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Assessing transport across the peritoneal membrane: Precision medicine in dialysis

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> The good physician treats the disease; the great physician treats the patient who has the disease.
>
> Sir William Osler (1903)

Peritoneal dialysis (PD) is the leading form of home-based dialysis therapy for patients with kidney failure.[1] The efficiency of PD depends on its ability to remove excess of water and small uremic solutes from the organism, through fundamental mechanisms of osmosis and diffusive and convective transport across the peritoneal membrane.[2,3] According to Fick's laws of diffusion, the transport of small solutes across the peritoneal membrane (named the peritoneal solute transport rate, PSTR) is primarily determined by the effective peritoneal surface area (i.e. the number of perfused peritoneal capillaries in contact with the dialysate), the intrinsic permeability of the membrane, its thickness and the concentration gradient between blood and dialysate. The PSTR can readily be measured by the peritoneal equilibration test (PET), formalized by Twardowski, Nolph and colleagues in 1987.[4] Patients starting PD present a large variability in PSTR, conditioning the maintenance of the osmotic gradient, and thus the rate of ultrafiltration (UF) across the membrane.[5] Higher PSTR has been associated with a greater risk of technique failure and with an excessive risk of death among patients on PD.[6,7] It can be mitigated by PD prescription, that is, shortening dialysate dwell time or using alternate osmotic agents.[3,5] A proper assessment of membrane transport properties at baseline and during exposure to PD is thus of major importance for individualized prescription and for precision dialysis.

The peritoneal membrane consists of three major components layered between the plasma and the dialysate: the capillary endothelium, the interstitial tissue and the mesothelium. The capillary endothelium represents the rate-limiting barrier for water and solute transport during PD, restricting the solute exchange to less than 0.1% of its total surface area. In the capillary endothelium, the major route for small solute and fluid exchange corresponds to the small pores, located to interendothelial clefts. The functional radius (approximately 40–50 Å) of these small pores restricts the leak of albumin and other large molecules, such as immunoglobulins, across the endothelium. A small number of large pores (radius approximately 250 Å), which account for only 0.01% of the total pore population, allows the permeation of large proteins into the peritoneal cavity, driven by hydrostatic pressure. A third population of ultrasmall pores (radius approximately 2.5 Å), corresponding to the water channel aquaporin-1 (AQP1), is present in the endothelium, facilitating water transport driven by an osmotic gradient generated by crystalloid agents (typically, glucose). The AQP1-mediated water flow explains the rapid dilution of the dialysate sodium concentration during the first part of the dwell (denoted 'sodium sieving'), best observed when using hypertonic (3.86%) glucose dialysate.[3]

To date, AQP1 is the only molecular counterpart to peritoneal transport identified in the peritoneal membrane.[3] Modelling and experimental studies indicated that the AQP1 water channels mediate up to half of the UF when using hypertonic glucose dialysate and that their integrity is reflected by the sodium sieving.[3,8,9] Further studies confirmed that the type of osmotic agent influences the kinetics of water transport. Very small osmotic agents (e.g. glycerol) will exert a low osmotic effect on the small pores, and thereby act primarily on water-only pores. Glucose, the typical crystalloid agent, will drive water flows equally partitioned between ultrasmall and small pores. High molecular weight polymeric glucose molecules, such as icodextrin, will drive water mainly via colloid osmosis across the small pores.[10]

Despite the importance of assessing peritoneal membrane transport for individual dialysis prescription, more

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than 10 years elapsed since the last recommendations on that topic were published.[11] New insights from large epidemiological studies and increasingly sophisticated experimental methods justified a fresh look at the question. In this issue of *Peritoneal Dialysis International*, a team of experts appointed by the International Society for Peritoneal Dialysis (ISPD) provides updated recommendations for the evaluation of peritoneal membrane dysfunction in PD.[12] Based on the knowledge gained from clinical and experimental studies, they describe the main categories of membrane dysfunction, clarifying the terminology and discussing pathophysiological mechanisms and clinical implications. Based on this classification, they review the tests that can be used to assess the membrane properties and to substantiate potential dysfunction. They explain how to interpret these tests and how they can guide appropriate clinical management. The global value of these recommendations is sustained by the assessment of clinical practices in Europe, United States, South America and Asia.

The current recommendations of the ISPD for evaluating the peritoneal membrane can be summarized as follows. The PSTR should be analysed early in the course of PD and whenever indicated, with a 4-h PET using either 2.27/2.5% or 3.86/4.25% glucose/dextrose-based solution, to identify patients with fast PSTR who are exposed to lower UF and to the risk of fluid overload. Mitigation strategies for fast PSTR include the use of automated PD coupled to the colloid osmotic agent icodextrin for the long daily dwell or, when these modalities are not available, using dialysates with higher glucose concentrations. Identification of low UF capacity should be based on insufficient net UF during the standard PET or a clinical situation of fluid overload. The most frequent causes of a low UF capacity include fast PSTR or intrinsic membrane dysfunction. The diagnosis of intrinsic membrane dysfunction, corresponding to a poor efficiency of glucose as osmotic agent (i.e. low osmotic glucose conductance), should be substantiated by measuring the sodium sieving at 1 h using 3.86% glucose/4.25% dextrose exchange, which corresponds to the facilitated water influx into the peritoneal cavity through the AQP1 water channels. Like the fast PSTR, an intrinsic membrane dysfunction can be present at the onset of PD or develop over years on PD. The later situation is associated with structural changes in the membrane, including vascular proliferation, vasculopathy, infection/inflammation, fibrosis or, very rarely, encapsulating peritoneal sclerosis. In fact, the loss of UF and osmotic conductance to glucose is an early and independent predictor of the risk of EPS.[13,14] These changes are not related to a loss of AQP1 but instead to the amount of thick collagen fibres in the interstitium, restricting water transport.[14] Mitigation strategies for poor intrinsic UF are limited – reflecting the current lack of options to rescue structural changes in the peritoneal membrane. Other causes of membrane dysfunction include mechanical problems affecting the dialysate drainage, leaks of dialysate, high intraperitoneal pressure causing reverse fluid absorption or excessive lymphatic absorption: they can also be assessed by specific tests.[12]

Where do we go from there? Clinical practice recommendations and guidelines are important tools to improve and standardize patient care. They need to rest on a systematic, rigorous review of the available evidence, a transparent and consistent grading and a global perspective that includes healthcare providers and patients from different regions. The quality of evidence has long been a challenge in nephrology, with methodological problems hampering the realization of large, high-quality clinical studies.[15] This limitation is also true in the field of PD, where important questions ranging from the choice of solutions to the treatment of peritonitis or long-term membrane dysfunction remain debated.[1,16–18] Yet, guidelines and recommendations may contribute to quality improvement provided they are implemented, used to develop policies and evaluated in terms of impact on clinical practice.[19]

In such context, actualized recommendations for evaluating peritoneal transport have the potential to significantly impact on the field. Since peritoneal transport properties are intimately linked to PD outcome and prescription, implementing standardized methods will be helpful to educate and guide practitioners and to further improve individualized patient care. Naturally, such recommendations will have to be integrated with other guidelines addressing the prescription of PD.[20–23] Standardized evaluation of membrane transport will also be crucial to set-up large cohorts to analyse factors influencing the inter-individual variability in PSTR and UF capacity and how these factors may affect outcomes. In particular, the precise evaluation of transport properties will be very useful to weight the influence of genetic factors on such individual variability, for instance by using genome-wide association studies or candidate gene studies.[24,25] In conjunction with other biomarkers, information about genetic factors will contribute to develop predictive tools to better evaluate risks and tailor prescription.[1] In terms of drug development, precise membrane testing is crucial for developing and assessing the value of new osmotic agents and PD solutions and for monitoring potential effects on structural and functional changes.[1,3,5,26] On a global scale, implementing practical and cost-effective transport studies may help to solve the substantial heterogeneity observed in PD practice and performance across the world.[27,28]

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