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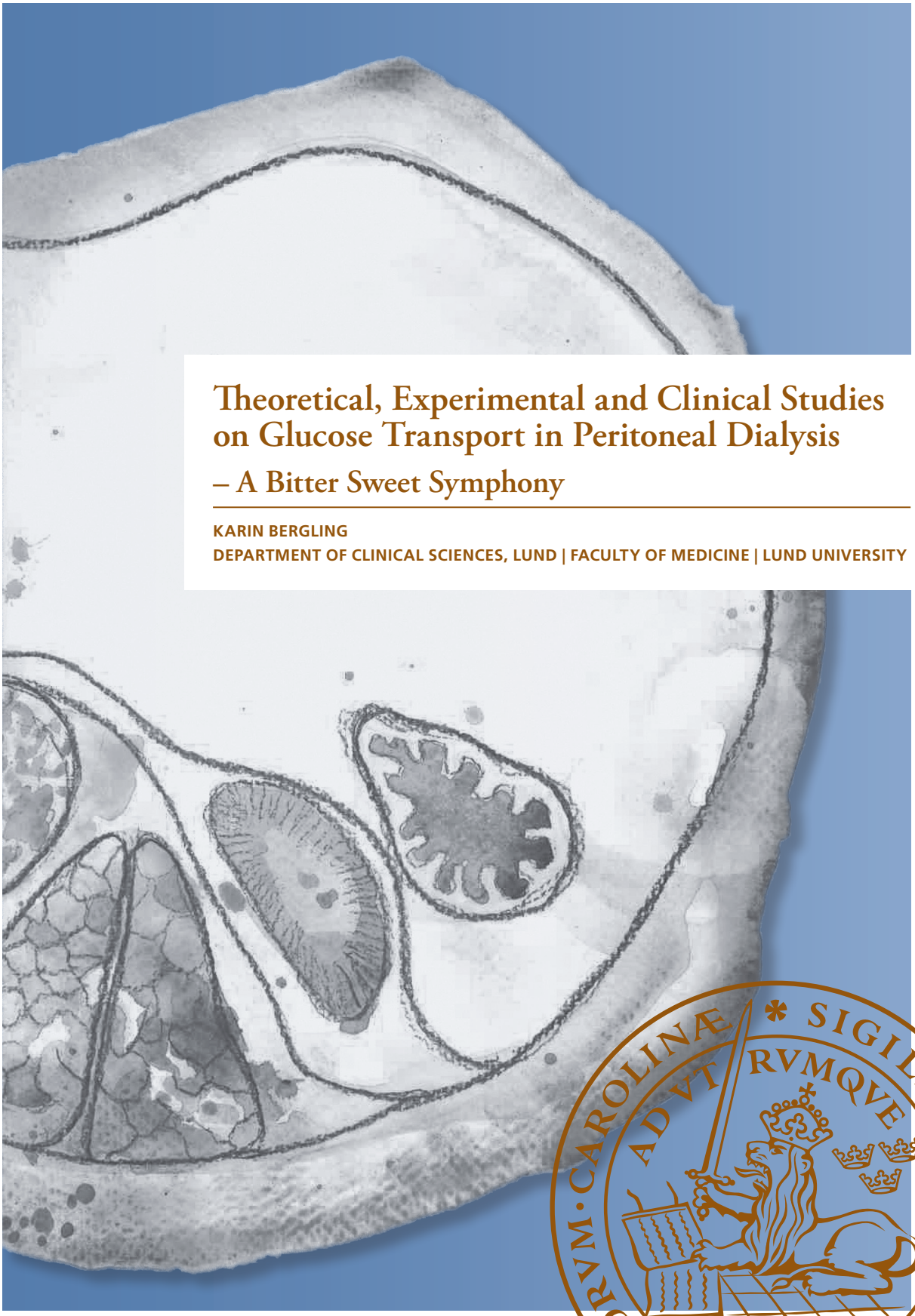

Theoretical, Experimental and Clinical Studies on Glucose Transport in Peritoneal Dialysis

– A Bitter Sweet Symphony

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Glucose-containing dialysis fluids are widely used in peritoneal dialysis, despite systemic glucose absorption leading to metabolic side effects. The overall aim of this thesis is to investigate methods to reduce systemic absorption of glucose, while maintaining effective treatments. Results from these clinical, experimental and theoretical studies indicate that glucose itself might affect the transport properties of the peritoneal membrane, and that transport is not only facilitated through paracellular pathways as previously thought, but also by trans-cellular glucose channels. In addition, by drug-induced blockage of these glucose transporters, glucose absorption was heavily reduced and the water removal improved during peritoneal dialysis in rats. These results strongly challenge previous knowledge and raise hope for improved peritoneal dialysis treatments in the future!

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– A Bitter Sweet Symphony

Karin Bergling

LUND
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DOCTORAL DISSERTATION

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Paper III demonstrates that intra-peritoneal administration of the facilitative glucose channel blocker phloretin reduces glucose absorption by 30% and increases water removal per gram of glucose absorbed by 50% during peritoneal dialysis in rats. This study is the first to suggest that glucose channels participate in transperitoneal glucose transport, a process previously thought to occur exclusively via paracellular pathways. These results imply that blockage of facilitative glucose channels could possibly serve as a future glucose sparing strategy in peritoneal dialysis.

Paper IV is a two-centre retrospective analysis of small solute diffusion capacities during 1-hour 1.36% and 3.86% glucose dwells. Small solute diffusion transfer rates were faster during hypertonic dwells, indicating that glucose per se increases peritoneal small solute diffusion capacity. Possibly, the observed deviation between pre-study predictions (paper I) and outcomes (paper II) could be explained by this effect. In paper IV, a phenomenological model adjusting for dialysate fluid glucose effectively reduced the suggested glucose-effect on diffusion capacities in one cohort, however results were not reproduceable in the control cohort.

Key words: Peritoneal dialysis, glucose, ultrafiltration efficiency, phloretin, GLUT-inhibition

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Peritoneal dialysis
– a first-class therapy,
for first-class patients
by first-class doctors

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Acknowledgements

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Abstract

Glucose-containing dialysis fluids are widely applied in peritoneal dialysis, despite systemic glucose absorption leading to metabolic side effects and glucose induced membrane damage. The overall aim of this thesis is to investigate methods to reduce systemic absorption and membrane exposure to glucose, while maintaining effective water removal. Paper I and II describes the first clinical pilot study of bimodal "optimized" treatment, where outcomes of consecutive 3.86% glucose water removal dwells and 0.1% glucose clearance dwells were compared to a "standard" 1.36% glucose treatment. Pre-trial computer-aided simulations predicted reduced glucose absorption during the optimized treatment while water removal and small solute clearances would be comparable to the reference treatment. In contrast, both water removal and clearances were enhanced by optimized treatments, while there was no significant difference in glucose absorption.

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Popular Scientific Summary

The kidneys are one of the body's sophisticated sewage plants. Around the clock, the kidneys clean the blood from waste products and keep the amount of body water in perfect balance by discarding excess water though urine. Unfortunately, the increasing prevalence of diabetes and high blood pressure along with a generally expanding lifespan increase the number of patients developing kidney failure. If the kidney function is impaired, patients tend to accumulate waste products and toxins in the blood and some cases experience declining urine volumes which could lead to overhydration. Left untreated, patients with severe kidney failure die. Some patients can be treated with peritoneal dialysis, a treatment where a dialysis fluid is pumped into an abdominal space, and the blood is cleaned as the dialysis fluid attracts water and waste products. The abdominal space is outlined by a thin membrane, called the peritoneal membrane, which acts as a filter between the blood and the dialysis fluid. After a while, often a few hours, the dialysis fluid is drained from the patient and replaced by fresh fluid. Exchange of fluid is performed a few times throughout the day, leading to a continuous cleansing of the blood. The dialysis treatment thereby compensates for the loss of kidney function and gives the patient a chance to continue living.

The dialysis fluid used during peritoneal dialysis contains high concentrations of glucose, where the glucose molecules attract water thereby drain the patient's blood stream from accumulated water. As glucose is a small molecule, the body will absorb some glucose during the dialysis treatment, which leads to metabolic side effects such as weight gain, diabetes type 2, and high blood cholesterol. The absorbed amount of sugar can correspond to 30% of the recommended daily intake of energy! In addition, the dialysis fluid glucose induces wear and tear of the peritoneal membrane, which eventually leads to loss of dialysis efficiency. The negative side effects of glucose in peritoneal dialysis fluids have been recognised for decades. Despite several attempts to develop glucose-free fluids, glucose-based fluids remain the most commonly used as they are inexpensive and well-tolerated by most patients. This doctoral thesis contains four scientific publications, all aiming to evaluate new strategies to reduce the absorption of glucose during peritoneal dialysis.

There are several dialysis fluids commercially available, in particular, the concentration of glucose differs and thereby how effectively the fluid absorb water from the patient. The same glucose strength is often used for all exchanges during

the day. Computer model calculations have suggested that it could be beneficial to use dialysis fluids with different glucose concentrations during the same day, where about half of the treatment utilizes high-concentration glucose fluids and thereby effectively absorb water, while the remaining treatment utilizes dialysis fluid with very low glucose concentrations, contribution only to waste removal. According to calculations presented in study I, such "optimized" treatments could reduce the amount of glucose absorbed by 10 grams per treatment compared to a commonly used standard treatment, where a low glucose fluid is used throughout the entire treatment. In study II, we performed the first-ever clinical study of these theoretical glucose sparing optimized treatments, predicted to reduce the amount of glucose absorbed while maintaining water removal and waste product clearance compared to the reference treatment. Twenty-one patients underwent an optimized and one reference treatment, and outcomes were compared. Contrary to the predicted results, the patients absorbed a similar amount of glucose during the two different treatments, while the water removal was increased during the optimized treatment, which means that the patients removed more water per absorbed gram of glucose during the optimized treatment. The removal of waste products was also improved slightly during the optimized treatment, which was unexpected. One can only speculate why the pre-study predictions did not agree with the results of the clinical study, but we suspect that there were faulty assumptions in the computer model used to design the treatment prescriptions.

Dialysis fluids contain low concentrations of the waste products the dialysis treatment aims to clear the blood from. This creates a concentration gradient between the blood and dialysis fluid, inducing diffusive transport between the blood and dialysis fluid. As the gradient is at its greatest immediately after fill of fresh fluid, the clearance rate of waste products is highest after fill and declines as equilibrium is reached. However, several studies on patients have demonstrated that the membrane itself also seems to facilitate faster diffusive transport after fill of fresh fluid, regardless of the concentration gradient of waste products. This alteration in diffusion capacity is almost twice as large directly after new fluid has been installed compared to a few hours later. In study IV, data from a Swedish and a Belgian patient dataset, collected during a short treatment with low glucose concentration and a consecutive high glucose fluid treatment were compared. In both cohorts, the membrane diffusion capacity of waste products was faster during the strong glucose treatment, which indicates that the glucose might affect how fast the peritoneal membrane transfers waste products. If this "glucose effect" exit, such effect could possibly explain the observed deviance between the predicted and actual results of study I and II, as the computer model utilized to predict results and design the optimized treatment included assumed constant membrane transport parameters, while the glucose concentration changed.

Another strategy for reducing the absorption of glucose is to block the transport between the dialysis fluid and the blood. In the dialysis research community, there

is a broad consensus that glucose is transported across the peritoneal membrane through spaces in between the cells that make up the membrane. In study III we performed experiments on rats, where the animals went through a peritoneal dialysis treatment with or without the addition of the drug phloretin in the dialysis fluid. Phloretin is a substance that occurs naturally in the bark of apple trees and has in previous research shown to block glucose channels. Such glucose channels have been demonstrated present in the peritoneal membrane. The rats which were treated with phloretin spiked dialysis fluid absorbed 30% less glucose compared to the rats with ordinary dialysis fluid. In addition, the phloretin-treated animals removed 50% more water during the treatment.

The results of the studies in this thesis suggest that glucose is transported not only in-between the cells of the peritoneal membrane, as previously thought, but also through cells. The results of study III are the first of their kind, as we were able to successfully block some absorption of sugar and extensively improve the water removal. Insights on how dialysis fluid glucose might influence the transport properties of the peritoneal membrane, could help refine computer models used in peritoneal dialysis research, improving future outcomes. Although comprehensive research is needed to test the safety and feasibility of glucose-blocking drugs in humans, and further studies are needed to evaluate the glucose sparing effects of optimized treatments, these studies raise hope for improved treatments in the future!

Populärvetenskaplig Sammanfattning

Njurarna är ett av kroppens sofistikerade reningsverk. Dag och natt rensar njurarna blodet från slaggprodukter och kissar ut precis rätt mängd urin för att hålla kroppens vätskemängd i balans. Dessvärre bidrar ökad förekomsten av diabetes, högt blodtryck och ständigt stigande ålder att fler och fler patienter drabbas av allvarlig njursvikt. Vid njursvikt klara njurarna ej längre klarar av att rena blodet och man kissar mindre urinmängder och riskerar att ansamla vätska i kroppen, vilket obehandlat leder kan leda till döden. En del patienter med njursvikt får behandling med peritonealdialys, en behandlingsform där blodet renas genom att en dialysvätska som drar till sig vatten och slaggprodukter pumpas in i bukhålan. Bukhålan omsluts av ett tunt membran, bukhinnan, där filtrering av vatten och slaggprodukter sker från blodet till dialysvätskan. Efter en tid, oftast mellan en till fyra timmar, töms dialysvätskan ut, nu fylld med slaggprodukter och vatten, och ny dialysvätska tappas in. Byten av dialysvätska sker flera gånger per dag vilket ger en kontinuerlig rening av blodet. Dialysbehandlingen ersätter därmed njurarnas funktion och ger patienten chans till fortsatt överlevnad.

Dialysvätskan som används vid peritonealdialys innehåller höga koncentrationer av socker. Sockermolekylernas uppgift är att via osmos suga åt sig vatten från blodet och därmed tömma kroppen på överskottsvätska. Då socker är en liten molekyl, absorberar kroppen socker från dialysvätskan under dialysbehandlingen, vilket ger upphov till biverkningar såsom viktuppgång, utveckling av diabetes typ 2 och stigande blodfetter. Den absorberade sockermängden kan motsvara hela 30% av det dagliga energiintaget! Dessutom bidrar dialysvätskans socker till att bukhinnan, det membran i bukhålan där transporten av vatten och slaggprodukter sker mellan blodet och dialysvätskan, slits ut vilket försämrar dialysbehandlingens effektivitet. Sockrets negativa bi-effekter varit kända sedan årtionden tillbaka, trots flera försök att utveckla alternativa dialysvätskor och reducera användandet av socker, kvarstår sockerbaserade dialysvätskor som de mest frekvent använda då de är billiga och tolereras väl av de flesta patienter. I den här doktorsavhandlingen ingår fyra vetenskapliga arbeten som syftar till att undersöka nya strategier för att minska absorptionen av socker under peritonealdialys.

Det finns flera varianter av dialysvätskor, framförallt skiljer sig koncentrationen av socker och därmed hur effektivt de drar vätska från patienten. Ofta används samma glukosstyrka till samtliga av dygnets dialysbyten, och blodrening och vätskedragning sker parallellt. Teoretiska beräkningar utförda med hjälp av en

datormodell har visat att det kan vara fördelaktigt att använda dialysvätskor med olika sockerhalt under samma behandling, där ungefär halva behandlingen sker med hög koncentration av socker som effektivt drar vätska, medan resterande behandlingen sker utan socker och då endast bidrar till blodreningen. Enligt beräkningar presenterade i Arbete I kan en sådan ”optimerad” behandling minska mängden absorberat socker med 10 gram per behandling jämfört med en vanligt förekommande referensbehandling, där en och samma svag sockerhalt används. I arbete II undersöks för första gången på människa huruvida dessa teoretiskt sockersparande behandlingar med två olika sockerstyrkor kan minska mängden absorberat socker och samtidigt ge lika mycket vätskedragning och blodrening som referensbehandlingen. Totalt genomgick 21 patienter den nya ”optimerade” behandlingen samt en referensbehandling och resultaten jämfördes. Tvärt emot de förväntade resultaten, absorberade patienterna lika mycket socker under de båda behandlingarna men vätskeborttaget var mer effektivt under den optimerade behandlingen, vilket innebar att patienterna blev av med mer vätska per absorberad mängd socker. Spännande nog verkade även blodreningen mer effektiv under den optimerade behandlingen. Det är omöjligt att helt fastställa varför resultaten inte överensstämde med de förväntade resultaten, men troligen beror skillnaden på felaktiga antaganden i den datormodell som användes för att designa studien.

Dialysvätskan innehåller låga koncentrationer av de ämnen som dialysen ämnar rensa blodet från, detta ger en koncentrationsgradient mellan blodet och dialysvätskan, vilket gör att slaggprodukter diffunderar in i dialysvätskan. Därmed är reningshastigheten som snabbast direkt efter intappning av ny vätska och avtar därefter successivt då dialysvätskan blir allt mer mättad. I flera tidigare studier på människa har det observerats att bukhinnans genomsläpplighet av små lösta ämnen såsom slaggprodukter och socker över bukhinnan verkar variera under ett dialysbyte. Blodreningen verkar vara nästan dubbelt så effektiv direkt efter intappning av ny vätska relativt efter ett par timmar, trots att koncentrationsgradienten av slaggprodukter är den samma. I arbete IV genomfördes beräkningar baserad på patientdata insamlad i Sverige och i Belgien, där samtliga patienter genomgått en behandling med svag sockerlösning, och en lika lång behandling med stark sockerlösning. I båda dataseten sågs en markant snabbare rening av slaggprodukter under behandling med den starka sockerlösningen relativt den svaga, vilket tyder på att dialysvätskanssocker påverkar hur genomsläppligt bukhinnan är. Om dessa resultat visar sig stämma, kan denna ”sockereffekt” möjligen förklara skillnaden i beräknade och faktiska resultat i studie I och II, där bukhinnans genomsläpplighet antogs konstant, medan sockermängden i dialysvätskan varierade.

En annan strategi för att minska kroppens upptag av socker är att blockera upptaget av socker över bukhinnan. I forskningsfältet råder koncensus kring att socker endast kan transporteras över bukhinnan mellan de celler som bygger upp bukhinnan. I arbete III genomfördes experiment på råttor, där råttorna genomgick en 60 minuter

lång peritonealdialys behandling med eller utan tillsats av läkemedlet phloretin i dialysvätskan. Phloretin är ett ämne som finns naturligt i exempelvis äppelträdsbark och i tidigare forskning visat sig blockera sockerkanaler som bland annat finns i bukhinnans celler. De råttor som fick tillsats av phloretin i dialysvätskan absorberade 30% mindre socker jämfört med råttorna i kontrollgruppen. Under behandlingen avlägsnade dialysen även 50% mer vätska efter tillsats av phloretin.

Resultaten från studierna i denna avhandling ger ledtrådar till hur dialysbehandlingens sockerinducerade biverkningar kan minskas och behandlingen effektiviseras. Med insikter om att sockerhalten i dialysvätskan kan påverka hur genomsläpplig bukhinnan är, kan optimerade behandlingar designas med högre precision. Resultaten från arbete III är de första av sitt slag, det verkar som att socker inte bara transporteras mellan celler i bukhinnan utan också via glukoskanaler, vilket är nya rön. Dessutom blockerade tillsats av phloretin i dialysvätskan effektivt dessa sockerkanaler vilket gav minskad sockerabsorption och ökad vätskedragning. Trots att det är lång väg från råttexperiment till läkemedel för människa väcker phloretin-studien hopp om förbättrade behandlingar framöver!

List of Papers

This thesis is based on the following publications or manuscripts, referred to in the text by their Roman numerals. All papers are found appended in the back of the thesis and permission to re-print have been obtained from the respective publishers.

Paper I

Bergling K, de Arteaga J, Ledesma F, Öberg CM. Optimized vs. Standard Automated Peritoneal Dialysis Regimens (OptiStAR): study protocol for a randomized controlled crossover trial. *Pilot Feasibility Stud*. 2020;6:81.

Paper II

Bergling K, de Arteaga J, Ledesma F, Öberg CM. Optimised versus standard automated peritoneal dialysis regimens pilot study (OptiStAR): A randomised controlled crossover trial. *Perit Dial Int*. 2022;42(6):615-621.

Paper III

Bergling K, Martus G, Öberg CM. Phloretin Improves Ultrafiltration and Reduces Glucose Absorption during Peritoneal Dialysis in Rats. *J Am Soc Nephrol*. 2022;33(10):1857-1863.

Paper IV

Bergling K, Martus G, Goffin E, Morelle J, Öberg CM. Influence of Dialysate Glucose on Small Solute Diffusion Capacity in Peritoneal Dialysis. Draft manuscript. 2022.

Abbreviations

RRT	renal replacement therapy
PD	peritoneal dialysis
APD	automated peritoneal dialysis
Å	ångström unit, 1 Å = 0.1 nm
AQP-1	aquaporin-1
FWT	free-water transport
IPV	intraperitoneal volume
MTAC	mass-transfer area coefficient
PS	permeability surface area-product
UF	ultrafiltration
LpS	ultrafiltration capacity
OCG	osmotic conductance to glucose
PET	peritoneal equilibration test
UFF	ultrafiltration failure
GDPs	glucose degeneration products
AGEs	advanced glycation end-products
SGLT	sodium glucose linked transporters (1 and 2)
GLUT	facultative glucose transporter (1 to 14)
CAPD	continuous ambulatory peritoneal dialysis

Introduction

Peritoneal Dialysis

The prevalence of end-stage kidney disease continues to rise worldwide (1, 2), with a parallel need for renal replacement therapies (RRT), such as kidney transplantation or dialysis. All forms of RRT are expensive, and require resources in the form of educated healthcare personnel, advanced healthcare infrastructure, and expensive materials and medications (3). Consequently, RRT is not available for all patients in need. Already in 2010, 2.6 million patients received some version of RRT, while the actual demand has been estimated to somewhere in-between 4.9 to 9.7 million in the same year (1). The number of patients receiving RRT is anticipated to double by 2030, to 5.4 million patients, mainly due to an increasing burden of hypertension and diabetes (4-6), conditions known to accelerate kidney failure, as well a growing and aging population and prolonged life expectancy of those already receiving RRT (7). Given the growing need RRT, it is evident that present dialysis therapies must be improved meet needs of the growing patient population, while keeping healthcare resources and expenditures in check.

Peritoneal dialysis (PD) is considered the first-choice dialysis modality in many parts of the world (8). Yet, only about 11% of the global dialysis population receive PD (9, 10), with large geographic variations (8). Patients receiving peritoneal dialysis are often able to perform manual exchanges of dialysis fluid or manage their automated machine-assisted PD (APD) treatment independently in their own home, promoting autonomy and reducing the need of health-care infrastructure and resources. In comparison with institution haemodialysis, outcomes of PD are comparable (11-14), and costs are generally lower (15, 16). Even when PD patients require in-home assistance by trained health-care personnel to perform their treatment, costs are still lower compared to institutional haemodialysis (17). PD is an advantageous RRT in many aspects. However, optimization regarding individualized treatments, improved treatment efficiency and reduction of side-effects are necessary to meet the demands of a growing end-stage renal disease population. In conclusion, it is clear that PD is currently underutilized, at least on a global scale, and a way to treat more patients using limited resources is to increase the number of patients receiving PD and prolonging their time on treatment.

Peritoneal Membrane Structure and Physiology

The peritoneal membrane, with an approximate size of 1 to 2 m^2 in adults (18-20), outlines the possible intra-peritoneal space, known as the peritoneal cavity. The peritoneum also serves as a conduit for nerves, and blood- and lymph vessels. During PD, the peritoneum essentially functions as a semi-permeable membrane, being structured in three adherent layers. First, at the innermost aspect of the peritoneal cavity, we find the mesothelial cell layer, covering a matrix of connective tissue. In the healthy, non-peritoneal dialysis patient, the mesothelial cells engage in maintaining homeostasis by secretion of cytokines, growth factors and production of a protective lubricative serum, reducing mechanic stress and serving as a first line of defence against infectious agents (21). The peritoneal interstitial matrix consists of various proteins such as collagens (22), fibroblasts and adipocytes (23), and provides structure to the membrane. Embedded in the sub-mesothelial matrix is a delicate network of blood and lymphatic vessels, supplying the peritoneal cells with nutrients while removing metabolic waste products. Importantly, the peritoneal microcirculation enables transport between the peritoneal cavity and the systemic circulation.

The peritoneal vascular network consists of microvascular resistance arterioles, fine capillary beds and postcapillary venules (24), and receives a total blood perfusion of somewhere in between 60 mL/min to 100 mL/min (25). The 0.5 μm thick capillary wall, consisting of a basal lamina and single layer of endothelial cells, is proposed to be the rate limiting barrier in dialysis induced transperitoneal transport, while the mesothelial cell layer and interstitial matrix are usually assumed to induce negligible hindrance. In addition to the pore-related theories presented herein, there are some alternative peritoneal membrane transport models where the interstitial matrix is considered to contribute to functional transport hindrance(26-29). The endothelial cells of the capillary wall are held together by specialized junction “protein bridges”, forming inter-endothelial filtration slits with an uniform width of 60-70 Å (6-7 nm) (24), enabling paracellular and transcapillary mass transfer of small molecules such as water, ions and creatinine. Although the intercellular clefts meander around the vessel in three dimensions, the intercellular clefts are usually modelled like straight cylindrical pores, with radial transport assumed neglectable, enabling one-dimensional transport equations to describe transport from the blood stream to the peritoneal cavity (30). These pores, herein denoted small pores, are estimated to represent about 0.1% of the total capillary wall surface area, having a strict radius of 40-50 Å (31), and enable the vast majority of passive, transmembrane transfer of water and smaller molecules.

Observation of transcapillary solute mass transfer indicates a bimodal size selectivity (32), with a high abundance of small and very few “large pores” facilitating transport of larger molecules. Larger molecules, such as the ellipsoid

shaped albumin molecule, with a molecular Stokes-Einstein radius of 35 Å, and thereby a theoretical diameter of about 70 Å should not be able to pass the small-pores due to its bulky size. Yet, molecules such as albumin with large Stokes-Einstein radius appear in the dialysis fluid. Contrary to the endothelial inter-cellular clefts, whose existence and distribution have been mapped through electron microscopy, no structure enabling peritoneal transmembrane transport of large molecules has been identified. Similarly, no structural pathways enabling large molecule transport has been found in the renal glomerular filtration membrane. However, as albumin is a ellipsoid molecule, it has been observed to slip through the glomerular membrane filtration slits (33, 34). In peritoneal dialysis, daily loss of albumin via PD could be approximately 4-6 g each day (35), reflecting a significant mass transfer of albumin. Based on clinical observation data, the large pores with a radius of 250 Å are enabling macromolecule transfer (36-38). During a PD dwell, the sieving coefficient of albumin can be estimated to 0.1, and a commonly observed clearance of albumin via PD is circa 0.1 mL/min (35).

In addition to small and large pores enabling transfer of solutes and water, the membrane hosts intracellular water-only pores called aquaporin-1 (AQP-1), allowing passive transport of water molecules across the peritoneal membrane (31, 38-40). Contrary to small and large pores, AQP-1 channels appear to be strictly water-selective, causing passive, osmotically driven free-water transport (FWT) (41-44). In summary, according to present knowledge, the peritoneal membrane has three different pathways for water transport of which two also enable solute transport, constructing a porous, heteroselective membrane (45).

Peritoneal Transport Mechanisms

During PD, the semi-permeable peritoneal membrane separates the blood compartment from the dialysate compartment, and we can herewith assume a two-compartment model (46), with a blood pool concentration of solute i, $C_{P,i}$ and dialysate compartment with solute concentration $C_{D,i}$.

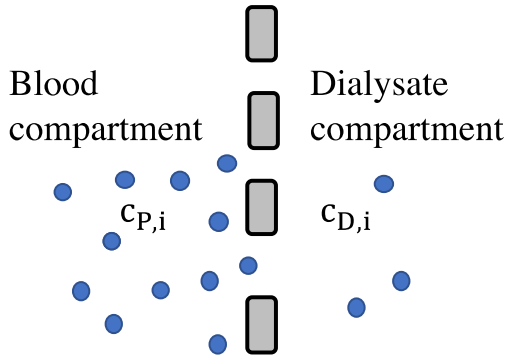

Figure 1. A two-compartment model of the blood stream and peritoneal cavity, with peritoneal membrane separating them.

Small Solute Mass Transfer – Diffusion

Peritoneal mass transfer of small molecules such as creatinine, urea and potassium, occurs mainly via diffusive transport. Diffusion arises due to Brownian motion, thermally induced random irregular movement or "wiggling" of molecular compounds, such as ions, water or gas particles (47, 48). As these wiggling molecules collide with each other, change in their trajectories eventually causes spread from areas of high concentrations towards areas of lower concentrations, due to gradual decrease in frequency of collisions altering the movement trajectory. The total net flux of a molecule down its concentration gradient, induced by Brownian motion, is denoted the process of diffusion (49). As time passes, concentration gradients in a medium vanish, ultimately reaching complete equilibrium and diffusion force termination.

The built-in characteristics of a solute i and the medium in which diffusion occurs are described by the solute's diffusion coefficient D, reflecting the average velocity of the diffusing solute, in response to a concentration difference across some distance x in the medium, as described by the Einstein relation (47). If there is no concentration difference the solute is equally likely to go in any direction, and the average velocity is zero. The diffusion coefficient D_i depends on the solute radius a_i, temperature T and viscosity η of the medium. There are multiple variants of the Einstein relation equation depending on the characteristics of the diffusing molecule and medium properties, however, most applicable in the case of transmembrane mass transfer, where transport is assumed to occur in a small pore with laminar fluid flow, is the Stokes-Einstein equation;

$$D_i = \frac{RT}{6\pi\eta a_i} \quad (1)$$

where R is the gas constant. As stated by Fick's first law (49), the quantity of solute i, (q_i) transferred across the membrane with an area facilitating transport A and membrane thickness dx, at each time unit dt, determines the diffusive mass flow J_i during influence of a concentration gradient $\frac{dc_i}{dx}$,

$$J_i = \frac{dq_i}{dt} = \frac{RT}{6\pi\eta a_i} A \frac{dc_i}{dx} = D_i A \frac{dc_i}{dx} \quad (2)$$

If the system allows complete mass conservation, i.e. no chemical reactions alter solute mass or alternate solute transport processes occur, Fick's first law can be extended to predict solute concentration accumulation or depletion with respect to time, as stated in Fick's second law.

As the peritoneal membrane is a porous, semipermeable membrane, with two distinct pore types thought to enable solute transfer, transmembrane diffusion is also limited by the membrane permeability of the specific solute, i.e. effects of steric restrictions and hydrodynamic interactions between the transported molecule and the pore wall (30, 50). Due to the passive nature of the peritoneal transport, being governed by convection and the laws of diffusion, transmembrane flow can be bi-directional; the direction of flow is therefore not only determined by the direction and extent of the concentration gradient, but also the direction and magnitude of water transport.

The ability of the peritoneal membrane to permit small solute diffusion clearance for a particular solute is quantified in terms of diffusion capacity, defined as the theoretical maximum diffusive clearance rate, occurring whenever the concentration on one side of the membrane is exactly zero (and that of the other side is non-zero). In case of small solutes such as creatinine, urea and glucose, it is best expressed in units of mL/min. The diffusion capacity of creatinine, urea and glucose is highly individual (51), and also changes with time on dialysis, as will be discussed later on. Diffusion capacity is determined by the membrane permeability of the specific solute, and the area to thickness ratio of the membrane area in contact with dialysis fluid, $\frac{A_0}{dx}$. In the clinic, the area enabling diffusion is difficult to quantify, because it is dependent on the intraperitoneal volume (IPV), as well as the extent of tissue vascularisation and blood perfusion (52). For example, it has been suggested that only approximately 25-50% of the available peritoneal capillaries are perfused (53, 54). For simplification reasons, the membrane area and the permeability coefficient are grouped into a more convenient parameter – the diffusion capacity – sometimes called the mass-transfer area coefficient (MTAC), or commonly used permeability

surface area-product (PS). In line with Fick's first law (49), the diffusive transfer of mass, driven by the solute concentration gradient, is calculated by

$$q_i = -MTAC_i(c_{D,i} - c_{P,i}) \quad (3)$$

Hence, the maximal diffusive clearance rate, or MTAC, reflects the mass transfer immediately after fresh dialysis fluid fill, when in general, the solute concentration gradient across the membrane is at its greatest. This is only true under the assumption that solute transport during PD is not blood flow limited (55).

Small Solute Mass Transfer – Convection

Convective small solute transfer occurs as an effect of solvent drag, as the bulk flow of water across small and large pores drags small solutes through the peritoneal membrane. Hence, convective small solute transfer in PD is mainly dependent on osmotically induced water transport. However, the convective solute mass transfer does not directly reflect the rate of small and large pore water flux, as membrane permeability to the specific molecule might alter passage. The convective hindrance factor has many similarities with the diffusive hindrance factor, as the main factor limiting passage is the molecular size (50). Convective flow also appears in the direction towards the bloodstream, via lymphatic absorption. The large size of lymphatic vessels compared to inter-endothelial clefts means that this transport is not size-selective, at least for the majority of solutes.

Water Transport

Effective water removal is gaining more and more clinical interest (56-58), as the previous focus on target-based toxin removal seems unwarranted since small solute transport (Kt/V urea, weekly creatinine clearance etc.) appear to have little influence on patient outcomes (59, 60). Water removal in PD occurs by a complex interplay of physical forces; osmotic and, oncotic pressure gradients and , to a small extent, also the hydrostatic capillary-to-intraperitoneal pressure gradient alter the magnitude of transcapillary water transport (61). There are four suggested pathways of water transfer; through small and large pores, transcellular AQP-1 channels as FWT, and intraperitoneal lymphatic drainage (62). The process of transcapillary water transport in the peritoneal dialysis context is commonly denoted ultrafiltration (UF), *i.e.* the net flow of water absorbed from the patients' bloodstream into the peritoneal cavity. The word UF origins from haemodialysis, although it there refers to the removal of water by the development of a hydrostatic rather than osmotic pressure difference across the membrane.

The main force driving transcapillary UF is either crystalloid osmosis, induced by high contents of glucose, or colloid osmosis induced by large molecules *e.g.* polyglucose icodextrin in the fresh dialysate fluid (63). Osmosis is a passive transport mechanism, very similar to diffusion where water molecules transfer from an area of high concentration to low concentration. Water is a small molecule, passing the peritoneal membrane without any known significant hindrance. In the case of our two-compartment model, the water molecules will transfer due to osmosis between the two compartments until equilibrium (*i.e.* the same solute concentration on each side of the membrane) has been reached.

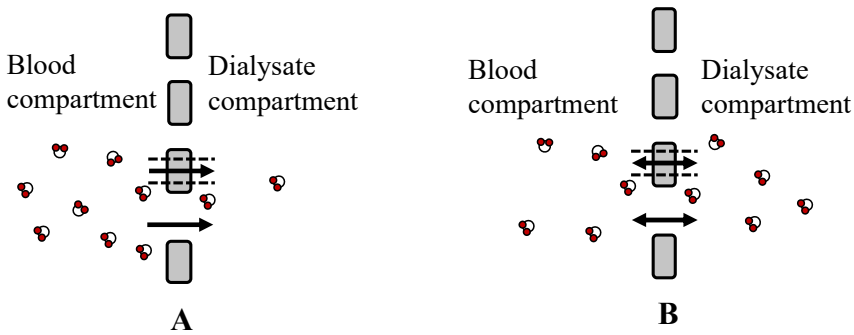

Figure 2. A. Uni-directional water flow through paracellular and transcellular pathways. **B.** Bi-directional flow across the membrane as osmotic forces ceases.

All commercially available dialysis fluids contain glucose or other osmotic agents such as the polymer mixture icodextrin, in order induce an osmotic pressure and produce UF. As seen in Figure 3, the osmotic agent displaces the water molecules, inducing osmotic forces and thereby UF which act to equalize the concentrations of the osmotic agent on each side of the membrane.

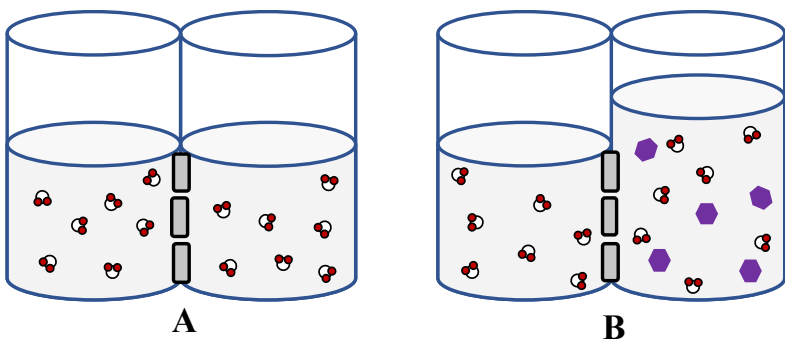

Figure 3. A. Equilibrium of water without osmotic agent present. **B.** Equilibrium of water-filled compartments, with osmotic agent (purple hexagons) impermeable to the membrane in one.

However, glucose - the most commonly used osmotic agent - is a small molecule and will therefore eventually dissipate from the dialysate fluid into the blood stream, as an effect of the transmembrane concentration gradient and diffusion mechanism. This leads to treatment induced glucose absorption and eventually loss of osmotic force. Hence, the crystalloid osmotic pressure is at its greatest in the beginning of the dwell, as reflected in changing rates of UF during dwell time (62).

The water permeability of the membrane, denoted the ultrafiltration coefficient (LpS), is a product of the hydraulic permeability Lp, and the peritoneal surface S available for water transport. It is defined as the maximal water clearance rate per unit pressure. In the case of peritoneal dialysis, LpS reflects the maximal UF rate an osmotic agent can elicit per mmol/L and is therefore also referred to as the UF capacity of the membrane. The *osmotic conductance* is a similar concept, which – by multiplication with the osmotic reflection coefficient (σ_o) - takes into account the fact that an osmotic agent is not 100% effective to produce osmosis. For example, glucose has a σ_o of about 5% and, the osmotic conductance to glucose (OCG) in the size order of about 4 μL/min/mmHg in PD patients (64-66). Small pores account for about 90% of the peritoneal membrane LpS, while large pores represent 8% of LpS, leaving only 2% of LpS to ultra-small AQP-1 mediated FWT (45). However, FWT has been observed to contribute to between 35-44% of the total UF in humans during short dwells (42-44, 67). This discrepancy is explained by the reflection coefficient (σ) of glucose, being 100% for AQP-1 compared to 3% for small solutes, inducing about 30 times larger osmotic force across the pore and thereby effective UF (45). The large-pore contribution to volumetric flow is almost negligible, as the glucose osmotic reflection coefficient across large pores (σ_L) is only <0.01%. Since FWT contributes to UF, but not to solute mass transfer, FWT induces a phenomenon called solute sieving. Sodium sieving occurs during the initial part of the dwell when UF rates are sufficiently high to counteract sodium diffusion, diluting sodium and other dialysate solutes (40).

Peritoneal Membrane Evaluation Methods

There is a wide consensus of the clinical benefits of frequent and adequate testing of peritoneal membrane transport functionality (68). The original gold standard membrane evaluation method, the peritoneal equilibration test (PET) (69), is a resource consuming clinical test, requiring several samples of the dialysis fluid over a time period of four hours. The outcomes, especially the 4-h dialysate to plasma ratio of creatinine, is used to classify patients into solute transport categories, which could be useful to design treatment regimens and predict outcomes. Since the publication of the 4-h PET in the late 1970s, several membrane estimation methods have been proposed, often sharing simplified data collection protocols. For example,

small solute MTAC can be estimated using the isovolumetric Henderson-Nolph method (70),

$$MTAC_i = \frac{IPV(t)}{t} ln \frac{c_{P,i} - c_{D,i}(0)}{c_{P,i} - c_{D,i}(t)} \quad (4)$$

which is further developed by addition of terms accounting for some influx of UF (71),

$$MTAC_i = \frac{IPV(t)}{t} ln \frac{IPV(0)(c_{P,i} - c_{D,i}(0))}{IPV(t)(c_{P,i} - c_{D,i}(t))} \quad (5)$$

and eventually even further advanced by Waniewski *et al.*(72, 73) by the addition of a convective correction factor F and utilization of the mean IPV,

$$MTAC_i = \frac{IPV_{mean}}{t} ln \frac{IPV(0)^{1-F}(c_{P,i} - c_{D,i}(0))}{IPV(t)^{1-F}(c_{P,i} - c_{D,i}(t))} \quad (6)$$

Other MTAC estimation methods requiring computer-aided calculations are the three-pore model, (described in the Methods and Materials section of this thesis) and the recently published isocratic model (74). The isocratic MTAC estimation method is an expansion of the Henderson-Nolph equation, Eq. 4, with the addition of an isocratic convective flow, contributing to IPV by

$$IPV(t) = IPV(0) + J_v t \quad (7)$$

where half of the isocratic flow J_v is considered convective, contributing to small solute mass transfer and the remaining water flow is free-water transport. Thus, a limitation of this model is that it does not take into account variations in AQP1 number and function (75). Moreover, convective transport of small solutes like glucose were assumed to be unhindered (W= 1) and MTAC was continuously scaled with respect to recruited peritoneal membrane area in accordance with the square

cube law. Finally, the differential equation describing change in $c_{D,i}$ with respect to time is

$$\frac{dc}{dt} = \frac{1}{IPV(t)}\left(\left[\frac{IPV(t)}{IPV(0)}\right]^{\frac{2}{3}} MTAC_i\left(c_{P,i} - c_{D,i}\right) + J_v \frac{W}{2}\frac{\left(c_{P,i} + c_{D,i}\right)}{2} - J_v c_{D,i}\right) \quad (8)$$

The isocratic MTAC estimation method has so far only been applied in a rat model, with good agreement compared to MTACs estimated using the three-pore model (74).

Dialysis Induced Alterations in Membrane Function and Structure

The efficiency of peritoneal solute and water transport is as described earlier in this thesis, a product of numerous factors, such as the solute concentration and osmotic gradient, transcapillary pressures, membrane permeability and the area available for transport. Several clinical observation studies have witnessed both long- and short-term alterations in the transport properties of the membrane, effecting both small solute and water removal efficiency (76-80).

Clinical observational studies have demonstrated that small solute transport properties are subjected to change during long-term PD (78, 81). In general, small solute mass transfer rate increases with time on PD, making patients acquire a faster transport type. Also, there is evidence to suggest that the small solute diffusion capacity varies also during the course of a single dwell, being two times larger initially and then decaying exponentially during the first 1-2 hours of the dwell (82-84). The diffusion capacity, frequently assumed to describe a static membrane attribute, thus appears to be much more dynamic than is commonly thought, which could lead to faulty conclusions in the study of treatment outcomes if assumed constant.

Loss of ultrafiltration is a common phenomenon that reduces the effectiveness of PD, alongside changes in small solute transfer rates, with prevalence rising with treatment duration (76, 80, 85). Although clinical fluid accumulation is multifactorial, depending on UF volume, fluid intake and urinary output, loss of UF ability is a common reason for PD technique failure. UF failure (UFF), usually defined as less than 400 mL drained UF after a 4-hour 3.86%/4.25% glucose dwell (68, 86), is thought to occur due to four mechanisms (UFF type 1 to 4), where a

functional “large vascular surface” (UFF type 1), inducing faster small solute transport and dissipation of glucose induced osmotic force, is typically described to be the most common reason. The incidence of fast transport status increases over time on PD (76, 80, 85, 87, 88). However, such increments in functional vascular surface area should theoretically also increase the OCG, since the UF coefficient LpS increases with a larger vascular surface area, S. Hence, to explain UF failure with an increment in vascular surface area, small solute transport should increase more in relation to LpS (77).

An alternative cause for acquired UFF is loss of OCG (UFF type 2), sometimes defined as an OCG below 2 μL/min/mmHg (64). Both LpS and the glucose reflection coefficient σ influence the ability of the peritoneal membrane to achieve UF in response to a glucose concentration gradient. In particular, reduction of OCG could be due to a reduction of AQP-1 mediated FWT, usually accounting for a large proportion of UF during hypertonic dwells (44). At least in some patients demonstrating UF failure, sodium sieving is reduced, possibly indicating reduction in FWT mediated UF volume (76, 89). However, a reduction in UF for any reason, *e.g.* using a lower glucose strength, will also reduce the sodium sieving, and thus the amount of FWT must be put in relation to the total UF volume.

Contrary to UFF type 1, where a “large peritoneal surface area” is suggested to induce a more rapid loss of the osmotic gradient and reduced UF, a small peritoneal membrane area is also suggested to induce insufficient UF (UFF type 3). A small surface reduces both the UF coefficient LpS and small solute diffusion capacity, simply due to insufficient membrane area, similar to performing haemodialysis with a small hemodialyzer. Reduction of peritoneal surface is considered rare and occurs due to adhesions or fibrosis, such as in encapsulation peritoneal sclerosis (90, 91). The last causative mechanism (type 4) ascribes UF failure due to increased lymphatic absorption into the systemic circulation and adjacent tissues (92), but is considered very rare. Other causes of extraperitoneal fluid loss must be excluded before UF failure type 4 can be diagnosed.

In patients with progression towards a fast transport status, sufficient UF and small solute clearance can often be maintained by increasing the dialysate flow rates, typically by shortening dwell times and adding dwells to preserve transport inducing blood-dialysate concentration gradients (93, 94). Also, UF may be improved by using icodextrin as osmotic agent (95, 96). In the case of UF failure due to a large small solute diffusion capacity (UF failure type 1), “peritoneal resting” including a four week long temporary break from PD has shown interesting effects with sustained reduced small solute diffusion capacity and improved UF, enabling prolongation of PD (97). However, this UF failure treatment method does not seem to be clinically applied to a wide extent (98). Despite measures to improved therapy, both UF failure and insufficient clearance, are common reasons for technique failure (78, 99-103).

Despite extensive research, the exact mechanisms or causes leading to decrease and ultimately loss of UF have not been pin-pointed, but hypothetically, structural membrane changes result in function alterations (104). For example, in patients with a fast small solute transport status, biopsy verified peritoneal sclerosis is more prevalent (105). As described earlier in this text, transport of solute and water occur at rates dependent on a sophisticated interplay of physical forces. Hence, functional alterations of the peritoneal membrane could very well be of multifactorial origin. Especially, multiple morphological changes have been identified in peritoneal biopsy studies. PD treatment induces loss and degeneration of mesothelial cells, and the transformation from mesothelial to mesenchymal phenotype cells (106, 107), which might play a central role in the development of membrane fibrosis development (108). Peritoneal biopsies have not only demonstrated a show thickening of the sub-mesothelial collagenous zone, but also vasculopathy with vascular subendothelial hyalinization (105, 109). The extent of both sub-mesothelial collagen thickening and vasculopathy appears to be closely correlated to the time on PD (109), supporting the hypothesis that PD itself induces structural and functional changes of the membrane. Another important morphological alteration in biopsies from PD patients are progressive membrane fibrosis and increased vascular density (105, 109), which could explain the increased diffusion of small solutes in patients with fast transport rate. Short-term, transient alterations in transport rates observable during a dwell, are more likely attributed transient vasodilation and/or increased vascular perfusion than actual structural changes (83, 84, 110-113).

Treatment induced alterations of the peritoneum may not be the only explanation behind variations in peritoneal function. Interestingly, the sub-mesothelial collagen zone was also thicker in uremic patients (105, 109), and in haemodialysis patients compared to healthy controls (109). In patients with uraemia, substances such as nitric oxide, vascular endothelial growth factor, inflammatory cytokines and advanced glycation end-products are elevated and have been hypothesised to affect the peritoneal membrane (114).

Dialysis induced alterations in peritoneal membranes are commonly thought to occur due to mechanic stress, osmotic stress and exposure to non-physiological concentrations of components in dialysis fluids, such as glucose or lactate *etc*. In addition to episodes of peritonitis, known to induce functional and structural membrane changes (115), long-term changes are often attributed to the use of bioincompatible and non-physiological dialysis fluids. Dialysis fluids with a low pH and high lactate concentrations are thought to induce membrane stress and in some cases pain when instilled, as well as the very high, non-physiological concentration of glucose. Before the early 2000's, peritoneal dialysis fluids often had a "bioincompatible" composition, with high lactate concentration, low pH and high contents of glucose degeneration products (GDPs). GDPs and advanced glycation end-products (AGEs) are thought to induce fibrosis and vasculopathy (116), since the local exposure of both GDPs and AGEs impairs the viability of the mesothelial

cells and alters their expression of proinflammatory cytokines and growth-factors (117-120). Since about 20 years ago, more biocompatible dialysis fluid are available, with lactate and/or bicarbonate buffer, neutral pH and less GDPs (119, 121). The clinical benefits of this new generation of dialysis fluids are however still questionable, and study results inconclusive (121-125). Nevertheless, new low GDP fluids have been suggested to preserve residual urine function (121), and reduce the occurrence of inflow pain (122, 126).

Despite reduced GDPs, most commercial dialysis fluids still contain extremely high glucose concentrations compared to physiological concentrations and are still considered the major factor inducing membranous stress and long-term membrane property alterations (78). Glucose is suggested to damage the peritoneal membrane due to acute and chronic local membrane exposure *per se*, but also via the exposure to GDPs (120). The formation and deposition of membrane damaging AGEs occur mainly due to the presence of GDPs, which are reduced with the new generation of fluids. However, AGEs and glycation of proteins will still occur as long as high concentrations of glucose molecules are present (127). Local membrane exposure to glucose is hypothetically vasodilatory, which could at least partly explain short-term, transient alterations in small solute transport. However, small solute transfer rates at different glucose strength dialysis fluids are inconclusive (53, 66, 82, 83, 128, 129).

Glucose Transport in Peritoneal Dialysis

Transperitoneal transfer of glucose molecules during peritoneal dialysis is thought to mainly occur across the blood vessels' paracellular small and large pores. As glucose molecules are impermeable to cell membranes, the transfer of glucose into cells must occur through designated transport proteins. Sodium glucose linked co-transporters 1 and 2 (SGLT1 and SGLT2), are secondary active glucose and sodium co-transporters, demonstrated to be present in the peritoneum mesothelial cell layer in humans (SGLT1) (130), and in rats (SGLT1 and 2). Facilitative glucose transporters (GLUTs), are a family of protein structures enabling passive passage of hexose sugars, such as glucose, fructose, mannose, galactose and urate ions (131). To date, 14 different GLUT transporters have been identified throughout the human body, where GLUT1 to GLUT4 and GLUT14 are glucose transporters, GLUT5, 7, 9 and 11 are fructose transporters, and the remaining non-selective transporters (131). GLUT1 and 3 are expressed in human mesothelial cells (130, 132).

Glucose Sparing Strategies

There have been many attempts to reduce the burden of intraperitoneal and systemic absorption of glucose, while maintaining sufficient UF (133). Systemic absorption of glucose is a major and unavoidable disadvantage of glucose-based PD, which might account for 100 to 300 g of glucose each day, representing 12-34% of recommended daily energy intake (134). Glucose is added to PD fluids for one purpose only: the creation of an osmotic gradient to achieve UF. Hence, there is a price to pay for UF, the so-called metabolic cost of UF, usually quantified as the amount of UF in millilitres per gram of glucose absorbed. Unwanted glucose absorption is suggested as the main cause for the development of *de novo* metabolic diseases, presenting in about half of the PD population (135).

Use of the glucose polymer icodextrin is a clinically widely used strategy to achieve UF at a lower metabolic cost (95, 96). Replacing one exchange of glucose-fluid with icodextrin has been shown to reduce glucose induced peritoneal membrane changes (79), and to reduce the risk of developing diabetes (136), compared to glucose-only prescriptions. Other commercially available alternative osmotic agents are amino acids-based fluids, which have been proven to be effective as osmotic agent and seem to be metabolically beneficial, especially by compensation of protein loss via PD (137, 138). However, amino acid-based dialysis fluids are only recommended to replace 1 out of 4 exchanges per day in continuous ambulatory PD (CAPD). Glycerol-based fluids were abandoned due to risk of development of systemic hyperosmolarity (139). In an experimental PD model using mice, an AQP-1 agonist, AqF026 increased UF by 20% (140). However, to date, such pharmacological interventions have not been explored in clinical studies.

SGLT2 inhibitors are widely used in clinic, in patients with heart failure, renal failure and diabetes mellitus type 2 (141, 142). In two recent publications, SGLT2 inhibition as glucose-sparring drug has been evaluated in models of acute PD in rats (74, 143). In the first experimental set-up, empagliflozin (SGLT2 inhibitor) was administered intragastric for three consecutive days and glucose absorption quantified at day 4, by performing a hypertonic 4-hour PET, and comparing dialysate glucose at dwell start and after 4 hours. Compared to the control group, the animals administered with empagliflozin showed reduced glucose absorption and increased initial-to-final dialysate glucose ratio, which was interpreted as blockage of peritoneal glucose absorption via SGLT2 transporters (143). In another experimental trial, rats had a 2 hour long peritoneal dialysis dwell with 1.36% glucose strength, with or without addition of intraperitoneal empagliflozin. There were no detectable differences regarding glucose absorption or glucose diffusion capacity between the SGLT2-inhibitor treated animals and the control animals, yet empagliflozin induced systemic effects such as increased glucosuria (74). Hence, potential effects of SGLT-2 inhibition on glucose absorption remain uncertain and

further studies are needed to determine potential benefits of SGLT2 inhibition in PD patients.

In another experimental rat model, almost identical to the second SGLT-2 study described above (74), rats undergoing a single acute PD dwell received either dialysis fluid with the addition of phlorizin, a dual blocker of SGLT1 and 2, or regular PD fluid. In animals receiving intraperitoneal phlorizin, glucose absorption and glucose diffusion capacity were reduced, suggesting that SGLT1 and/or SGLT2 channels mediates transperitoneal glucose transport and that this transport was to be inhibited in these experiments (144). However, phlorizin is metabolized to phloretin, an unselective GLUT-channel inhibitor. Hence, the observed alterations in glucose transport attributed to the effects of dual SGLT1 and 2 inhibitions by phlorizin, could rather be the result of GLUT-inhibition. However, despite lacking evidence on effects on glucose absorption *per se*, SGLT2 inhibition has also been suggested to reduce the risk of glucose induced peritoneal fibrosis (145). To date, neither GLUT inhibition nor SGLT1 inhibition has not been tested in a clinical study as a glucose sparing strategy in PD.

Another theoretically glucose sparing strategy is using so called “bi-modal” PD treatments, where some dwells are high glucose “UF-dwells” designed to enhance UF, and other dwells are low glucose “clearance dwells” (93, 146). Supported by TPM simulations, such bi-modal treatments could achieve similar UF and small solute outcomes as conventional treatment regimens, but at a lower “metabolic cost”, *i.e.* more UF per gram glucose absorbed. Application of such bi-modal treatments would enable a new strategy of treatment optimization, especially if treatments can be tailored to achieve individual outcomes regarding both UF and clearance then conventional PD (93, 146).

Aims and Hypothesizes

Paper I and II

These papers describe the study protocol (Paper I) and a final study (Paper II) of a randomized clinical pilot trial of a bi-modal ("optimized") PD treatment, consisting of hypertonic "UF-dwells" and ultra-low (physiological) glucose (5 mM) "clearance-dwells". The optimized treatment was designed to result in similar outcomes as a "standard" reference PD treatment.

The main aim was to test the feasibility of optimized PD treatments. Secondary, we aimed to elucidate whether outcomes of optimized treatments are comparable to standard treatments, in terms of small solute transport and UF. The main hypothesis is in these studies is that similar outcomes in terms of such transport can be achieved with less glucose absorption.

Paper III

In this article, we hypothesized that SGLT1 and/or GLUT transporters contribute to glucose absorption during peritoneal dialysis. The aim of this experimental study in rats was to test whether blockage of SGLT1 using a specific blocker, and/or unspecific GLUT blocker phloretin leads to reduced glucose transport during PD.

Paper IV

In this study, the potential influence of the dialysis fluid glucose concentration on small solute diffusion capacity is analysed in detail using retrospective data from 2 clinical centres. We here hypothesised that local exposure to hypertonic glucose fluids increase small solute diffusion capacity during clinical PD. Such effects were explored using the TPM and a novel isocratic estimation method for small solute diffusion capacity.

Materials and Methods

Three-Pore Model Simulations

The TPM can be used to model the flow of water and solutes across the peritoneal membrane, as originally described by Rippe (31, 36). It must however be noted that the TPM is designed based on observations of human transperitoneal transport. The core assumptions of the TPM are that mass transfer can only occur through the three distinct pore types and that the capillary wall in which the pores are considered to reside in, is the only transport rate limiting barrier. For example, transport pathways such as SGLT and GLUT channels, or the contribution of other pathways contribution to water or solute transport, are not defined in the TPM. The original TPM had to be modified early on with regards to glucose and sodium transport, increasing the MTAC of the former and decreasing MTAC of the latter to fit clinical data (36). Although the TPM is a simplification of the transport barrier, the model is considered to describe clinical transperitoneal transport well and thereby a widely used tool in peritoneal dialysis research. Older models of PD typically have the disadvantage that they do not describe free-water transport via AQP-1 and are therefore nowadays only rarely used.

In this thesis, TPM simulations are used to predict outcomes and optimize treatments (Study I and II) and to estimate transport parameters by curve fitting (Study III and IV). In study I and II, a human version of the TPM is used, while study III and IV utilizes a scaled down rat version of the TPM. The following section describes the basic principles of the TPM. Specific parameter values, assumptions and possible alterations applied in Study I to IV are found in the respective manuscripts.

Water transport induces change in the IPV as a function of dwell time due to peritoneal cavity in- and out flow of fluid, according to

$$IPV(t) = J_{v,c}(t) + J_{v,s}(t) + J_{v,l}(t) - L + J_{fill}(t) - J_{drain}(t) \qquad (9)$$

Here J_{fill} and J_{drain} represents inflow of fresh dialysis fluid and dialysate draining, respectively; L reflects the lymphatic absorption, generally considered constant

throughout dwell time. The trans-peritoneal flow of water through each of the respective three different pore types, AQP-1 ($J_{v,c}$), small and large pores ($J_{v,s}$ and $J_{v,l}$), are herein described by the term $J_{v,pore}$. The total extent of trans-peritoneal fluid flow, J_v at time *t* through each pore type is driven by the transcapillary net pressure gradient, arising due to a difference in hydrostatic, colloid osmotic and oncotic pressure gradient across the peritoneal membrane, according to

$$J_v\,(t) = \Delta P - \Delta\Pi_{prot} + \sigma\Delta O(t) \tag{10}$$

This interplay of transcapillary forces was originally described by Starling (147), versions of this equation are thereby commonly referred to as the Starling equation. In humans, the intraperitoneal pressure is typically about 8 mmHg during rest (148), and the intracapillary pressure circa 17 mmHg (24). This induces a hydrostatic pressure gradient ΔP of about 8 or 9 mmHg, in this thesis considered constant. It can be noted that, compared to the osmotic pressure gradient during PD, ΔP has rather limited influence on J_v. ΔP can also be estimated with respect to mean arterial pressure and IPV (93). The colloid osmotic pressure gradient $\Delta\Pi_{prot}$ depends on the plasma albumin concentration (24, 76), here set constant to 22 mmHg (93). The crystalloid osmotic pressure $\sigma\Delta O(t)$, in Study I to IV induced by glucose as osmotic agent, reflects the difference in dialysate and plasma osmolality. Regardless of osmotic agent used on a perfect semipermeable membrane, each mOsm/L induce exert an osmotic pressure of 19.3 mmHg, as stated in the Van't Hoff law of osmosis. Hence, the osmotic pressure induced by glucose is described by

$$[\sigma\Delta O(t)]_{glucose} = \sigma_{glucose}(C_D(t) - C_P) \cdot 19.3 \tag{11}$$

where $\sigma_{glucose}$ is the glucose reflection coefficient and C_D and C_P are dialysate and plasma glucose concentrations. It can be noted that no regard is usually taken to the fact that the plasma water concentration is slightly (5-7%) higher than the plasma concentration, since 1) this is difficult to assess in individual patients and 2) affects all solutes equally (149). The flow through each pore at time t, can be calculated using

$$J_{v,pore}(t) = \alpha_{pore} L_p S \left(\Delta P - RT \sum_{i=1}^{n} \varphi_i \sigma_{pore,i} (C_{P,i} - C_{D,i}(t)) \right) \tag{12}$$

where α_{pore} is the pore specific fractional hydraulic conductance, LpS is the UF coefficient, R is the ideal gas constant and T the body temperature in Kelvin and RT≈19.3 mmHg/(mmol/L). φ_i is the osmotic coefficient and $\sigma_{pore,i}$ the osmotic reflection coefficient, and $C_{P,i}$ and $C_{D,i}$ plasma and dialysate concentrations of solute *i*.

The small and large pores enable solute transfer according to the Patlak equation

$$J_{s,pore,i}(t) = J_{v,pore}(t)(1-\sigma_{pore,i})\left(\frac{C_{P,i}-C_{D,i}\,e^{-Pe_{pore,i}}}{1-e^{-Pe_{pore,i}}}\right) \quad (13)$$

where the Péclet numbers $Pe_{pore,i}$ is the ratio between the convection- and diffusion capacity of the membrane, calculated according to

$$Pe_{pore,i}(t) = \frac{J_{v,pore}(1-\sigma_{pore,i})}{MTAC_{pore,i}} \quad (14)$$

The $C_{D,i}(t)$ is influenced by the residual volume concentration $C_{D,i}(0)$, the concentration of the solute in the fresh dialysis fluid inserted to the cavity, and transmembrane mass transfer of the solute and dilution by UF (and FWT). In total, change of $C_{D,i}$ with time is described by

$$\frac{dC_{D,i}}{dt} = \frac{\sum_{p=1}^{2} J_{s,p,i}}{IPV} - C_{D,i}\frac{\sum_{p=1}^{3} J_{v,p} + J_{fill}}{IPV} + \frac{C_{f,i}J_{fill}}{IPV} \quad (15)$$

Here $C_{f,i}$ is the solute concentration in fresh dialysis fluid. Various applications of the TPM apply different assumptions, but in general, plasma concentrations of solutes are considered constant throughout dwell time.

Experimental Protocol

Animal models have been of great value in PD research and there are many models aiming to mimic both acute and long-term PD in various animal species (150). In Study IV, experiments were performed in a rat model of acute PD. A very similar (74), and identical (144), set-up has been used in previous trials also investigating effects of intraperitoneal drug administration. A detailed protocol describing the experimental set-up, procedures and drug dosage is found in the respective papers.

Statistical Analysis and Non-Linear Regression Parameter Estimation

Data was analysed using non-parametric tests due to small sample sizes in all three studies, and data are presented as median and interquartile ranges. Non-parametric tests are more robust to outlier data points which may have undue influence on the results of statistical tests when sample sizes are small. Another advantage of non-parametric tests is the lack of distributional assumptions, which can be difficult to verify for a small number of observations. Statistical analysis was performed in R Studio for Mac (version 1.2.1335)

Parameter estimation was achieved by experimental data and model curve fitting using non-linear least squares regression. Regression was performed using a Gauss-Newton algorithm in R (nls, stats version 3.6.2) or GNU software utilizing a Levenberg-Marquardt algorithm (151).

Results

Paper I and II

- Optimized bi-modal treatments were feasible.
- Optimized 2.27% and 0.1% glucose treatments did not reduce the absorbed amount of glucose compared to reference 1.36% treatment. However, UF was greater during optimized treatments, improving the UF efficiency (ml per gram glucose absorbed).
- Both creatinine and urea weekly Kt/V were unexpectedly improved during optimized treatments. There was no significant difference in sodium removal.

Paper III

- Phloretin (GLUT inhibitor) reduced glucose absorption by 30% compared to control animals. Using three different diffusion capacity estimation methods, all implied reduced diffusion capacity of glucose.
- Phloretin treated animals demonstrated an increased UF efficiency of 50%.
- Mizagliflozin (SGLT1-blocker) treated animals did not appear to affect glucose transport measures or UF compared to control animals.

Paper IV

- 1-hour dialysate to plasma ratios and glucose diffusion capacities were higher in 3.86% dwells when compared to 1.36% glucose dwells in both a Swedish and Belgian patient cohort.
- On the basis of observed differences in diffusion capacities in the Swedish cohort (development cohort), a phenomenological model for the variation of small solute MTACs as a function of glucose concentration was developed.

This model did not however completely explain observed differences in diffusion capacities in the Belgian cohort.

- Parameter estimation using the Isocratic model showed high conformity with TPM outcomes, validating the use of isocratic MTACs in PD patients.

Discussion

Glucose remains the most commonly used osmotic agent used in PD fluids. Glucose-based fluids have several benefits. Its use is well established in clinical practice and is considered safe even in long term PD. Glucose is also relatively inexpensive compared to alternative osmotic agents and generates sufficient UF in many patients at a reasonable cost. However, scientific investigation has repeatedly and consistently demonstrated the (bitter-)sweet (side-) effects of glucose-based fluids achieving low-cost UF at the price of metabolic complications and damage to peritoneal tissues. Over the years, there have been many attempts to replace glucose by another osmotic agent. However, this has proven difficult, conceivably because even the slightest toxicity of the osmotic agent is detrimental given the continuous nature of PD. For example - the glucose polymer icodextrin is the by far most commonly used non-glucose osmotic agent. However, use of icodextrin is limited by the metabolic break-down of icodextrin into maltose, which accumulates in the body in patients with little or no residual kidney function since there is no enzymatic break-down of maltose outside the small intestine or kidney proximal tubule in humans. Another important aspect in the search of alternative osmotic agents is that one of the major advantages of PD compared to haemodialysis is its lower cost. Hence, utilizing a more expensive osmotic agent may therefore reduce the incentive to choose PD. Despite the attempts in this thesis to limit the glucose burden of PD, it is clear that much work remains to be done to refine, reduce and replace the use of glucose as an osmotic agent in PD.

Systemic absorption of glucose can be reduced by two principles, either by reduction the glucose load, *i.e.* the amount of glucose available for absorption over time, or by blocking the absorption process itself. In the planning stage of the first study (Paper I and II), the TPM was applied to predict and design a bi-modal optimized treatment, with similar UF and small solute clearance outcomes, but a reduction glucose absorption by 10 g. Although, there are many pitfalls and built-in errors in simulation-based predictions, the clinical results deviated more than expected from the predicted outcomes. Furthermore, compared to the reference standard treatment, optimized treatments did not demonstrate lesser glucose absorption, but rather improved UF and small solute clearance. At publication, this deviance from predicted outcomes was speculatively ascribed inherent limitations of the TPM and a small sample size. However, post-trial simulations using the TPM, suggested that small solute diffusion capacities and OCG needed to be about 30%

higher than assumed in the pre-trial simulations to achieve the observed results. Such increased transport rates were suggested to be an effect of vasodilation or a "stirring effect" given the higher dialysate flow rates used in the optimized regimens. Later on, in Study IV, analysis of clinical data revealed higher diffusion capacities of glucose, creatinine and urea in high, compared to low glucose dwells. These results indicate that diffusion capacity is not a static membrane parameter, as was assumed in study I-II, but is a rather dynamic entity in PD. Even though transient changes in diffusion capacity have been proposed earlier, the results of study IV demonstrate that a high glucose concentration may directly and transiently induce changes in the membrane transport properties. With these valuable insights in mind, the seemingly surprising results of Study I and II could at least partly be explained by faulty assumptions regarding static diffusion capacities in the pre-trial TPM simulations for study II. Hence, whether bi-modal treatments consisting of hypertonic "UF-dwells" and ultra-low glucose "clearance-dwells" could serve as a glucose sparring technique remains unanswered in this thesis, but a natural next step would be the simulation of bimodal PD-regimens utilizing the phenomenological model derived in paper IV.

Transperitoneal glucose transport is widely considered to occur parallel to the transfer of similar sized water-soluble solutes, such as creatinine and urea, across the paracellular small pore pathways of the in the capillary wall. These assumptions are also at the core of the Three-pore model. To my knowledge, no alternative glucose transport pathways have been considered nor demonstrated to contribute to glucose transport until recently. In a research field were little has happened since the launch of icodextrin in the mid-nineties, the recently published studies evaluating contribution of transport pathways such as SGLT and GLUT channels are ground-breaking. In Study III, we were able to effectively block the absorption of glucose and improve UF efficiency by intraperitoneal phloretin (a non-selective GLUT blocker) in rats. In addition to the reduced glucose membrane transport, observations also proposed reduction in transperitoneal urea transport. It is well-known that phloretin inhibits urea transporters in for example the kidney (152). These results strongly challenge the two-pore concept of small solute transport in PD, which is suggested to occur either through selective paracellular pathways or weakly-selective large pores. Rather, one may need at least four, and probably even more pores to accurately describe solute transfer in PD. However, at least in the case of urea and glucose, the majority of small solute transport still appears to occur via the small-pore pathway, making it quantitatively the most important route of solute transport in PD.

In Study III, a non-selective blocker of GLUT channels was drug of choice since the aim of the study was to investigate whether GLUT channels contribute to glucose transport in PD or not. Although a few GLUT channel variants have been demonstrated to occur in rat mesothelial cells, our study design does not investigate to what extent the different GLUT channels contribute to glucose transport, or where

in the peritoneal barrier the channels are located. Membrane blockage of glucose pathways such as GLUT channels could potentially reduce systemic absorption of glucose, and thereby reducing systemic side-effects of PD, while maintaining the crystalloid osmotic gradient and thereby achieve a high UF efficiency. Further research is needed to evaluate the feasibility and safety of GLUT-blockade in clinic. It is conceivable that systemic absorption of GLUT-blocking drugs may affect GLUT channels in the rest of the body, with non-beneficiary effects. For example, blockage of GLUTs in the liver, may mimic hypoinsulinemia and stimulate ketogenesis which may potentially result in side-effects such as ketoacidosis. Thus, clinical feasibility and safety of such treatments is impossible to predict at this early stage. In conclusion, these studies provide a solid basis upon which further research can be performed.

Conclusions

- Absorption and exposure to glucose during PD can be reduced, for example by altering the prescription or, possibly, via pharmacological interventions.
- It is possible that glucose exposure *per se* induce a "glucose effect", which influences the peritoneal membrane and is responsible for short-term, transient variations in transport properties. This highlights a short coming in the current TPM, where peritoneal membrane characteristics are commonly assumed static. Further investigations and evaluation regarding the presence and extent of this hypothesised glucose effect is needed to improve understanding of transperitoneal transport and improve accuracy of TPM simulations.
- Experiments in rats suggest contribution of GLUT channels in peritoneal glucose transport. This strongly challenges the prevailing consensus of solute transport occurring through paracellular pathways. Despite a small sample size, dialysis fluids with addition of phloretin seems to effectively block GLUT facilitated glucose transport, reducing glucose absorption and improving the UF efficiency. Potential glucose sparing effects and the safety profile of GLUT blockers need to be further studied. Although its a long way to a clinically available drug, the phloretin results in rats demonstrate that blockage of glucose absorption during PD is possible.

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