Physiology of fluid and solute transport across the peritoneal membrane

Authors
Anna Rita Aguirre[1]
Hugo Abensur[1]

[1] Medical School of the University of São Paulo.

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Correspondence to:
Anna Rita Aguirre.
University Hospital - Medical School of the University of São Paulo.
nº 255, 7º andar, Cerqueira César. São Paulo, SP, Brasil.
CEP: 05403-000.
E-mail: anna.rita@hc.fm.usp.br
Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

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Abstract

In this review, phenomena involved in fluid and solute exchange through the peritoneal membrane, both in the physiologic and in the peritoneal dialysis settings, are explained. For that purpose, mathematical models developed for the study of molecule transport through the membrane, such as the "Pore Model" and the "Distributive Model" are used. Scientific accomplishments in the field are described and areas that require additional research are also cited. Knowledge about the physiologic mechanisms involved in this renal replacement therapy modality, concerning events directly related to the peritoneal membrane itself, is synthesized in this manuscript.

Keywords: epithelium; peritoneal dialysis; peritoneal fibrosis.

Peritoneal dialysis as a therapeutic strategy in chronic kidney failure

Peritoneal dialysis (PD) has been used as an option in renal replacement therapy (RRT) in the management of chronic kidney disease (CKD) since the 60's.[1,2] In Brazil, the first chronic PD programs started in the 80's.[3,4]

According to the Brazilian Society of Nephrology, it is estimated that 91,314 patients are on RRT in the country. Of these, 9.4% would be in PD, or 8,600 people,[5] which matches world statistics.[6]

DP uses biophysical properties inherent to the peritoneal membrane (PM) for solute clearance and excess fluid removal. In this review we will discuss the biological phenomena involved in the transport of molecules through the PM.

Peritoneal membrane

The peritoneal mesothelium derives from embryonic mesenchyme. Throughout embryogenesis, this leaflet undergoes bending processes, forming a cavity. The parietal leaflet is irrigated by the arteries of the abdominal wall and the visceral leaflet by the celiac and mesenteric arteries. Eighty percent of the lymphatic drainage of the cavity is made by subdiaphragmatic lymphatics to the right lymphatic duct and left thoracic duct at a rate of 0.5 to 1 mL/min in PD, varying according to respiratory frequency, position and intraabdominal pressure. Innervation is made by the nerves: phrenic, thoracoabdominal, subcostal and the lumbosacral plexus.

The peritoneal mesothelium, a simple squamous epithelium, is separated from the submesothelial layer, made up of collagen, fibroblasts, adipose tissue, blood and lymph vessels, by the basal membrane.

Transport through the membrane

Among the layers of resistance to the passage of fluids and solutes between blood and intracavitary fluid, the primary barrier is the vascular endothelium of capillaries and post-capillary venules of the peritoneum.[7] The endothelium basement membrane, the interstitial matrix, cells of the interstitium, the mesothelium and its basement membrane offer virtually no hurdle to the transport of small molecules.[8]

Transport models were developed to study the phenomena involved in the exchange through the PM, both in physiologic and pathologic contexts, including variables that can interfere in these exchanges, enabling the simulation of specific clinical situations and the objective analysis of clinical cases. The best known among these models is the so-called "pores model".

According to the pores model developed by Rippe *et al.*[9], three pore sizes would be present in the membrane, regulating the passage of molecules of different radii and molecular mass. The large pores of 250 A represent less than 0.01% of the pores and allow the passage of molecules with a higher molecular mass, like proteins. Small pores allow the passage of 99.7% of small solutes, and ultra-small pores (or ultra-pores) allow the passage of water molecules only.

Of the total peritoneal ultrafiltration coefficient (LpS), the small pores represent 90% and have been defined, from their structural point of view, as the intercellular endothelial clefts,[10,11] which has not yet been fully accepted.[12] The ultra-pores have been accepted ad as aquaporin -1 molecules. However, the large pores are still a controversial issue. There are those who argue that they would be represented by vesicular vacuolar organelles (VVO), clusters of vesicles and cytoplasmic vacuoles in clusters interconnected by fenestrae with opening and closing regulated by diaphragms.[13] The VVOs have been associated with the vascular permeability of tumors, being positively stimulated by vascular endothelial growth factor (VEGF).[13] Other candidates for representing large pores are intercellular gaps, 3-4 times larger than regular intercellular clefts.[14] Despite the uncertainty concerning the structural identity of the pores, the three pores model (TPM) proves suitable from the mathematical point of view, to the study of most of the phenomena involved in the transport of fluids and solutes in PD.

During transportation through the PM, the interaction of the molecule with the pore can be understood according to the concepts of drag or convection (S, from the English word "sieving", which defines the magnitude of solute transport coupled to water transport) and reflection (σ, which determines its osmotic effectiveness) of solutes. Thus, the total mass of solute that interacts with the membrane splits into the portion that is able to cross it and that which is reflected by it, creating osmotic force in the source compartment.

$$S = 1 - \sigma \quad \text{(equation 1)}$$

Starling forces acting on each of the compartments are essential in determining the amount of exchange through the membrane after a certain period. Differences in osmotic, hydraulic and colloid osmotic pressures directly influence this quantity. From a practical standpoint , the concentration of the osmotic agent used, usually glucose, infused volume and the intra-abdominal pressure it exerts are the parameters defined by PD prescription which interfere with Starling vectors.

Subsequently to the TPM, there was a concept that the damage caused to the PM over chronic treatment such as increased thickness, neoangiogenesis and mesothelial loss, could change the parameters previously used in its simulations.[15] Thus, in a newly developed model, entitled "distributive", they added the distance between each capillary vessel to the peritoneal cavity.[16] The longer the treatment, the more important this becomes, as the treatment time, since PM thickness - characteristic of long-term injury, makes variable the contribution from each vessel to the overall transport of molecules according to its depth in the interstitium.

In the distributive model, the endothelial glycocalyx also started to be considered. The glycocalyx - composed of negatively charged proteoglycans and glycosaminoglycans are located on the luminal surface of endothelial cells. There is indirect evidence that they prevent the movement of other negatively charged molecules (proteins) through the PM.[17] This factor also interferes in the study of PM changes over time, since the current concept is that its capillaries generated by neoangiogenesis, influenced by TGF-β and VEGF, secondary to a hyperglycemic environment exposure, have less exuberant glycocalyx and facilitate protein loss.[18]

The combination of these concepts makes it clear that unlike a synthetic hemodialyzer, the PD-related parameters involved in the exchange vary substantially and are less predictable, since the PM is a biological system and, as such, has interindividual variability; in the same individual over time and in accordance with the processes of injury and repair that it is submitted to.

Fluid transport

Transcapillary ultrafiltration (TCUF) occurs in both directions, directed to the cavity and the capillary lumen. The flow of fluids from the capillaries to the peritoneal cavity occurs through small interendothelial pores and through cells by aquaporin-1. The peritoneal cavity fluid lymphatic absorption occurs mostly by the subdiaphragmatic area lymph vessels and, in a lower intensity, the lymph draining the mesothelium in other regions in the cavity. The flows vary through these pathways according to hydrostatic, osmotic and oncotic pressure differences.

In the initial phase of a glucose solution residence in the cavity, when the dialysate-plasma gradient concentration of osmotically active molecule (glucose) is at a maximum, the TCUF is also the most intense. As the osmotic gradient decreases, the flow of water decreases in the small and ultra-small pores, to be equal in magnitude to the flow through the lymphatic vessels in the opposite direction. At this point we find the maximum volume of intracavitary fluid. Fluid absorption via the lymphatics occurs in a continuous manner and varies mainly according to the hydraulic pressure gradient between the cavity and the vascular lumen.[19]

Some studies have evaluated changes in fluid flows according to changes in intra-abdominal pressure (IAP). When liquid is injected into the cavity, part of the intracavitary pressure is transmitted to the inferior vena cava and is propagated in a retrograde manner to the peritoneal capillaries. Thus, the pressure gradient generated between the cavity and the capillary lumen is smaller than the absolute increase in IAP. Abensur *et al*.[20] assessed nine stable patients in CAPD, and found a positive correlation between the IAP and the TCUF.

In a simplified manner, at the initial stage of a glucose solution stay in the cavity, the TCUF in the cavity's direction is the main component of water transport through the PM and, reducing the gradient, the lymphatic absorption becomes more important.

With icodextrin-based solutions - a glucose polymer with an average molecular weight of 5000-6500 Daltons, the UF curve profile is changed. Icodextrin does not exercise its ability to promote UF through osmotic force, such as glucose, but it generates UF by maintaining intraperitoneal colloid osmotic pressure. The absorption of this polymer is basically through the lymphatics - around 40% of the infused volume after 12 hours of residence.[21]

In clinical practice it is recommended to study the transport of fluids using the Twardowski's peritoneal equilibration test (PET).[22] A simple way to do it is by measuring the UF volume after 1 hour of glucose solution residence at 3.86%.[23] When less than 400 mL - a condition called ultrafiltration failure (UFF), there is an association with a worse clinical outcome, especially in terms of cardiovascular outcomes. Other ways to study the transport of fluids have been described, such as the addition of dextran 70 to the bag, to quantify the lymphatic absorption by determining effluent dosage, and quantify the initial decrease in the sodium concentration in the dialysate ("sodium dip"), designed to measure the transport intensity driven by osmotic concentration difference.

More recently, it has been suggested that besides AQP-1, AQP-4 also plays a role in the transport of water moved by osmotic gradient.[8] The search for other water transport pathways happened because the typical fluid flow measured through biological membranes is about 1μL/min/cm^2 at a gradient of 500 mOsm/kg, and according to calculations, the vessels near the peritoneum would not be able to maintain, by themselves, the water transit rate. AQP-4 molecules were found on submesothelial muscle cell membranes, which are relatively large and are exposed to different concentrations of solutes in their opposing faces - since the osmotic agent concentration in the tissue decreases as their distance from the cavity increases. Thus, the AQP- 4 allows liquid flow in favor

of the osmotic gradient on each side of the membrane face, so that it would establish a continuous flow of water toward the cavity. As the cell loses water to the interstitium in its peritoneal face, its cytoplasmic osmolarity would increase, with water entering the other side, where the interstitium becomes hypotonic. The concepts pertaining to this process are still based on theoretical studies;[24,25] and more consistent studies are needed.

Solute transport

Today, it is considered that the passage of solute molecules across the membrane occurs through large and small pores, influenced by many factors.

According to the first Fick's law of diffusion, the overall rate of solute transport depends on the peritoneum's permeability to the molecule, which is the ratio between the free diffusion coefficient of the solute on the distance to be traveled beyond the surface area available for exchange and the solute concentration gradient between the compartments.

In equation 2, J_S is the solute transfer rate, D_f is the free diffusion coefficient, A is the surface area and ΔC, the concentration gradient between the compartments.

$$J_S = D_f/D\chi.A\Delta C \quad \text{(equation 2)}$$

The product of the permeability by the surface area ($D_f/D\chi.A$), also known as MTAC (mass transfer area coefficient), is one of the parameters clinically used to define a person as to the rate of transport of small solutes. MTAC greater than 11 mL/min may define a patient as having a large effective peritoneal surface area, which is interpreted as being a high (or fast) transporter.[26] However, in our settings, Twardowski's traditional PET is the most widely used test for this purpose, for being a simple and inexpensive test, with good clinical correlation.

Solute convective transport, or drag, happens together with the transport of water. It is determined by water flow (J_V), the average solute concentration in the membrane and the Staverman reflection coefficient (σ) which, for an ideal semipermeable membrane is equal to 1 and for a membrane that offers no resistance, it equals zero.

Molecule size is one of the most influential factors. The lower the molecular mass (MM) the easier the transport.

$$MM = 4/3\pi r^3 \quad \text{(equation 3)}$$

One can also describe the PM selectivity by relating the MTAC of various solutes with the diffusion coefficient in water, rather than with its MM, which is not the sole determinant of its diffusion rate, molecule density and shape could also influence its movement.

Theoretically, the solute electrical charge contribution could also interfere in its transit through the PM, but most evidence points to the lack of charge selectivity in the transport of larger molecules, perhaps because of the low density of fixed negative charges in the peritoneum, in comparison, for example, with the glomerular basement membrane.

One possible explanation is the loss of negative charges by continuous exposure of peritoneal tissue to high concentrations of glucose from the dialysis solutions, with loss of the endothelial glycocalyx. Glomerular loss has been reported in patients with diabetic nephropathy.[27]

From the hemodynamic point of view, PM blood flow has a weak relationship with the intensity of exchange of solutes and, in experimental models, only with flow reductions of more than 70% there is a significant reduction in the exchange intensity. On the other hand, the effective vascular surface area, which is the area actually in contact with the dialysis solution, has direct influence on solute transit.

Electrolytes

The sodium concentration more often present in the solutions is close to or slightly lower than that in the plasma. Thus, sodium transport is primarily by convection.[28] Similar mechanisms apply to calcium transport.[28,29]

For potassium, the diffusive clearance is about 17 ml/min in intermittent peritoneal dialysis[30] with mean MTAC between 12 and 16 ml/min in CAPD with 24 ml/min in the first hour.[31-33] It is likely that those values are high because of potassium output from mesothelial cells, promoted by low pH and/or

hyperosmolar solutions. This translates into a high "sieving" coefficient of potassium already reported as greater than 1.0.[34] One may conclude that charged electrolytes are transported at rates lower than expected by the molecular masses, regardless of the charge being positive or negative. For potassium, its output from intracellular sources in the initial residence phase is favored.

The standard peritoneal dialysis solution contains 1.75 mmol/L of Ca^{++} and 0.75 mmol/L of Mg^{++}. The normal ion concentrations of these electrolytes in the plasma are 1.25 mmol/L for Ca^{++} and 0.55 mmol/L for Mg^{++}. Therefore, peritoneal dialysis causes the mass transfer of these electrolytes, from the dialysate into the circulation, particularly when solutions which induce little convective transport are used. Positive Ca^{++} (0.96 mmol/4h) and Mg^{++} (0.21 mmol/4h) balances were found in stable patients on CAPD with glucose solutions at 1.36%.[35] The balance approaches zero when more concentrated glycosylated solutions (3.86%) are used for increasing blood convection to the dialysate, offsetting the diffusion in the opposite direction.[28,35] There are also solutions with low calcium (1.25 mmol/L to 1 mmol/L), to promote neutral or negative calcium balance.

Macromolecules

Macromolecules such as serum proteins are transported from the circulation to the peritoneal cavity at a rate lower than that of low MM solutes. Thus, their concentrations are generally low in the dialysate, without reaching equilibrium with the serum ones.

The transperitoneal transport of macromolecules occurs mainly by the large pores and, unlike the transport of low-weight solutes, depends largely on the peritoneum functional surface area, the transport of macromolecules is determined by both the surface area, as by the intrinsic permeability of the membrane, dependent on its size.[36] There are controversies as to the primary mechanism of macromolecule transport, whether it is convection induced by hydrostatic force[37] or size-restricted diffusion.[38,39]

In general, we can consider that the current knowledge regarding the transport of fluids and solutes across the peritoneum allowed the construction of mathematical models able to lead to understanding of several experimental and clinical situations involved in peritoneal dialysis, despite the lack of clarification regarding the physiological details which determine the transport components. Molecular analysis of tissue samples have enabled naming these components, and what we notice is that the mathematical models created before these findings can be considered visionaries. It is necessary to continue research in this field, since many issues still permeate our theoretical way of understanding the biological phenomena involved in peritoneal transport.

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