Chapter 2
Physiology of Peritoneal Dialysis

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Peritoneal Anatomy

The peritoneum is the serosal membrane that lines the peritoneal cavity. It has a surface area similar to that of body surface area, ranging 1–2 m^2 in adults. It consists of two parts: the parietal peritoneum which covers the abdominal wall and the diaphragm and the visceral peritoneum which covers the intra-abdominal organs. The parietal peritoneum accounts for 20% of the total peritoneal surface area. It receives blood supply from the lumbar, intercostal, and epigastric arteries and drains into the inferior vena cava. The visceral peritoneum accounts for 80% of the total peritoneal surface area. It receives blood supply from the mesenteric artery and drains into the portal system. The total peritoneal blood flow is estimated to range from 50 to 100 mL/min [1].

Peritoneal Membrane Histology

The peritoneal cavity is lined by a monolayer of mesothelial cells equipped with microvilli and covered by a thin layer of peritoneal fluid. The peritoneal fluid provides lubrication and allows free movement of visceral organs during respiration and peristalsis [2]. The mesothelial cells modulate the peritoneal microcirculation

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by secretion of vasodilators, e.g., prostaglandins, nitric oxide, and the vasoconstrictor endothelin. The mesothelial cells play an important role in the initiation of the local immune response through secretion of chemokines that regulates leukocyte infiltration [3]. Underneath the mesothelium is the interstitium, which is comprised of a gel-like matrix containing adipocytes, fibroblasts, collagen fibers, capillaries, nerves, and lymphatic vessels [2, 4].

Models of Peritoneal Transport

As solute and water move across the peritoneum from blood into the peritoneal cavity, they encounter six resistance barriers: the unstirred fluid layer overlying the endothelium of the peritoneal capillaries, the capillary endothelium, the endothelial basement membrane, the interstitial space, the mesothelium, and the unstirred fluid layer overlying the mesothelium [5]. Of these barriers, the two unstirred fluid layers and the mesothelium are thought to offer negligible resistance to solute and water transport; the major transport barrier is the capillary endothelium [6]. Several models have been proposed to explain the physiology of peritoneal transport, which we will discuss in details below.

The Three-Pore Model

Based on his observations regarding the nature of the transcapillary movement of solutes and water into the peritoneum, late Bengt Rippe postulated the existence of three pores of different sizes in the capillary endothelium. The "large pores" with a functional radius of 200–300 Å (20–30 nm) refer to wide interendothelial clefts. They allow transport of macromolecules such as albumin and other proteins and account for approximately 5–8% of the total pore area. The "small pores" with a functional radius of 40–60 Å (4–6 nm) refer to smaller clefts between endothelial cells. They allow transport of water and small solutes such as sodium, potassium, urea, and creatinine. Approximately 90–93% of the total pore area consists of the small pores, and they are responsible for the majority of fluid transport. Finally, Rippe postulated the existence of "ultrapores" with a functional radius of 2–4 Å (0.2–0.4 nm) which allow transport of water only. This prediction, made entirely of the basis of physiological observations, predated the discovery of aquaporins. The ultrasmall pore has since been demonstrated to be aquaporin 1 (AQP1) [7]. The ultrapores account for about 2% of the total pore area but can contribute up to 40% of the total capillary ultrafiltrate [6, 8, 9].

The Pore-Matrix Model

As noted above, the large and small pores are both interendothelial cell clefts. The pore-matrix model states that it is the density of the glycoprotein matrix on the luminal side of the cleft that determines whether a particular cleft functions as a large or small pore. At clefts endowed with a dense glycoprotein matrix, only small solutes can pass through the interendothelial space; these clefts function as "small pores." In contrast, clefts endowed with only a loose glycoprotein matrix allow both small solutes and macromolecules to pass through the interendothelial space; these clefts function as "large pores" (Fig. 2.1). Thus, in this model, there are no defined "small pores" or "large pores"; the difference in transport characteristics depends on the density of the glycoprotein matrix that fills the interendothelial space [10].

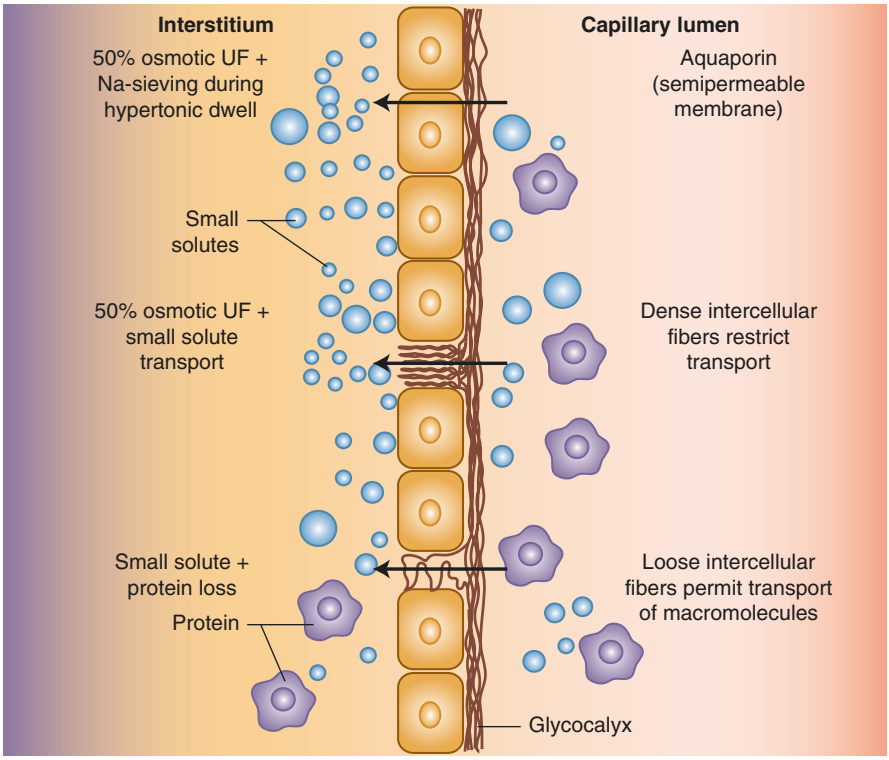

Fig. 2.1 Pore-matrix model. (Modified from Flessner [10])

The Distributed Model

In the distributed model, capillaries are assumed to be distributed uniformly throughout the interstitium at variable distances from the mesothelium. Solute transport is affected by the distance of each capillary from the mesothelium and the overall density of the peritoneal capillaries. The distance of each capillary from the mesothelium determines its relative contribution. The collective contribution of all the peritoneal capillaries determines the effective surface area for solute transport (Fig. 2.2). Therefore, two patients with the same anatomical peritoneal surface area could have different peritoneal vascularity and thus different effective peritoneal surface areas for solute transport. Within a given patient, the effective peritoneal surface area could vary depending on the clinical scenario. For example, inflammation, as seen in peritonitis or after prolonged exposure to high dextrose-containing fluid, increases vascularity and leads to increased effective peritoneal surface area. In this model, the degree of vascularity within the peritoneal membrane is the major

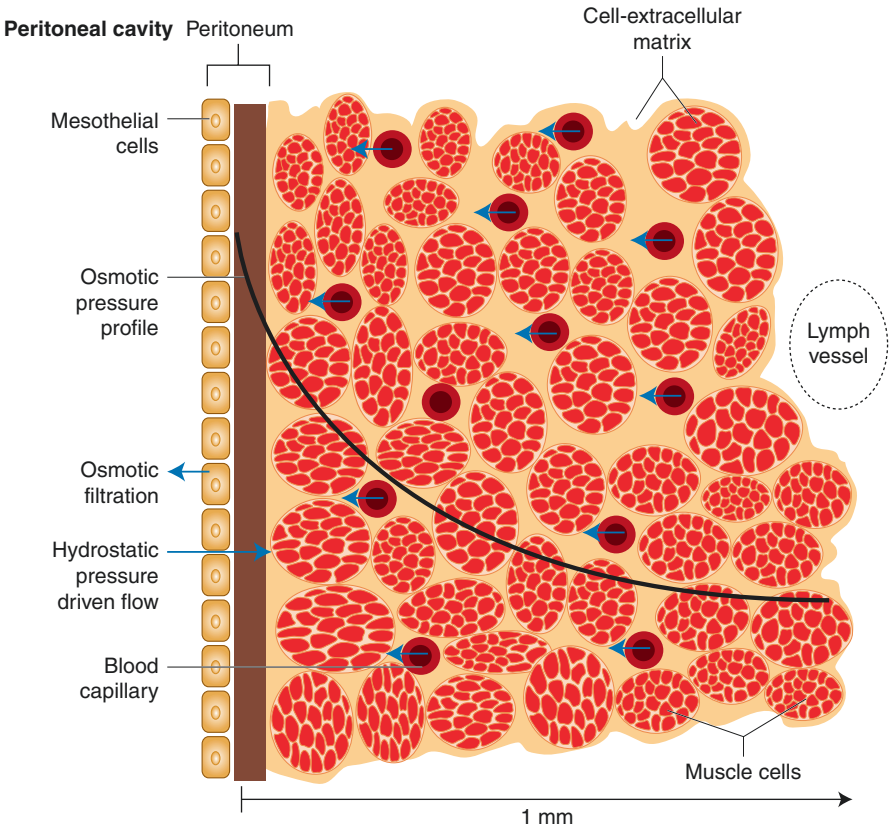

Fig. 2.2 Distributed model. (Modified from Flessner [10])

determinant of solute transport [9, 11, 12]. It must be emphasized that these three models of peritoneal transport are not mutually exclusive. Rather, they should be viewed as complementary with one another, forming a cohesive whole.

Physiology of Peritoneal Transport

Solute Transport

During peritoneal dialysis (PD), solutes are transported bidirectionally between the peritoneal capillary blood and the peritoneal cavity, mainly by diffusion and to a lesser extent by convection. Diffusion refers to the movement of solutes from a region of high concentration to a region of low concentration. For example, diffusion of urea from capillary blood to the peritoneal cavity is at its maximum at the start of a PD dwell, when the concentration of urea in the dialysate is zero. With ongoing diffusion, the concentration gradient across the peritoneal membrane diminishes. In addition to the concentration gradient, other factors affecting diffusion of solutes during PD include the total peritoneal surface area that is in contact with the dialysate, peritoneal vascularity, molecular weight of the solute, and intrinsic permeability of the peritoneal membrane. In clinical practice, increasing the fill volume recruits more peritoneal membrane to be in contact with dialysate, which then improves solute clearance. Keshaviah and colleagues studied the relationships between dialysate fill volume and the peritoneal transport constant (KoA) of small solutes in patients on chronic dialysis. They found that the KoA of urea, creatinine, and glucose increase in an almost linear fashion with fill volumes between 0.5 L and 2.0 L [13]. The authors attributed the increase in KoA to recruitment of more peritoneal surface area with larger fill volume.

Vasodilatory agents augment peritoneal solute clearance by increasing peritoneal capillary surface area and vascular permeability. Administration of intravenous dopamine or intraperitoneal nitroprusside has been shown to improve creatinine and urea clearances in animal models [14, 15]. Acute peritonitis is associated with an increase in small-solute transport, as a result of inflammation-induced increases in peritoneal capillary surface area and vascular permeability [16–18]. Permeability of the peritoneal membrane is an intrinsic property dependent on the number of pores per unit surface area, the density of the peritoneal capillaries, and the distance between capillaries and the mesothelium [1, 19]. It is different in each individual patient and can be characterized by using the peritoneal equilibration test.

Convective transport refers to the movement of solutes as a direct result of fluid movement into the peritoneal cavity (i.e., solvent drag). The magnitude of convective transport of a given solute is determined by transperitoneal ultrafiltration (UF) and the sieving coefficient of that solute [19]. The sieving coefficient is the fraction of the solute which passes through the membrane with the water flow, ranging between 0 and 1. Because no solutes pass through the aquaporins, there is no

convective transport at these sites. On the other hand, small solutes do move through the small and large pores resulting in significant convective transport.

Ultrafiltration

Ultrafiltration in PD is achieved either by creation of an osmotic gradient across the peritoneal membrane using crystalloid agents (e.g., dextrose, amino acids) or by inducing water flow with a colloidal agent (e.g., icodextrin). When using a crystalloid agent, the osmotic gradient is maximal at the start of a PD dwell; it diminishes with time due to dilution of the dialysate osmotic agent concentration and the absorption of the osmotic agent into lymphatics and tissues. This gradient can be maximized by using dialysate with a higher concentration of the osmotic agent (i.e., a higher dextrose concentration). Using 1.36%, 2.27%, and 3.86% anhydrous glucose dialysis solutions (equivalent to 1.5%, 2.5%, 4.25% dextrose solutions, respectively) for 6-hour dwells in patients on continuous ambulatory peritoneal dialysis (CAPD), Heimbürger and colleagues demonstrated a positive relationship between net UF rate and glucose concentration in the dialysis solution [20]. If icodextrin, a large molecule with a molecular weight (MW) of 13,000–19,000 Da, is used as the osmotic agent, the absorption is much slower compared to glucose (MW 180 Da), resulting in a more sustained osmotic gradient and UF.

In addition to the osmotic gradient, other factors affecting UF include the hydraulic conductance of the peritoneal membrane, the effective peritoneal surface area, the reflection coefficient of the osmotic agent, the hydrostatic pressure gradient, and the oncotic pressure gradient [1, 2]. The hydraulic conductance of the peritoneal membrane differs between patients and likely reflects the density of aquaporins versus small and large pores and the distribution of capillaries in the interstitium [1]. The reflection coefficient (σ) of a given solute at a particular pore, which ranges between 0 and 1, refers to the extent to which that solute is prevented from traversing that pore. A value of $\sigma = 1$ indicates that 100% of the solute gets reflected back from the membrane, i.e., that the membrane is completely impermeable to that solute [21]. In contrast, a value of $\sigma = 0$ suggests that the membrane is completely permeable to that solute. One would ideally wish to use an osmotic agent with a high reflection coefficient at the small pores. However, glucose has a low reflection coefficient of only 0.03 at the small pores; therefore, large concentrations are needed to achieve ultrafiltration [22]. In contrast, icodextrin has a hydrodynamic radius greater than the functional radius of the interendothelial cell clefts (the small pores) and consequently a high reflection coefficient [23]. Therefore, with prolonged dwell time, icodextrin is more effective in sustaining the osmotic gradient than glucose.

Under normal conditions, peritoneal capillary pressure is higher than the intraperitoneal pressure, creating a hydrostatic pressure gradient that favors movement of fluid from capillary blood into the peritoneal cavity. This gradient may be greater in a volume-expanded patient and lower in a volume-depleted patient [1]. Oncotic pressure acts to keep fluid in the blood and therefore counterbalances the

hydrostatic pressure and opposes UF. If the oncotic pressure is low, such as in hypoalbuminemic patients, UF may be greater than expected [1]. An increase in intraperitoneal pressure reduces the hydrostatic gradient and may lead to decreased UF. Wang and colleagues investigated the effect of increased dialysate fill volume on peritoneal fluid and solute transport in Sprague Dawley rats and found that an increase in dialysate fill volume resulted in higher intraperitoneal hydrostatic pressure and lower net UF [24]. Intraperitoneal pressure rises from the supine to the upright position and is highest when patients are seated. This is demonstrated in the study by Twardowski and colleagues, measuring the intra-abdominal pressure in 18 patients on CAPD in the supine, sitting, and upright positions [25].

Sodium Sieving

Heimburger and colleagues observed a decrease in dialysate sodium concentration during the initial period of a 6-hour PD dwell which is most prominent when using 3.86% anhydrous glucose solution [22]. Simultaneously, plasma sodium concentration increases slightly. This is due to the fact that aquaporins, which generate up to half of the total ultrafiltrate in response to glucose, are totally impermeable to sodium. Therefore, free water entering the peritoneal cavity dilutes the intraperitoneal sodium and decreases its concentration (lower D/P_{Na}), while the sodium reflected by the aquaporins remains in the blood. As seen in Fig. 2.3, this "dip" in dialysate sodium concentration is most marked at 60–90 minutes. Over time, as sodium begins to enter the dialysate via diffusion through the small pores, the dialysate sodium again rises [26]. This is clinically relevant, as repeated short dwell times with very hypertonic dialysate may result in hypernatremia and increased

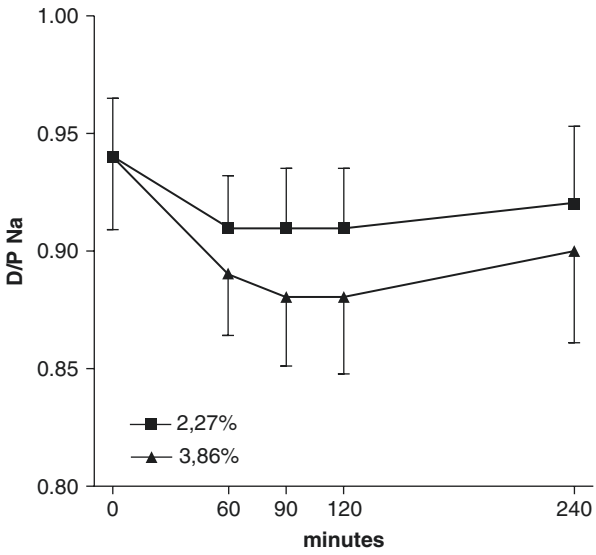

Fig. 2.3 The ratio of dialysate sodium concentration to plasma sodium concentration (D/P Na) in 2.27% and 3.86% dextrose solutions. The dialysate sodium concentration is the lowest (i.e., lowest D/P Na) at 60–90 minutes. Afterward, sodium then enters the dialysate via diffusion through the small pores, and dialysate sodium concentration rises gradually with time. (From Gomes et al. [26]. Reprinted with permission of Oxford University Press)

thirst sensation. Note that while this phenomenon has become known as sodium sieving, it is physiologically due to the *reflection* of sodium at the aquaporin.

Fluid Absorption

During PD, fluid is lost continuously from the peritoneal cavity via the lymphatic vessels and by absorption into the surrounding tissues of the abdominal wall. It is subsequently taken up by local lymphatics and peritoneal capillaries due to Starling forces [19, 27]. Lymphatic absorption mainly occurs through the lymphatic stomata in the diaphragm, which return peritoneal lymphatic drainage through the right lymphatic duct (70–80%) and the thoracic duct (20–30%) [28]. Lymphatic absorption is dependent on diaphragmatic movement, intraperitoneal pressure, and posture. In the setting of hyperventilation, lymphatic absorption increases. A rise in intraperitoneal pressure, such as with increased intraperitoneal volume, results in increased lymphatic absorption [28]. Upright posture is associated with a lower rate of lymphatic flow, presumable due to decreased contact of dialysate with the diaphragm [28, 29].

Studies have shown that the rate of macromolecular marker appearance in plasma is only approximately 10–20% of its disappearance rate from the peritoneal dialysate [30, 31]. Heimbürger and colleagues investigated the relative contributions of direct lymphatic absorption and absorption into tissues to the total peritoneal fluid absorption in CAPD patients with UF failure [31]. Using radioiodinated human serum albumin (RISA), they compared the disappearance rate of RISA from the dialysate with its appearance in the plasma, assuming that the rate of appearance of RISA in the plasma correlates with the lymphatic absorption rate. They found that the appearance rate of RISA in the plasma is much lower than its disappearance rate from the dialysate. In addition, the plasma RISA concentration continued to rise in an almost linear fashion for up to 16 hours after termination of the study dwell. Based on these findings, the authors concluded that direct lymphatic absorption is of only minor importance for the total fluid absorption in PD patients and that the interstitial compartment serves as a reservoir of macromolecules, which are then absorbed by local lymphatics. It is estimated that total fluid absorption from the peritoneal cavity in man occurs at a rate of 60–90 mL/hr, with 10–20 mL/hr flowing into lymphatics and 50–80 mL/hr flowing into the surrounding tissues [27, 32]. It should be recognized that this “bulk” fluid absorption results in loss of both UF and solute clearance, as the reabsorbed fluid had previously been equilibrated with solute.

Kinetic of a Single Peritoneal Dialysis Dwell

Taking into account both transcapillary UF of fluid *into* the peritoneal cavity and lymphatic reabsorption of fluid *from* the peritoneal cavity (so at any point in time, *net* UF represents the algebraic sum of transcapillary UF and lymphatic

reabsorption), the kinetics of a dwell may be summarized as follows: At the start of a PD dwell, transcapillary UF rate is at its maximum, and intraperitoneal volume increases quickly. Over time, the UF rate declines, as the osmotic gradient diminishes due to dialysate glucose being absorbed from the peritoneal cavity. Intraperitoneal volume continues to increase as fluid moves from the peritoneal capillaries into the peritoneal cavity, until the rate of lymphatic reabsorption equals the UF rate. Thus, to capture maximum net UF, one would ideally wish to drain the abdomen at this time. Once the rate of transcapillary UF falls below the rate of lymphatic reaborption, intraperitoneal volume begins to decline. When osmotic equilibrium between the blood and the dialysate is reached, UF ceases entirely; intraperitoneal volume continues to fall by virtue of lymphatic reabsorption.

Peritoneal Equilibration Test

The peritoneal equilibration test (PET) is used in clinical practice to evaluate the transport characteristics of the peritoneal membrane in an individual patient. It was first standardized by Twardowski and colleagues in the 1980s with regard to the sampling procedure, duration of the dwell, and evaluation of the results [33]. The test is done by instilling 2 L of 2.5% dextrose dialysate into an empty abdomen while the patient is supine, dwelling for 4 hours, with the drain volume recorded at the end. Dialysate samples are taken at 0, 2, and 4 hours, and a plasma sample is drawn at 2 hours. As illustrated in Fig. 2.4 and summarized in Table 2.1, patients are categorized into one of four transporter groups based on the dialysate to plasma creatinine ratio (D/P Cr): high, high average, low average, and low [33]. The ratio of dialysate glucose at 4 hours to dialysate glucose at time 0 (D/D_0 G) is used as a control to assess the accuracy of the PET. If D/P Cr and D/D_0 G differ by more than one transport category, the PET is likely inaccurate [33].

Patients who are high (rapid) transporters have the most rapid equilibration of creatinine because of high intrinsic membrane permeability. Similarly, dialysate glucose diffuses rapidly into the blood through the highly permeable membrane. Thus, these patients rapidly dissipate the glucose-induced osmotic gradient and have low ultrafiltration (Fig. 2.4). In contrast, low (slow) transporters have the slowest equilibration of creatinine, due to low membrane permeability. Dialysate glucose diffuses into blood slowly, they maintain the glucose-induced osmotic gradient longer, and they, therefore, have higher net UF. In the clinical setting, rapid transporters tend to have good small-solute clearance but may have suboptimal UF, while slow transporters tend to have good UF but may be deficient in small-solute clearance. Theoretically, rapid transporters would benefit from frequent short-duration dwells such that UF is maximized. In contrast, slow transporters would be better served with long-duration large-volume dwells, to maximize solute diffusion.

The net UF is calculated as the difference between the drain volume and the instilled volume and is used to evaluate UF capacity during the PET. The use of 4.25% dextrose solution instead of 2.5% dextrose solution – known as the modified

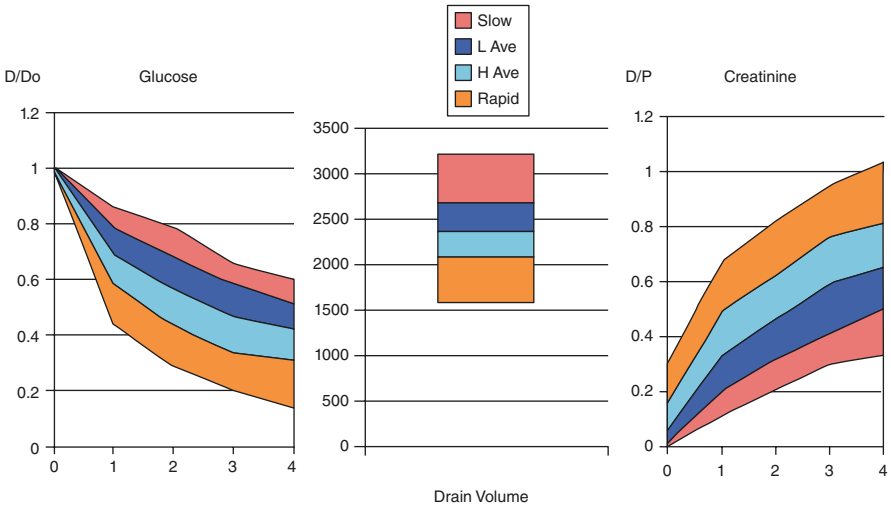

Fig. 2.4 Peritoneal equilibration test. (Adapted from Twardowski et al. [47])

Table 2.1 Classification of transporter groups

Transporter group	Standard PET with 2.5% dextrose D/P Cr	Standard PET with 2.5% dextrose D/D_0 G
High	> 0.81	< 0.26
High average	0.65–0.81	0.26–0.38
Low average	0.5–0.65	0.38–0.49
Low	< 0.5	> 0.49

PET peritoneal equilibration test, *D/P Cr* ratio of dialysate creatinine to plasma creatinine, D/D_0 *G* ratio of dialysate glucose at 4 hours to dialysate glucose at time 0

PET – is more sensitive in capturing patients with UF failure, because the change in UF volume is more pronounced when using a more hypertonic solution [34–36]. Solute transport characteristics do not differ between the standard and modified PETs [36]. However, using computer simulated modeling, Rippe demonstrated that the difference in UF volume over a 4-hour period between patients with normal UF capacity and those with UF failure is about 400 mL when using 4.25% dextrose solution compared to 200 mL with 2.5% dextrose solution [35]. Clinically, ultrafiltration failure is commonly defined as net UF < 400 mL after a 4-hour dwell using 4.25% dextrose solution, and the routine use of the modified PET rather than the standard test is therefore recommended by many PD experts [37].

A 1-hour "mini-PET" using 4.25% dextrose solution has been proposed by La Milia and colleagues to be a simple and fast method to evaluate solute transport and free water transport in patients on PD [38]. The authors performed standard and mini-PETs in 52 patients on PD using 4.25% dextrose solution. They found that

results of net UF and categorization of transport groups using the mini-PET correlate well with those obtained using the standard PET.

Changes in the Peritoneal Membrane with Time on Peritoneal Dialysis

Over time, morphological changes occur in the peritoneal membrane in patients on long-term PD. Prolonged exposure to glucose and glucose degradation products (GDP) leads to production of various proinflammatory and angiogenic factors, including nitric oxide (NO), transforming growth factor beta (TGF-β), and vascular endothelial growth factor (VEGF). These then lead to neo-angiogenesis of peritoneal capillaries, which in turn increases the effective peritoneal surface area with resultant augmentation of small-solute transport [39]. Comparing peritoneal biopsies obtained from healthy subjects (control), uremic patients not yet on PD, patients on short-term PD (< 18 months), and patients on long-term PD (> 18 months), Combet and colleagues demonstrated that nitric oxide synthase (NOS) activity and upregulation of VEGF are positively correlated with the duration of PD. Moreover, patients on long-term PD had a 2.5-fold increase in the density of peritoneal capillaries, compared to the control subjects [40].

Davies and colleagues examined the effects of dialysis on longitudinal changes in peritoneal kinetics using serial PETs to quantify changes in small-solute transport (D/P Cr) and UF over a period of 5 years. They found a significant increase in D/P Cr during the first 6 months of PD therapy, and there was a further increase over the next 4 years [41]. With increased small-solute transport across the peritoneal membrane, glucose diffuses into the peritoneal capillaries more rapidly, resulting in rapid loss of the osmotic gradient and a decline in net UF. Accordingly, Heimbürger and colleagues found significant correlations between time on PD and increasing D/P Cr as well as decreasing drained volume and D/D_0 G [42]. In a separate study, Heimburger and colleagues compared solute and fluid transport characteristics in CAPD patients with loss of UF capacity to that in patients with intact UF capacity. They found that there is a higher diffusive mass transport coefficient for small solutes (sodium, creatinine, urea, etc.) in patients who lost UF capacity, resulting in rapid absorption of glucose and loss of the osmotic driving force [43].

Long-term exposure to dialysis solution that is hyperosmotic, hyperglycemic, and acidic often causes chronic inflammation and injury to the peritoneal membrane. Yanez-Mo and colleagues demonstrated that peritoneal mesothelial cells undergo a transition from an epithelial phenotype to a mesenchymal phenotype, when they are subjected to peritoneal dialysis solution [44]. This process – referred to as epithelial to mesenchymal transition (EMT) – leads to mesothelial denudation, submesothelial fibrosis, and reduction of vascular permeability [45, 46]. This culminates in reduced permeability of the peritoneal membrane, leading to a decline in solute and fluid transport.

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