Various aspects of peritoneal water transport

Smit, W.

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Chapter 1

General Introduction
1. The peritoneal membrane

1.1. Anatomy

During peritoneal dialysis, the peritoneal cavity is used as a reservoir for the dialysis solution and the peritoneal membrane functions as a transport filter. The peritoneal membrane contours the majority of internal organs on the visceral site and covers the inner abdominal wall on the parietal site [1]. The anatomical surface of the peritoneum was previously considered to average 1 m² in post-mortem studies [2,3]. A recent estimation of the functional surface area, using computerized tomography scans, revealed a surface of about 0.55 ± 0.04 m² [4]. Under normal conditions the peritoneal cavity is lined with a thin layer of mesothelial cells and contains a small amount of fluid, which is most likely for lubrication of the internal organs to allow their movement [5]. About 60% of the peritoneal membrane consists of visceral peritoneum, 10% is parietal peritoneum and the remainder consists of mesentery and omentum. The contribution of the various parts of the peritoneum to solute transport in PD may be different. The role of the peritoneum covering the liver may be important, because of the close relationship with the liver sinusoids [6]. Evisceration in rats [7,8] and in a child after extensive resection of the small intestine [9] did not lead to important reduction in small solute transport. The diaphragmatic part of the peritoneum is especially involved in the absorption of solutes and fluid from the peritoneal cavity into the lymphatic system [10].

Blood supply of the parietal peritoneum is derived from arteries perfusing the abdominal and pelvical walls. The visceral peritoneum derives its arterial supply from mesenteric and coeliac arteries. Venous return on the parietal site is via the local systematic veins. The visceral veins drain into the portal vein [5]. Parietal lymphatic drainage is mainly through subdiaphragmatic gaps, which collect the lymph in the peritoneal diaphragmatic plexus. In addition some of the lymphatic drainage of the peritoneal cavity passes into the thoracic duct. Visceral lymphatics drain into parietal lymph nodes and from there to the thoracic duct [10].

1.2. Morphology

The peritoneal ultrastructure consists of a mesothelial cell layer, covering the interstitium. In the interstitium the peritoneal blood vessels are located. A monolayer of mesothelial cells, resting on a basement membrane contours the visceral and parietal peritoneum. Mesothelial cells are secretory cells, that produce among many other substances, lubricants, such as phosphatidylcholine and hyaluronan, to prevent friction of serosal surfaces [11]. Another secretion product is cancer antigen 125, a 220 kD glycoprotein, which can be detected in the
effluent of PD patients, but also in the supernatant of cultured mesothelial cells. Therefore it can be used as a marker for mesothelial mass or cell turnover [12-15]. The mesothelial layer is assumed to be insignificant as a transport barrier [16].

The interstitium is composed of loose connective tissue, containing bundles of collagen, fibroblasts and mast cells, within a mucopolysaccharide hydrogel [17]. In the interstitium, capillaries, venules and lymphatics are embedded. The restrictive ability of the interstitium is uncertain. No size selectivity was found in cat mesentery [18], but in vivo microscopy in rat mesentery suggested the opposite [19]. In humans the restriction of the interstitium to macromolecules is unclear [20]. It is possible that the interstitium adds some additional barrier to transcapillary transport resistance and slows the diffusion of solutes from the blood to the dialysis fluid [21].

The peritoneal capillaries contain one layer of endothelial cells, laying on a basement membrane. The endothelium is mainly of the continuous type, but a small amount of fenestrated capillaries have been found in human parietal peritoneum [22]. The peritoneal wall is considered to be the most important barrier for solute transport. This transport is generally assumed to be size-selective and occurs through a system of pores [23]. A model consisting of three sets of pores with different sizes has been postulated based on computer simulations [24-26]. According to this model, a large number of small pores is present, through which low molecular weight solutes and water pass. The radius is estimated to be about 40Å. The interendothelial clefts are considered as the anatomical equivalent of these pores. A few large pores, with a mean size of >150Å are present to allow transport of macromolecules, like serum proteins. Interendothelial gaps that can be induced by local application of some vasoactive substances, such as histamine, may be the anatomical equivalent [27,28]. The third set of pores have radii of <5Å and are therefore called ultra small pores. As a result of their extremely small size these pores are exclusively permeable to water, and not to solutes. This explains the effectiveness of a small solute such as glucose as osmotic agent. In addition the presence of the ultra small pores clarifies the observed dissociation of water and solute transport, usually observed in the first phase of a hypertonic dwell [29,30]. This set of pores has morphologically been identified as aquaporin-1 and is present in peritoneal capillaries and venules of humans [31-34] and rats [35-37].

1.3. Morphological changes with time on PD
After long-term PD marked alterations can be present in the peritoneal tissues. They consist of an increased thickness of the submesothelial compact collagenous zone of the parietal peritoneum, sometimes accompanied by loss of surface mesothelium [38,39]. Also in omental
tissues fibrosis can be found [40]. In addition, extensive vascular abnormalities have been described, including subendothelial hyalnosis of venules and arterioles [39,41]. Also an increased number of vessels has been found [40], especially in patients with ultrafiltration failure [39]. A correlation has also been described between the number of peritoneal vessels and the fibrotic alterations [40]. In patients with peritoneal sclerosis these fibrotic and vascular abnormalities are also present, but much more severe.

1.4. Functional characterization of the peritoneal membrane

Every membrane can be characterized by its surface area and its intrinsic permeability. A comparison has been made between the transport characteristics of urea and inulin in peritoneal dialysis and hemodialysis with cuprophan and cellulose-acetate membranes of a defined surface area. It appeared that the effective surface area of the peritoneal membrane, i.e. the part that actually participated in solute transport, had to be considerably less than the 1 m² that was found in anatomical studies [42]. This can be explained by the observation that under basal circumstances only about a quarter of the peritoneal capillaries is perfused [43]. Environmental changes can alter the blood flow, such as the instillation of dialysis fluid [44]. In addition, studies with intraperitoneally administered nitroprusside, have made it likely that the effective peritoneal surface area is mainly dependent on the number of perfused peritoneal capillaries [43,45-48]. This implies that the effective vascular surface area is not a static property of the peritoneum, but that it can vary depending on internal and external factors. The intrinsic permeability represents the size selectivity of the peritoneal membrane. For macromolecules it is mainly dependent on the large pore size. Because of the dynamic properties of the membrane, functional characterizations have been developed for surface area and permeability.

The functional characterization of the intrinsic permeability and the effective peritoneal surface area can be made by relating the transport of a solute (mass transfer area coefficient: MTAC, or clearance) to its free diffusion coefficient in water $D_w$. on a double logarithmic scale. The slope of this power-relationship, that is MTAC or clearance$= constant \cdot D_w^n$, represents the restriction coefficient [49-51]. A restriction coefficient of 1.0 implies that the diffusion rates of solutes are determined by their free diffusion coefficient in water. A higher restriction coefficient implies the presence of a size selective barrier. The higher the restriction coefficient, the lower the intrinsic permeability. The restriction coefficient to macromolecules averages 2.37 [50], based on the peritoneal clearances of the serum proteins β-2-microglobulin, albumin, IgG and α-2-macroglobulin. This indicates a restricted diffusion from macromolecules from the circulation to the peritoneal cavity. Since this restriction coefficient expresses size selectivity, it can be used to
characterize the peritoneal intrinsic permeability. The transport of low molecular weight solutes, such as urea, creatinine and urate, is expressed as mass transfer area coefficients (MTAC). The MTAC of a solute is the maximum theoretical clearance by diffusion at time zero, so before transport has actually started. A power relationship also exists when the MTACs of this small solutes are plotted against their molecular weights on a double logarithmic scale [52,53]. The slope of this regression line is 1.24 [50,54]. This implies that the transfer of these low molecular weight solutes across the peritoneum mainly occurs by diffusion, with minimal restriction of the size selectivity of the peritoneal membrane. Therefore, the MTAC of a small solute can be used as a representative of the effective peritoneal vascular surface area. A change in the MTAC of, for instance, creatinine in individual patients is likely to reflect a change in their anatomic or effective vascular surface area.
2. Peritoneal transport

During peritoneal dialysis solutes and water are transported. Water is removed from the circulation under influence of an osmotic gradient, provided by the dialysis solution. This dialysis solution generally induces a crystalloid osmotic pressure gradient (more detailed description of osmotic agents is given in section 3). Solute is removed by mechanisms of diffusion and convection. Diffusive transport is based on the difference in solute concentrations between two compartments. In peritoneal dialysis these compartments are the blood and the dialysis solution, separated by a membrane, the peritoneum. When free diffusion is present, no hindrance of the membrane is offered. In this case, the transport velocities will be linear to their free diffusion coefficients in water. When a membrane offers an additional hindrance to solutes, this is called restricted diffusion. Convective transport is determined by ultrafiltration rate, solute concentration and the sieving coefficient of the solute. The sieving coefficient is the quotient of the solute concentration in the ultrafiltrate and the circulation.

2.1. Solute transport

The transfer of low molecular weight solutes occurs mainly through the small pore system. The large pores are involved in the transport of macromolecules, like serum proteins. In peritoneal dialysis the transport of small solutes is mainly diffusive, whereas convective transport or solvent drag, becomes more important with increasing molecular weight [50,55-58]. Absorption of macromolecules from the peritoneal cavity to the circulation is linear in time, irrespective of size or concentration [59-61].

2.2. Fluid transport

Ultrafiltration is achieved by opposing mechanisms. Due to an osmotic pressure gradient between blood and dialysate, fluid transport is induced directed to the peritoneal cavity. This transcapillary ultrafiltration increases the intraperitoneal volume, which leads to increased uptake into the lymphatics. The transcapillary ultrafiltration is dependent of the hydrostatic pressure gradient, the colloid osmotic pressure gradient, the crystalloid osmotic pressure gradient, the hydraulic permeability of the peritoneal membrane and its effective surface area. The hydrostatic pressure gradient is determined by the difference between the pressure in the peritoneal capillaries and the intraperitoneal pressure. The pressure in the capillaries averages 17 mmHg [62]. The intraperitoneal pressure is dependent on posture, it can vary between 8 mmHg in supine position [63] and 20 mmHg in walking position [64] and it is also dependent on the
instilled volume [65]. The colloid osmotic pressure gradient that averages 26 mmHg in normals, but 21 mmHg in PD patients and is directed toward the circulation, and is induced by plasma proteins [62]. In dialysis solutions this pressure is negligible because of the low concentration of macromolecules. An exception is the icodextrin containing dialysate, see section 3. The crystalloid osmotic pressure gradient is determined by the osmotic agent that is applied, most frequently glucose. This is a very effective osmotic agent, despite its small size. The effectiveness of an osmotic agent depends on the resistance the peritoneal membrane exerts to its transport. This property is expressed as the osmotic reflection coefficient and can range from 0 in a free passage situation and 1, which implies total hindrance of a solute by an ideal semi-permeable membrane, Due to its small size of 2.9 Å, the reflection coefficient of glucose over the large pores is negligible and low over the small pores. Values ranging from 0.02 to 0.05 have been reported [66-68]. However, the reflection coefficient will be 1.0 over the ultra small pores, which explains the effectiveness of glucose as osmotic agent. The effect is most pronounced in the initial phase of a dwell, but decreases due to absorption of glucose, which leads to dissipation of the osmotic gradient [30,69]. The peritoneal water transport is mediated by the ultra small pores, or aquaporins [31,70]. These are permeable to water, but not to solutes. The function of these water channels can be estimated by the “sieving” of sodium during a hypertonic dwell [29,69,71]. The sodium concentration in blood and dialysate are similar, so a decrease in dialysate sodium concentration will occur in case of free water transport. However, a small concentration difference between dialysate and plasma concentration can cause diffusion of sodium from the circulation to the dialysate. In this situation a falsely decreased sodium sieving will be measured, incorrectly indicating loss of free water transport. To avoid this, a method to correct for sodium diffusion was developed by Zweers et al. [72]. In this method the amount of sodium present in the dialysate, solely due to diffusion was calculated using the MTAC of urate, because this was found to be similar to the MTAC of sodium [66]. This value could than be subtracted from the measured dialysate sodium concentration, resulting in the actual sodium sieving. Because the MTAC urate is not routinely assessed in a peritoneal permeability test, the correction method was also tested when the MTAC creatinine, which can easily be calculated from PET results, was used. It appeared that the use of the MTAC creatinine gave accurate results on actual sodium sieving [72]. Another manner to estimate free water transport is to determine the difference in net ultrafiltration between a 3.86% and a 1.36% solution. This is a rough indication, easy to calculate but time consuming [30]. Using a 3.86% glucose solution, the crystalloid osmotic pressure is much higher and exceeds the other pressure gradients; consequently the net ultrafiltration obtained, will be much more dependent on the number and function of the water
channels. Therefore, the difference in net ultrafiltration between a 3.86% and a 1.36% glucose solution will decrease in situations with impaired aquaporin-mediated water transport. The assumption that aquaporin-1 really is responsible for free water transport was tested in rats and rabbits. Aquaporin-1 was inhibited by administration of mercury-chloride intraperitoneally and as a result almost complete blockage of the sieving of sodium was present [35,73]. The contribution of the water-channel mediated water transport to the total fluid removal is estimated to be about 50%. These values, however, were assessed either by indirect methods [37,74], or with computer simulations [24,75]. A direct measurement of free water transport is described in chapter 5.

The net ultrafiltration is determined by transcapillary ultrafiltration and lymphatic absorption from the peritoneal cavity. Measurement of fluid absorption from the peritoneal cavity can only be done with indirect methods. The disappearance rate (clearance) of intraperitoneally administered macromolecular tracers, such as radio-iodated serum albumin (RISA) [69,76] or dextran 70 [77,78] can be used. The disappearance rates of these tracers are constant in time [79] and independent on molecular size [60]. Normal values in peritoneal permeability tests using a 1.36% glucose solution, ranged from 0.4 to 1.2 mL/min [80]. Increasing intraperitoneal pressure, either by external compression [63] or by increasing the administered dialysis volume [81], enhanced the disappearance rate of the volume marker substantially. This indirect measure can be applied as functional characterization of the effective lymphatic absorption rate. It implies that all pathways of peritoneal lymphatic drainage, both subdiaphragmatic and interstitial, are included in the definition.
3. Dialysis solutions

Glucose is the most widely used osmotic agent in peritoneal dialysis. However, since glucose is not an ideal solution, many other osmotic agents have been investigated. The most important ones will be discussed.

3.1. Glucose-based dialysis solutions

Glucose is the standard osmotic agent for peritoneal dialysis. It is a low molecular weight solute (MW 180 Dalton), available in different concentrations, that range from 70 to 220 mmol/L, with osmolarities ranging from 334 to 486 mosmol/L. Glucose yields high ultrafiltration. In addition, it is readily metabolized, not immunogenic, cheap and easy to manufacture. However, one of the disadvantages of glucose as a dialysis solution is its high absorption rate, which averages 66% of the instilled quantity during a four and 75% during a 6 hours exchange [69,80]. This can lead to hyperglycemia, hyperinsulinemia and to obesity, due to the high caloric load [82-84]. Because of the extensive uptake of intraperitoneally administered glucose, the peritoneal tissues are continuously exposed to extremely high glucose-concentrations. Not surprisingly, changes in peritoneal morphology closely resemble those observed in diabetic angiopathy [40,41,85,86].

Various toxic effects of glucose on peritoneal tissues have been described. Glucose damages the mesothelial cell layer by direct toxicity. This occurs either by inhibition of mesothelial cell proliferation, which is concentration-dependent and reversible with the withdrawal of glucose [87-89], or by the cytotoxic effect of glucose degradation products [90,91]. Glucose degradation products (GDPs) are formed during the heat-sterilization process of glucose. These GDPs are also classified as reactive carbonyl compounds and consist mainly of aldehydes and dicarboxyl compounds. The acute effects of GDPs on cell function of human peritoneal mesothelial cells include dose-dependent inhibition of cell growth, viability and cytokine release [92]. The most biologically active of all GDPs is 3,4-dideoxyglucosone-3-ene (3,4-DGE) [93]. When the concentration of glucose degradation products was lowered by sterilizing the glucose in a very acidic environment, separated from the electrolytes, this resulted in less cytotoxicity in vitro [90]. Another major disadvantage of GDPs is that they lead to the formation of advanced glycosylation end products [94]. GDPs trigger a chain of spontaneous non-enzymatic reactions with the amino group in peptides and proteins, referred as the Maillard reaction. The reaction between a carbonyl group and an amino group goes via reversibly formed Schiff's bases, which rearrange to intermediate Amadori products and may in the end result in the formation of stable carbohydrate cross-links between proteins, so called advanced glycated end-
products (AGEs) [95]. AGE modification preferentially occurs in long-lived structural proteins, such as collagen and eye-lens proteins, and is accelerated in diabetes mellitus. It is believed to contribute to diabetic complications, among which nephropathy. High plasma levels of AGE precursors and AGE-modified proteins are found also in non-diabetic renal failure patients [96]. This state of high reactivity in uremia is referred as "carbonyl stress" and it may be causative as well as a consequential factor in the progression of renal disease. Many detrimental effects of AGEs have been reported [97]. Accumulation of AGEs was described in peritoneal biopsies of non-diabetic patients on PD [98,99] which was already present after 3 months of PD. Monoclonal antibodies against AGEs were even more positive after 7 years of PD treatment, compared to a treatment duration of 3 years. This indicates a progressive accumulation with time on PD [99]. The accumulation of AGEs is most pronounced in the vascular wall. AGE formation leads to progressive cross-linking of collagenous tissues, inducing fibrosis [100,101]. Also vasoactive effects of AGEs on endothelial cells have been described [102]. They are probably responsible for the neoangiogenesis in patients with diabetic complications [103]. Most likely they are also able to cause neoangiogenesis in peritoneal tissues. Finally, the exposure to the high glucose concentrations can lead to a state of "pseudohypoxia" in the peritoneum. This leads to an effect on intracellular redox-status, which stimulates the release of growth factors, such as VEGF. VEGF induces neoangiogenesis [104,105]. With the formation of new vessels, enlargement of the effective vascular surface area occurs. This in turn will lead to increased solute transport, leading to a more rapid glucose absorption and the need for the use of higher glucose concentrations.

The detrimental effects of lactate buffered glucose solutions can be diminished by lowering the amount of GDPs in the dialysate. In new solutions the heat sterilization of glucose is performed in a more acidic environment, to decrease the formation of GDPs. This requires a double compartment bag, with mixing of their contents just before inflow. This results in a higher pH and less GDPs, and therefore better biocompatibility [106-108]. In ongoing studies higher dialysate CA-125 appearance rates were found after treatment with these solutions, and no differences in transport characteristics compared to the conventional glucose solutions were observed [109]. These solutions are now available commercially.

Peritoneal transport with glucose has been studied extensively, using 4 and 6 hour dwells with 1.36% glucose dwells in the standard peritoneal permeability analysis (SPA) [80] or with 2.27% glucose in the peritoneal equilibration test (PET) [110-112]. Recently the International Society of Peritoneal Dialysis (ISPD) committee on ultrafiltration failure suggested to perform the test with a 3.86% glucose solution, as this provides better information on ultrafiltration. This
is because the larger drained volume makes the result less subject to measurement errors, and is more sensitive to detect clinically significant ultrafiltration failure. In addition, the phenomenon of sodium sieving, associated with a hypertonic glucose solution, provides an assessment of free water transport [113].

3.2. Alternative solutions

3.2.1. Glucose polymers

Icodextrin is derived from hydrolyzed cornstarch and is a mixture of oligo- and polysaccharides, predominantly linked by α1-4 linkages and some α1-6 linkages. It has an average molecular weight of 16,800 Dalton, and induces colloid osmosis. Due to its high molecular weight it is only absorbed for 10-20% [60]. Glucose polymers are rapidly metabolized in the circulation by amylase. This leads to the production of maltose, which accumulates in the plasma, because no maltase is present in the circulation. This accumulation is a major disadvantage of the use of glucose polymers [114], although one single daily exchange of icodextrin results in a steady state level of maltose after about 10 days [115]. This level remains stable for months with no side effects and normalizes after the withdrawal of glucose polymer-based treatment [115].

The glucose polymer 7.5% lactate-buffered icodextrin solution is iso-osmotic to normal plasma. It induces ultrafiltration by colloid osmosis, and exerts its effect mainly over the small pores [116]. Icodextrin has a long-lasting effect, because of the low absorption of the osmotic agent [117]. Compared to a 3.86% glucose solution, similar net ultrafiltration was obtained using icodextrin in 8 hour dwells [118], and higher ultrafiltration was found in automated peritoneal dialysis, when icodextrin was used during the day [119].

Glucose polymers are particular effective in patients with ultrafiltration failure due to a large vascular surface area [116,120-122]. With the use of icodextrin the treatment of patients with ultrafiltration failure could be extended for about one year, whereas they otherwise would have been transferred to hemodialysis [120]. In peritonitis a transient state of a large effective vascular surface area is present, causing ultrafiltration failure due to high glucose absorption. The use of icodextrin in this situation has also been proven useful [122,123].

Icodextrin treatment is generally well tolerated, although some side-effects have been described. Skin rashes are the most frequent side-effects reported [124]. Also more severe reactions have been described, like acute allergic reactions [125] and interference with blood glucose measurements, leading to hypoglycaemia [126]. Recently a series of culture negative peritonitis was reported in patients using icodextrin [127-135]. This could, after extensive
research, be attributed to the presence of peptidoglycans in the dialysis solutions. These have now been omitted (unpublished data).

Reports on the biocompatibility of icodextrin are equivocal [136-140]. One in vitro study showed no difference in phagocytosis between icodextrin and glucose solutions at low pH [88], but another reported improved phagocytosis of polymorphonuclear neutrophils and monocytes after incubation with icodextrin [141]. In addition, some studies showed similar values for mesothelial cell mass markers [142,143], whereas another study showed a decrease of CA-125 appearance with the use of icodextrin compared to glucose [119] or enhanced apoptosis when icodextrin was used [144]. There was a beneficial effect on cell growth for icodextrin compared to glucose-solutions [106,140]. Nonetheless, icodextrin contains less glucose degradation products than a 1.36% glucose solution [145], and will therefore not lead to extensive AGE formation [146].

The peritoneal transport characteristics of icodextrin have been studied with standardized 4 hour dwells [74]. MTACs of small solutes and protein clearances were similar with icodextrin, compared to those obtained with glucose. Only the clearance of β-2-microglobulin was somewhat higher when icodextrin was used. This can be explained by the colloid osmotic pressure that exerts its effect over the small pores, leading to increased convective transport of this small protein, which can pass through these pores [116]. The increase of transcapillary ultrafiltration in time during a 4 hours dwell with icodextrin is linear, compared to the hyperbolic profile when glucose is used [74]. Therefore, because of the sustained ultrafiltration, icodextrin is most effective when used for the long dwells.

3.2.2. Amino acids
Amino acids as dialysis solutions have been developed to compensate for the loss of amino acids during peritoneal dialysis [147]. Because of their high absorption rates, averaging 80% [148], amino acids have been suggested for use in malnourished PD patients [149-151]. Plasma albumin levels increased and mortality rates decreased [151]. However, owing to the high absorption, a high nitrogen load limits the use to only once daily.

The solutions consist of a combination of different amino acids, buffered with lactate. The pH of this solution (6.7) is higher than the pH of glucose solutions. The effect on mesothelial cell cultures has been found less toxic [152,153] or similar to glucose [154].

The effects of amino acid solutions on peritoneal transport are equivocal [155]. Unchanged transport rates have been reported [156], but also slightly increased transport of small solutes and macromolecules was found, when a 1.1% amino acid solution was compared with a
1.36% glucose solution [157,158]. This difference could be ascribed to an increase in peritoneal blood flow.

3.2.3. Glycerol

Glycerol is the only osmotic agent that can totally replace glucose. It is a low molecular weight sugar alcohol of 92 Daltons, that is a normal physiological component of plasma. It is taken up by the liver for 70-90%, where it serves as an precursor for gluconeogenesis, and the remainder is metabolized by the kidneys and other tissues [159,160]. Long-term studies in stable patients, revealed good tolerance [161,162], although a high glycerol absorption can be responsible for a hyperosmolarity syndrome [160].

Glycerol was found to be less inhibitory on mesothelial cell proliferation in vitro than other osmotic agents [87,163]. An ex vivo study, however, suggested that glycerol-based dialysate inhibited phagocytosis of peritoneal macrophages more than glucose [164]. In patients starting with PD using only glycerol based solutions higher CA-125 concentrations after 1-3 months were found compared to patients starting with glucose-based solutions [165], suggesting that peritoneal viability is better preserved with glycerol.

Although glycerol is well tolerated, its use is limited because it induces less ultrafiltration per mOsmol than glucose [166], owing to its greater absorption, caused by the low molecular weight of glycerol (92 Da), compared to glucose (180 Da). In addition it has been assumed that a lower osmotic reflection coefficient compared to glucose, also contributed to this phenomenon. This possibility was investigated in chapter 9. The effect of a glycerol based dialysis solution on solute transport is similar to that of glucose solutions [167-169]. The effect on sodium sieving appeared to be very marked [167], suggesting an important role for the transcellular water channels.
Ultrafiltration failure (UFF) is a serious complication of peritoneal dialysis. It is characterized functionally by an insufficient ability to remove excess of fluid from the body. Eventually it can result in the necessity to prescribe a fluid restriction and to the use of higher dialysate glucose-concentrations, short cycle PD, or incidental ultrafiltration with a hemodialyzer. Sometimes it is the end of PD-treatment. A universal definition of UFF has been lacking for a long time, resulting in a wide variety of prevalence numbers. Some applied the inability to remain at a certain dry-weight as clinical definition. Others considered the use of more than 2 hypertonic bags per day as ultrafiltration failure [170-172]. Others used a definition based on a standardized exchange and considered UFF to be present, for instance when there was negative net ultrafiltration with a 1.36% glucose dwell [173,174]. The International Society of Peritoneal Dialysis (ISPD) committee on ultrafiltration failure has advised to perform a standardized test with 3.86% glucose, and considered a net ultrafiltration of less than 400 mL after a 4 hours dwell as UFF [113]. A cross sectional study in a small number of PD patients, using the 400 mL./4 hrs on 3.86% glucose definition reported a prevalence of 23% [174].

Although UFF can occur in any stage of peritoneal dialysis, it may develop in time [175,176], and is therefore especially important in long-term PD.

4.1. General causes of UFF

When a standardized dialysis dwell is used, a low drained volume can either be caused by mechanical problems or by peritoneal membrane failure. Non membrane related causes, such as catheter dislocation or subcutaneous leaks should be ruled out. There are different membrane-related causes of ultrafiltration failure. The presence of a large vascular surface area, characterized by a high mass transfer area coefficient (MTAC) or dialysate/plasma ratio of creatinine, is the major cause of ultrafiltration failure. It leads to high absorption rates of low molecular weight osmotic agents and therefore to a rapid disappearance of the osmotic gradient [177]. A large peritoneal surface area can be anatomic, due to neoangiogenesis in the peritoneum [40], or functional when more existing peritoneal microvessels are perfused. In addition, a high effective lymphatic absorption rate can be the cause of ultrafiltration failure, due to a decrease in intraperitoneal volume [178,179]. Impaired free water transport, caused by a decreased osmotic conductance to glucose, is also an important cause of ultrafiltration failure [30,34,180]. Osmotic conductance to glucose is the product of the peritoneal ultrafiltration coefficient \( L_p \delta \) and the reflection coefficient of glucose \( \sigma \) [181]. A reduced \( L_p \delta \times \sigma \) product will lead to a decrease in
peritoneal free water transport, and therefore to less sodium sieving. A very rare cause for ultrafiltration failure is the presence of an extremely small vascular surface area, e.g. in case of adhesions, where only a limited part of the peritoneum is available as a dialysis membrane [182,183]. A combination of factors may also be present.

4.2. Ultrafiltration failure in long-term PD

Ultrafiltration failure is the most frequent transport abnormality in long-term PD. Based on a clinical definition its prevalence increased from 3% after 1 year on PD to 31% for patients treated with PD for more than 6 years [178]. Ultrafiltration failure was the main reason for discontinuation of PD in 51% of patients after 6 years of PD treatment [184].

In long-term patients the presence of a large vascular surface area, as judged from fast transport rates of low molecular weight solutes, is by far the most frequent cause of ultrafiltration failure [181]. This fits well with the finding of an increased number of vessels in the peritoneal membrane of long-term PD patients [39,40]. High fluid absorption rates, measured as the clearance of intraperitoneally administered macromolecules, is regarded to be another important cause of ultrafiltration failure in long-term PD [185]. A decreased osmotic conductance to glucose estimated by the sieving of sodium is a third major cause of ultrafiltration failure [30,181].

A decreased osmotic conductance to glucose might in principle be due to a decreased peritoneal ultrafiltration coefficient or to a decreased aquaporin mediated water transport. As mentioned before, the ultrafiltration coefficient ($L_pS$) is the product of liquid permeability ($L_p$) and the peritoneal surface area (S). As S is increased in long-term PD, a marked reduction of $L_p$ would have to be present to explain the decreased osmotic conductance to glucose by a decreased $L_pS$. $L_p$ is unlikely to be low, as transport rates of low molecular weight solutes are high in long-term PD with ultrafiltration failure [186]. Therefore, it is more likely that a reduced $\sigma$ explains the decreased free water transport. $\sigma$ is to a large extent dependent on the function of peritoneal aquaporins, because these water channels are permeable to water and not to glucose. As they are also not permeable to sodium, the reduced peritoneal free water transport is likely to be caused by an impaired function of peritoneal aquaporin-1. The cause of this impairment is unlikely to be caused by a reduced number of water channels, because the expression of aquaporin-1 has been found normal in ultrafiltration failure [34]. Thus, the decreased water transport can most likely be attributed to a functional impairment of the water channels. The mechanism of this impairment is yet to be revealed. Various combinations of causes of ultrafiltration failure are present in long-term PD patients [174].
Long-term PD patients have lower mesothelial cell mass, resulting from lower dialysate CA-125 concentrations, in cross-sectional [187], as well as in longitudinal studies [142]. This is in accordance with the loss of mesothelial cells that has been found in long-term patients [39]. The finding that patients with low CA-125 had higher restriction coefficients than others [187], is also in accordance with the more severe fibrotic alterations in patients with absent mesothelium in their peritoneal biopsies [39].

4.3. Ultrafiltration failure in acute peritonitis

Infectious peritonitis is still a frequent complication of peritoneal dialysis. It is associated with morphological, as well as functional alterations, which are reversible in most cases. The morphological changes consist of destruction of the mesothelial cell layer [38,188-190]. In uncomplicated peritonitis this recovers within 10 days [189]. CA-125 levels have been found to be markedly increased in the acute phase of peritonitis, due to acute damage [191], followed by a second increase after a few days, reflecting peritoneal healing. After the recovery of peritonitis, CA-125 levels were similar to stable conditions. Stromal alterations during peritonitis consist of oedema and increased microvascular density. In the effluents increased concentrations of prostaglandins and cytokines are found, like IL-6 and TNFα [192].

Impaired ultrafiltration with CAPD is a transient phenomenon during acute peritonitis [52]. The high solute transport rates during acute peritonitis lead to a rapid dissipation of the osmotic gradient caused by augmented absorption of glucose from the peritoneal cavity [52,193-195]. The infection induced hyperpermeability is probably caused by increased secretion of vasoactive substances such as prostaglandins and cytokines [192,196] and an up-regulation of NO-synthase activity [70,195,197,198]. These mediators are likely to increase the number of perfused peritoneal capillaries, leading to a functional increment of the vascular peritoneal surface area. This leads to an increase in transcapillary ultrafiltration rate (TCUFR) in the first minutes of a dwell during peritonitis, compared to the stable situation [195]. In addition, vasodilation leads to a reduced size-selectivity, resulting in a decreased restriction coefficient to macromolecules [192]. Reports on alterations on lymphatic absorption rates in peritonitis are equivocal: increased [199] as well as similar [200] lymphatic absorption rates have been described in rats. Free water transport in peritonitis was investigated in rats by Combet et al. An impairment of sodium sieving was found in rats with acute peritonitis [70]. Since high diffusion rates were present in these rats, and no correction for sodium sieving was made, this could possibly have caused blunting of the D/P sodium ratio.
5. Aim and outline of the thesis

Peritoneal fluid transport is crucial for the success of peritoneal dialysis. Together with solute transport, it is subject to changes, either due to extrinsic or to intrinsic alterations. An extrinsic alteration can be the change to another dialysis solution. Another solution can have another osmotic effect, either due to a different crystalloid osmotic pressure gradient, a different reflection coefficient of the dialysis solution, or to another osmotic drive, like colloid osmosis. Intrinsic changes that can influence peritoneal fluid transport are chronic peritoneal membrane alterations, as seen in long-term peritoneal dialysis, and inflammation, as seen in acute CAPD peritonitis. The role of chronic inflammation or diabetes is uncertain.

The aim of this thesis was to analyze various aspects of peritoneal water transport, in different conditions in peritoneal dialysis patients.

In chapter 1 a review of data on peritoneal membrane status and peritoneal transport during peritoneal dialysis is described in the General Introduction. The current knowledge of changes in both is summarized. Also the different available dialysis solutions and their possible role in membrane alterations and transport characteristics are discussed. In addition a review is given of the causes of ultrafiltration failure in general, in long-term PD and in acute CAPD peritonitis.

Chapter 2 describes the comparison that was made between peritoneal function tests using a 1.36% glucose solution and a 3.86% glucose solution. Solute transport and fluid kinetics were assessed. In addition a comparison was made for the assessment of free water transport using the difference in net ultrafiltration of the two tests and the sodium sieving in a 3.86% glucose exchange.

In chapter 3 reference values for the peritoneal function test with 3.86% glucose are provided. Also an analysis of the causes of ultrafiltration failure in a subgroup of patients is given.

Chapter 4 offers a method to correct for sodium sieving in the assessment of sodium sieving, which is applicable in a peritoneal equilibration test (PET). This method was tested against the reference method, which requires the more advanced techniques of the standard peritoneal permeability analysis (SPA).

In chapter 5 a method was applied to quantify the volume of free water transport during a dwell. With this method sodium transport through the small pores was calculated, using dialysate sodium concentrations and intraperitoneal volumes obtained during one single SPA. This was then subtracted from the total transcapillary ultrafiltration, resulting in free water transport. The method was compared to other methods that estimate free water transport.
Chapter 6 describes free water transport and other transport characteristics in patients just starting with peritoneal dialysis. A comparison between diabetics and non-diabetics is made. Differences between the results in patients and in diabetic rats are discussed.

In chapter 7 a comparison was made in free water transport between patients with different types of fast transport status. Patients with acute CAPD peritonitis were compared with long-term patients, matched for MTAC creatinine and with patients with similar high transport rates at the start of PD treatment. The results are related to computer simulations by Rippe et al., and possible etiological factors are discussed.

Chapter 8 describes a multi-center study in which the prevalence of ultrafiltration failure in patients treated for more than 4 years in 11 dialysis centers in the Netherlands was investigated. Figures on the prevalence are given and an analysis of the causes of ultrafiltration failure is provided. Also a possible relation with peritonitis episodes or a chronic state of inflammation was examined.

In chapter 9 the peritoneal transport characteristics of a glycerol-containing dialysis solution were compared with a glucose-solution. Comparisons of sodium sieving and peritoneal reflection coefficients were made. Also direct cytotoxicity and the occurrence of hyperosmolarity as side effect were evaluated.

Chapter 10 describes the effects of treatment with non-glucose dialysis solutions in patients with severe ultrafiltration failure. A separate analysis was performed in patients with encapsulating peritoneal sclerosis. Differences between the peritoneal sclerosis and non-sclerosis patients are discussed.

Chapter 11 is a General Discussion, in which all aspects of peritoneal water transport are summarized and discussed. Chapter 12 is the Summary.

References

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