simulations [13].

A role for the glyocalyx?

Another issue debated by Flessner and Rippe is the potential role of the glyocalyx, a thin layer of proteoglycans, glycoproteins and glycosaminoglycans located on the luminal surface of endothelial cells. The glyocalyx confers a negative charge to the endothelium, which may be crucial for the glomerular filtration barrier [14]. It may also play a role in flow- and mechano-sensation, interaction with leukocytes and regulation of coagulation [15]. Flessner raises...
the possibility that the glycocalyx might affect the peritoneal permeability for macromolecules through the interendothelial gaps (large pores), behaving as a barrier for large molecular weight dextrans [2]. Indeed, the glycocalyx appears to be damaged in clinical situations such as inflammation, ischaemia/reperfusion and hyperglycaemia, all associated with an increased capillary permeability [15]. An alteration of the glycocalyx may thus facilitate the release of growth factors, cytokines or plasma proteins that could play a role in angiogenesis and expansion of the interstitial cell matrix in the peritoneal membrane. The view that the glycocalyx may contribute to the size selectivity of the capillary wall is not shared by Rippe, based on the intrinsic fragility of the structure and the lack of functional testing due to methodological constraints [3,16]. Furthermore, there is no experimental evidence for an alteration of the negative charge of the glycocalyx and the issue of the potential reversibility of the changes in glycocalyx structure during inflammation is unknown [3].

Evaluation of the peritoneal transport: back to patients

The above-mentioned views are probably more additive than antagonists and more important for academic research than for the daily clinical practice. What should the clinicians know about the transport of solute and water across the peritoneal membrane?

Classically, the transport characteristics of the peritoneal membrane are assessed by a peritoneal equilibration test (PET), as originally described by Twardowski et al. [17]. This test, performed during a 4-h dwell with a 2.27% glucose solution, evaluates the transport of low-molecular-weight solutes such as urea and glucose. The data allow the patients to be categorized into four groups from fast to low transport status and therefore provide information regarding the small pore density and the effective peritoneal surface area.

The PET focuses mainly on solute transport and not on UF capacity, an aspect of the membrane function that is rarely addressed. During a hypertonic dwell, approximately half of total UF is dependent on transport through small pores, whereas the remaining UF occurs through the ultrasmall pores. For this reason, the International Society for Peritoneal Dialysis committee on UF failure recently proposed performing the PET with a 3.86%-based solution instead of the 2.27% glucose PET [18]. This hypertonic PET gives similar information on small solute transport to the classical PET, but it also provides data on free-water transport through AQP1, by measuring the sodium sieving, i.e. the decrease in dialysate sodium concentration during the early stage of the dwell. The dialysate/plasma sodium concentration ratio or the magnitude of the sodium sieving at 60 min gives a semi-quantitative assessment of the ultrasmall pores, which could be too limited to characterize the various causes of UF failure in PD.

To address these problems, recent methods focused on obtaining data on urea and creatinine removal, together with water fluxes across the small and ultrasmall pores, using either simple volume drainage after a 1-h hypertonic dwell [19] or hypertonic peritoneal permeability analyses (SPA) using intraperitoneal dextran [20]. The former methodology is based on the principle that fluid transport via the small pores is accompanied by sodium, whereas transcellular fluid transport is by definition water-selective. By knowing the intraperitoneal mass of sodium removed at each time point, small-pore fluid transport can be determined as the sodium removal divided by the plasma sodium concentration. Free-water transport can easily be calculated by subtracting UF through small pores from total UF [19]. With the SPA, the dialysate sodium concentration and the intraperitoneal volume arising from transcapillary UF, as well as backfiltration and lymphatic absorption, can be assessed at different time points, allowing us to calculate total sodium transport. Free-water transport can then be obtained by subtracting transcapillary UF coupled to sodium transport from the total UF [20].

The clinical application of each methodology yielded interesting data. In the present issue of NDT, Parikova and Krediet used SPA in 80 PD patients to show the importance of the crystalloid osmotic pressure gradient for free-water transport [4]. Meanwhile, the osmotic pressure dependence is less pronounced for the small pores. In other words, the greater the glucose absorption rate through the peritoneal membrane, the lower the transfer of water across the ultrasmall pores. The authors also document a marginal fluid transport across water channels in the second half of the dwell and, interestingly, the lack of correlation between free-water transport and crystalloid osmotic pressure gradient on one hand and PD duration on the other hand. This observation could result from two changes associated with long-term PD: a lower amount of functional pores and an increase in the vascular peritoneal surface area [4]. These results are in keeping with the recent data of Asghar and Davies who confirmed that the variability in transcellular water transport observed in PD patients can largely be explained by the rate of small solute transport and that large amounts of fluid are being reabsorbed via the small pores proportionally to the small solute transport rate [21].

The two latter studies [4,21] may provide clues to explain the excessive mortality found in patients with a fast transport status, who exhibit poor UF due to the loss of osmotic gradient but also due to enhanced fluid reabsorption through small pores. This information should influence dialysis prescription, since such patients benefit from automated peritoneal dialysis together with icodextrin during long dwells [22]. The former ensures that the peritoneal cavity is drained at the optimal UF, i.e. before the dissipation of the osmotic gradient, while the later enhances the oncotic pressure gradient and fluid removal across the small pores [22].

The debate of Flessner and Rippe [2,3] and the clinical investigations of Parikova et al. [4] illustrate the vividness of research in peritoneal transport, with the aim to improve models and to better delineate the functional importance and the clinical relevance of molecular and cellular components of the peritoneal membrane.

Conflict of interest statement. None declared.

The impact of residual renal function on survival

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Keywords: haemodialysis; mortality; peritoneal dialysis; residual renal function

Dialysis patients have 10–20 higher mortality rates compared to controls. Factors discussed to influence mortality in dialysis patients are hypertension, left ventricular hypertrophy (LVH), increased pulse pressure, phosphorus, calcification, inflammation, malnutrition, fluid and sodium balance, interdialytic weight gain, removal of middle molecule uraemic toxins and residual renal function (RRF) [1]. LVH and hypertension are frequent findings in dialysis patients.