Dissertation

Renal Exit Examination

A Longitudinal Study of Peritoneal Transport in Patients on Continuous

Ambulatory Peritoneal Dialysis:

Experience in a Single Center

Leung Kay Tai, Franky

Supervisor: **Dr Yung Chun Yu**

Renal team head: **Dr Au Tak Cheung**

Renal Unit

Department of Medicine & Geriatrics

Tuen Mun Hospital

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I. Abstract

Background: Peritoneal dialysis (PD) is an established modality of treatment of end stage renal failure. The long-term use of PD is limited by acute peritonitis and ultrafiltration (UF) failure. The peritoneal equilibration test (PET) is a useful procedure in measuring the peritoneal membrane transport. Raised peritoneal membrane permeability is associated with technical failure and increased morbidity and mortality. However, the data concerning the longitudinal change of small solute transport yielded conflicting results.

Methods: A retrospective cohort study of patients on continuous ambulatory peritoneal dialysis (CAPD) was conducted to study the change in peritoneal small solute transport over time in a single dialysis center. Peritoneal equilibration test was performed to study peritoneal transport characteristic. Peritoneal transport of small solutes was expressed as dialysate-to-plasma ratio of creatinine at 4 hours (D/Pcr).

Results: Sixty-four patients were recruited in the study, of whom 30 were male and 17 were diabetics. No significant change in peritoneal transport was observed (D/Pcr 0.70 +/- 0.11 vs 0.69 +/- 0.11, p=0.426). A centripetal change in peritoneal transport over time was observed. The change in peritoneal transport did not correlate with duration of dialysis (p=0.917), diabetes mellitus status (p=0.229), peritonitis rate (p=0.964) or daily dialysate protein loss (p=0.82). A trend of higher daily dialysate protein loss in patients with diabetes mellitus was observed (10.17+/- 1.33 vs 9.33 +/- 2.11 gm/day, p=0.065).

Conclusion: The present study suggests a centripetal change in peritoneal transport over time, which may reflect a regression-to-mean phenomenon. In recent years,

clinical and morphological studies of the peritoneal membrane have emerged. Several mediators have been implicated in the pathogenesis of peritoneal membrane failure in CAPD patients. Therapeutic approaches are evolving to maintain the integrity of the membrane.

II. Introduction

Peritoneal dialysis (PD) is now an established modality of treatment of end stage renal failure. In developed countries, it accounts for approximately 15% of dialysis population [1]. In Hong Kong, it is the predominant mode of dialysis, accounting for approximately 80% of the dialysis population [2]. The continuous form of PD has been used for more than twenty years and has been proven to be better than hemodialysis in the preservation of residual renal function and lower overall social cost [3]. The use of PD is limited by acute peritonitis and ultrafiltration (UF) failure. Acute peritonitis rate declined with the use of newer technical devices. The remaining problem is the progressive deterioration of the peritoneal membrane structure and function, which can affect up to 50% of PD patients treated for more than 6 years [4].

II (a). The peritoneal membrane

An intact peritoneal membrane is essential for PD. Histologically, the peritoneal membrane includes the mesothelium, interstitial space and blood microvessels. Mesothelium is unlikely to be an important barrier to transport of small solute and thus not an osmotic barrier [5]. The barrier function of interstitial space is not well defined. The vascular walls, mainly through the capillary endothelium, are the main obstacles to small solute transport in PD. In 1992, Rippe et al [6] introduced the three-pore model and suggested that solute transport across the peritoneum occurs through a system of pores (Figure 1). Diffusion of low molecular weight solutes, such as urea, creatinine and glucose, across the peritoneal capillaries occurs through "small

pores" (radius 40-50 nm), which account for approximately 99% of the total exchange (pore) area. A small number of "large pores" (radius approximately 250 nm), accounting for 0.01% of the total pore population, allow the transport of macromolecules. An abundance of water-conductive "ultrasmall pores" (radius <5 nm) in the plasmalemma allow the transport of water but not of electrolytes and other solutes. The transcellular protein, aquaporin-1, in the peritoneal microvasculature of CAPD patients, has been demonstrated to be the molecular counterpart of ultrasmall pore [7]. The water channel aquaporin-1 is located in the apical and basolateral membranes of endothelial cells lining the non-fenestrated capillary. About one-half of the transperitoneal UF during PD occurs through aquaporin channel when glucose is used as the osmotic agent [8]. The molecular counterparts of small and large pores have not yet been specifically identified.

Figure 1. Diagrammatic representation of the three-pore system
Large pores allow the transport of macromolecules. Small solutes, such as urea, creatinine and glucose, traverse the peritoneal capillaries through the small pores. Ultasmall pores allow the transport of water molecules only.
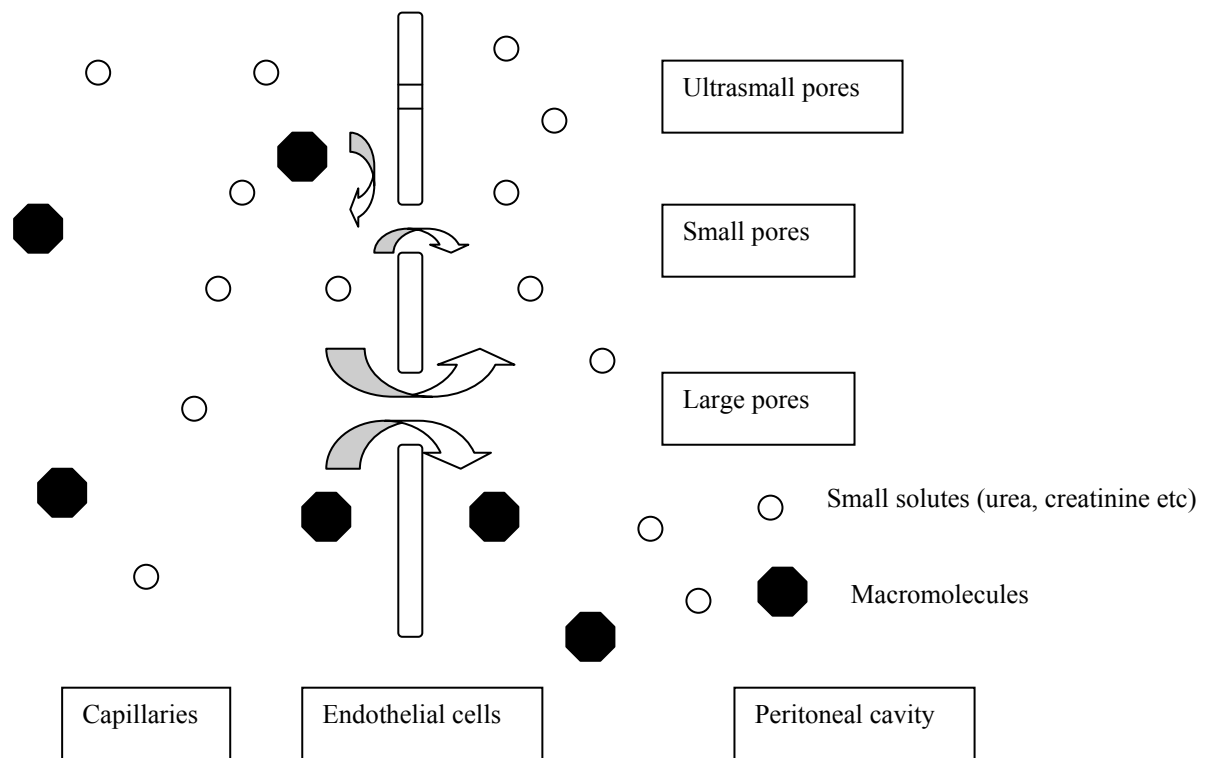
II (b). Peritoneal transport of low molecular weight solutes

The transport of low molecular weight solutes, such as urea and creatinine, across the peritoneal capillaries involves diffusion and convection. Diffusion is the most important transport mechanism for low molecular weight solutes through the small pore systems. The rate of diffusion is dependent on the mass transfer area coefficient (MTAC, the maximum theoretical clearance by diffusion at time zero) and the concentration gradient [9]. When the peritoneum is not a size barrier to solute transport, as for urea and creatinine, MTAC is determined by the available surface area, which is highly dependent on the number of perfused peritoneal capillaries, and thus the number of pores [10]. As the concentration gradient dissipates during the dwell of peritoneal dialysate, the diffusion rate decreases. In an equilibrium state, when the concentration gradient is zero, the mass transfer of solutes will be determined by the net water transport between blood and dialysate through the ultrasmall pore system. Thus UF rate also contributes to solute removal. This process of solute transport is called convection or solvent drag [9,11]. The convective solute transport can be expressed as the sieving coefficient (S), which is the ratio between the dialysate concentration of a solute and its plasma concentration when no transport by diffusion occurs. It can range from 0 (the solute is too large for transport by convectoin) to 1.0 (the membrane offers no hindrance to convection solute transport). Typical value for S of low molecular weight solutes is about 0.7. The sieving coefficient should not be confused with the reflection coefficient (σ), which is a measure of the effectivity of a solute to create a crystalloid osmotic pressure gradient across a membrane. It can range from 1.0 (no passage, ideal semipermeable membrane) to 0 (no osmotic effect). For a homoporous membrane, $S = 1-\sigma$. The

heteroporosity of the peritoneal membrane explains why the above equation does not apply in PD [12].

The importance of convection in solute transport is best demonstrated in the transport of sodium across the peritoneum. As the sodium concentration of most currently used peritoneal dialysis fluids is close to or slightly lower than the plasma sodium concentration, the diffusive transport component plays a minor role in peritoneal sodium transport. In general, convection dominates the sodium transport [11]. It has been observed that the dialysate sodium concentration decreases during the initial phase of a dialysis dwell with hypertonic solution, followed by a gradual rise [11,12]. This sieving of sodium is mediated by the transcellular water transport through the ultrasmall pores. Water transport from the circulation into the peritoneum is high during the initial phase of a hypertonic dwell. The decrease in sodium concentration is a dilutional effect. Gradual rise in sodium concentration is caused by diffusion of sodium from the circulation in subsequent hours. Thus, if short dwells with hypertonic dialysate are used, more water than sodium is removed during the initial phase of dwell. This can lead to hypernatremia. The magnitude of the dip in dialysate-to-plasma ratio (D/P) of sodium, measured at 60 minutes using 3.86% glucose dialysis fluid, is the simplest way to assess the magnitude of aquaporin mediated water transport [13].

II (c). Investigations of peritoneal kinetics

In standard PD using glucose as the osmotic agent, the peritoneal membrane exchange potential can be evaluated by three main approaches: the peritoneal equilibration test (PET), the standard permeability analysis (SPA) and the personal

dialysis capacity (PDC) test [14]. The PET and the SPA are single dwell procedures using direct measurements, whereas the PDC uses data from several exchanges performed during a twenty-four hour period. This information is then combined with a mathematical approach, employing the three-pore model, to estimate the parameters of membrane function. Each method gives information about solute (creatinine) transport characteristics, either as dialysate-to-plasma ratio (D/P) for PET, mass transfer area coefficient (MTAC) for SPA or the area parameter for PDC. Because transcapillary transport is the major process in PD, and because the peritoneum offers no size selective restriction barrier to the transport of low molecular weight solutes, these parameters are determined mainly by the vascular peritoneal surface area. Thus, these parameters can be used as an estimate of the vascular peritoneal surface area. Good correlation has been reported between D/P ratios and MTACs [15]. In addition, the SPA takes a more comprehensive approach to membrane function, making direct measurements of peritoneal permeability to macromolecules, peritoneal fluid reabsorption by use of the volume markers, and the estimation of sodium sieving. The later is designed to be a measure of the number of ultrasmall pores, although its use is questionable as it is also influenced by the rate of small solute diffusion.

The PDC, in addition to giving the area parameter, is able to extrapolate the rate of peritoneal reabsorption and the membrane permeability to macromolecules by estimating the flux of plasma proteins through the large pores.

All three approaches have been validated methodologically [14]. As would be anticipated, a considerable clinical database has now been evolved within the peritoneal dialysis literature for the PET, which is a relatively simple procedure

II (d). Peritoneal membrane failure

"Peritoneal membrane failure" in PD is not well defined. Usually, impaired transport of water and solutes is implied, but failure of local host defense mechanisms and development of peritoneal sclerosis are also signs of failure of the peritoneal membrane. Impairment of transport of water and solutes is the main focus of our discussion. The presence of a large vascular surface area, the so-called "effective peritoneal surface area" (EPSA) has been described as the most frequent cause of UF failure [16]. A high rate of peritoneal transport results in rapid absorption of glucose and thus dissipation of the osmotic gradient early in the dialysis cycle. In a proportion of patients, solute transport increases with duration of PD and is the factor most commonly associated with acquired UF failure [17]. For practical reasons, the change in the D/P ratio of creatinine or its MTAC can be considered to represent changes in EPSA. These changes can be either functional, indicating increased perfusion of capillaries or anatomical, indicating an increase in number of capillaries [18]. UF failure can be defined by use of various peritoneal dialysis fluids. With use of 3.86% solution, a net UF of less than 400ml/ 4 hour is considered as clinically important UF failure [19]. For 2.27% dialysate, net UF of less than 100ml/ 4 hours and for 1.36% dialysate, a value of less than –400 to 500ml/ 4 hour, are considered as impaired UF.

Apart from vascular proliferation, other pathological features include replacement of the mesothelium by an acellular layer of collagen, perivascular and submesothelial fibrosis [20] and diabetiform reduplication of the basement membrane of peritoneal capillaries. Various molecular events, including the up-regulation of the endothelial nitric oxide synthase (eNOS), over-expression of vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), basic fibroblast growth

factor (bFGF), accumulation of reactive carbonyl compounds (RCOs) and advanced glycosylation end-products (AGEs), have all been implicated in the structural modifications of the peritoneum in long-term PD patients [18].

Raised peritoneal membrane permeability is associated not only with technical failure, but also with increased morbidity and mortality [21]. Nevertheless, the data concerning the longitudinal change of small solute transport yields conflicting results. A progressive increase in peritoneal solute transport has been reported in some studies [22,23]. A centripetal pattern has been reported in several other groups [24-26]. In other prospective studies, peritoneal permeability remained stable [27].

III. Objective

The present study describes a retrospective cohort study of patients on continuous ambulatory peritoneal dialysis (CAPD), investigating the changes in peritoneal solute transport over time in a single dialysis center. Various factors, including duration of PD, diabetes status, peritonitis rate and total daily dialysate protein loss, and their roles on longitudinal changes in peritoneal transport are examined.

IV. Subjects and Methods

IV (a). Patient population and study design

This was a single center, observational, retrospective cohort study. Case records of patients commencing on the CAPD therapy between November 1996 and

October 2000 inclusive, regardless of etiology of renal failure and comorbid disease, were retrieved and reviewed. Patients with a peritoneal equilibration test (PET) performed within three months after initiation of CAPD were included in the analysis. The peritoneal membrane permeability to creatinine is expressed as the D/P ratio of creatinine at 4 hours (D/Pcr). Patient demography including age, sex, and diabetes status were recorded. Patients were treated with four exchanges per day using 2 liters of peritoneal dialysate. Duration of CAPD and number of episodes of peritonitis were retrieved from the case records. Total daily loss of protein from the dialysate was determined at the same time when the baseline PET was performed, within three months after initiation of CAPD.

IV (b). Peritoneal equilibration test (PET)

The peritoneal equilibration test was used to measure the peritoneal kinetics [28]. All measurements were performed when the patients were in euvolemic state and no episode of peritonitis was recorded within three months of the test. Briefly, a standard 4-hour dwell period was used (first exchange of the day), using a 2.27% glucose concentration 2-liter volume exchange (Dianeal: Baxter-Travenol). The patients used their usual overnight dialysis regime. Dialysate creatinine and glucose levels were measured at 4-hour. Plasma creatinine and glucose levels were measured at 2-hour. As glucose interferes with the assay for creatinine in a linear fashion, the true value for creatinine was obtained by subtracting the glucose level multiplied by a correction factor derived locally from the laboratory (0.36).

$$\text{True [creatinine]} = \text{measured [creatinine (}\mu\text{mol/L)]} - 0.36 \text{ [glucose (mmol/L)]}$$

The D/Pcr at 4 hours was used as an estimate of low molecular weight solute transport. Baseline PET (baseline D/Pcr) was defined as the test performed within three months of initiation of CAPD therapy. A second PET (second D/Pcr) was performed in patients who were currently still on CAPD therapy. Change in D/Pcr (Δ D/P) was calculated by subtracting baseline D/Pcr from second D/Pcr.

IV (c). Peritonitis

The number of peritonitis episodes was recorded and expressed as one episode of peritonitis per patient months of CAPD. Peritonitis was defined as the presence of at least two of the following three conditions: (1) symptoms and signs of peritoneal inflammation including abdominal pain, nausea, vomiting or diarrhea; (2) cloudy peritoneal effluent with an elevated peritoneal fluid white cell count ($>100/\mu L$) due predominantly ($>50\%$) to neutrophils; and (3) demonstration of bacteria in the peritoneal effluent by Gram's stain or culture. All episodes were treated empirically with intravenous vancomycin or intraperitoneal cefazolin therapy for Gram-positive organisms and intraperitoneal netilmicin or ceftazidime therapy for Gram-negative organisms until microbial sensitivities became available. Appropriate antibiotics according to sensitivity would then be started. Treatment was continued for fourteen days in clinically responding cases. An isolated episode was defined as an infection occurring in a peritoneum not infected in the previous two calendar months, and which resolved completely. Recurrent peritonitis was defined as further peritonitis episode with the same organism occurring within one calendar month of an isolated episode.

IV (d). Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, U.S.A.) version 10.0 for Windows software package. All data were expressed as mean values +/- standard deviation unless otherwise stated. Longitudinal change in peritoneal transport parameter was compared by paired Student t-test. The baseline peritoneal transport parameter was divided into quartiles. The longitudinal change in peritoneal transport parameters in the lower and higher quartiles were compared by Wilcoxon signed rank test. The Δ D/Pcr was correlated with baseline D/Pcr by Pearson correlation coefficient (r). Univariate correlation between continuous variables was calculated using the Pearson correlation coefficient (r) and Student t-test. A p-value less than 0.05 was considered statistically significant. All probabilities were two-tailed.

V. Results

Case records for patients commencing CAPD from November 1996 to October 2000 were reviewed. Patients with PET performed within three months of CAPD were included. A total of 166 patients were eligible. Ninety-two patients dropped out during this follow up period: sixty patients died during this period; five patients switched to hemodialysis; and twenty-seven patients underwent renal transplantation. Among the seventy-four patients who were still on CAPD, ten patients refused a second PET. Sixty-four patients completed the second PET (38.6%).

The demographic data for these 64 patients was summarized in Table 1. The mean age is 56.3 +/- 13.8 years. There were 30 male patients and 34 female patients. The mean duration of PD before second PET was 49.4 +/- 13.6 months (median 47.5 months). Diabetes mellitus was present in 17/ 64 (26.6%) patients. Thirty-three patients did not experience peritonitis episode whereas thirty-one patients had peritonitis (mean 1 episode in 36.5 patient months, range from 1 in 9.3 to 1 in 72 patient months).

Age	56.3 +/- 13.8
Sex (Male: Female)	30:34
Duration of PD (months)	49.4 +/- 13.6
Diabetes Mellitus (Present: Absent)	17:47
Peritonitis (Positive: Negative)	31:33

Table 1. Demographic data of the study group patients.
Continuous variables are expressed as mean +/- SD

The baseline transporter status of the patients was classified as described by Twardowski et al [28]. The baseline transporter status for the entire group (n=166) and the group with second PET performed (n=64) are listed in Table 2. Among the group with second PET completed, the transporter status was as follows: low transporter in 1 (1.6%) patient, low average transporter in 22 (34.4%) patients, high average transporter in 32 (50%) patients and high transporter in 9 (14.1%) patients (Figure 2).

Transporter status (baseline)	Entire group No. (%)	Study group No. (%)
Low	2 (1.2)	1 (1.6%)
Low average	54 (32.5)	22 (34.4)
High average	84 (50.6)	32 (50)
High	26 (15.7)	9 (14.1)
Total	166	64

Table 2. The transporter status of the entire group and the study group
Transporter status classified according to D/Pcr values as recommended by Twardowski: Low 0.34-0.49; low average 0.50-0.65; high average 0.66-0.81; high 0.82-1.03.
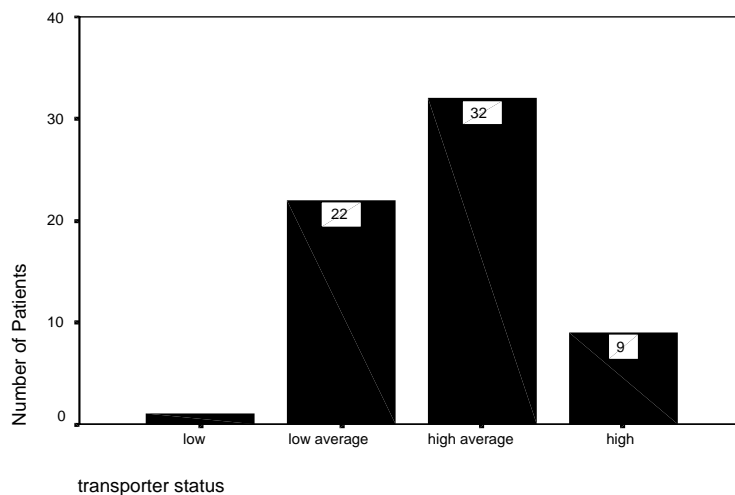
Figure 2. Transporter status of the study group
Number inside the bar represents the number of patients.

V (a). Centripetal change of peritoneal transport parameter

The mean baseline D/Pcr and second D/Pcr values were 0.70 +/- 0.11 and 0.69 +/- 0.11 respectively. Baseline D/Pcr was significantly correlated to second D/Pcr (r=0.324, p=0.009) and there is no statistical difference between the two values (p=0.426).

A centripetal pattern of longitudinal change in D/Pcr was observed. The D/Pcr value for patients in lower quartiles showed a significant rise after variable period of PD (0.57 +/- 0.04 to 0.65 +/- 0.11, p<0.05); the D/Pcr value for those in higher quartiles showed the reverse trend (0.82 +/- 0.05 to 0.71 +/- 0.10, p<0.05). The Δ D/Pcr was inversely correlated with the baseline D/Pcr (r= -0.583, p<0.001). The Δ D/Pcr followed a normal distribution with a mean of –0.012 +/- 0.122 (Figure 3). The Δ D/Pcr is not significantly correlated with duration of PD (r=0.013, p=0.917).

Delta dialysate-to-plasma creatinine
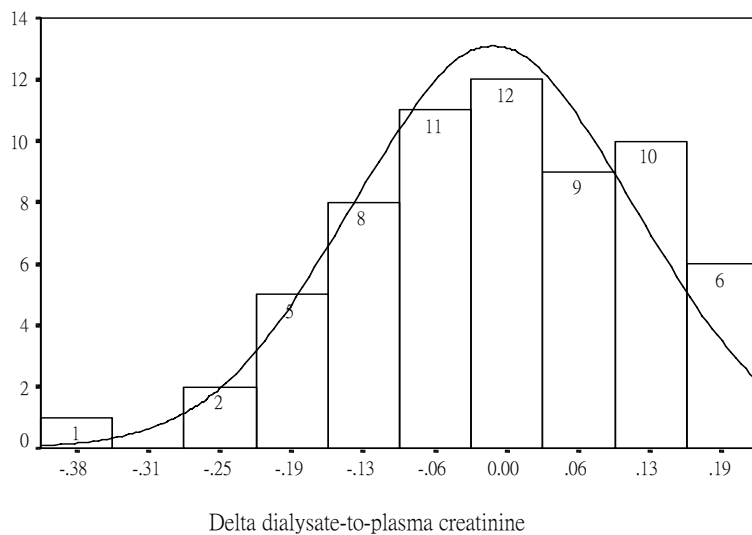
Figure 3. Frequency distribution of change in dialysate-to-plasma ratio of creatinine.
The line represents the simulated Gaussian normal distribution curve.

V (b). Effect of diabetes mellitus status on longitudinal change of peritoneal transport

For patients with diabetes mellitus, the mean baseline D/Pcr was 0.70 +/- 0.10. For patients without diabetes mellitus, the mean baseline D/Pcr was 0.70 +/- 0.11. No significant difference was present between the baseline D/Pcr values (p=0.993). Δ D/Pcr for subjects with and without diabetes mellitus were 0.014 +/- 0.092 and –0.022

+/- 0.130 respectively. Again, no significant difference in Δ D/Pcr was seen in patients with or without diabetes mellitus (p=0.229).

V (c). Effect of peritonitis on longitudinal change of peritoneal transport

Within the study period, there were a total of 63 episodes of peritonitis reported among the study group. Of all the 64 patients, 33 patients were peritonitis free. The peritonitis rate was 1 episode per 36.5 patient months. There was no difference in the baseline D/Pcr values between the patients with and without peritonitis (0.695 vs 0.699, p=0.173). The Δ D/Pcr of peritonitis free subjects was not significantly different from that of subjects who had experienced peritonitis during the follow up period (-0.023 +/- 0.126 Vs –0.001 +/- 0.118, p= 0.48).

V (d). Effect of daily dialysate protein loss on longitudinal change of peritoneal transport

The mean daily dialysate protein loss, as determined by the baseline PET, was 9.55 +/- 1.96 gm/day. The daily dialysate protein loss correlated significantly with the baseline D/Pcr (r=0.355, p=0.001). A trend of higher daily dialysate protein loss in subjects with diabetes mellitus was observed when compared to those with no diabetes mellitus, though not reaching statistical significance (10.17 +/- 1.33 Vs 9.33 +/- 2.11 gm/day, p=0.065). There was no significant correlation between the change in peritoneal transport and the daily dialysate protein loss (r=-0.029, p=0.82).

VI. Discussion

In the present retrospective cohort study, no significant change in the peritoneal transport characteristics can be demonstrated among a group of patients who received PD for a mean period of 49.4 +/- 13.6 months. The change in peritoneal transport followed a centripetal pattern. There was no significant difference in the change of peritoneal transport among various subgroups, including duration of PD, total daily dialysate protein loss, diabetes status, and number of episodes of peritonitis.

The PET was used as a measure of peritoneal transport of low molecular weight solutes for several reasons. Several authors have demonstrated that the 4-hour dialysate to plasma creatinine ratio was a good measure of low molecular weight transfer, comparing well with calculation of the MTACs [15,29]. The relative simplicity of the test allows it to be adopted as a general clinical practice in many centers. Use of this parameter allows other centers to compare the data presented with their own. Although other tests may give more information on the peritoneal kinetics, such as permeability to macromolecules and lymphatic absorption, these methodologies are both time-consuming and expensive [14]. However, the use of PET has its own limitation. While reproducibility is good for solute transfer, the measurement of UF with PET is subjected to much greater variation [30]. Since changes in UF are of greater clinical relevance than solute transfer in managing our CAPD patients, the serial change of UF is more difficult to demonstrate using the PET. Moreover, the D/P ratio tends to underestimate the MTAC at high range [15].

VI (a). Centripetal change of Peritoneal Transport

We have demonstrated that the longitudinal change of peritoneal transport follows a centripetal pattern. Several authors have reported similar results [24-26]. A decrease in D/Pcr with time was observed in high transporters whereas an increase was observed in low transporters. Wong et al [26] suggested the observed longitudinal change of D/Pcr is likely a biased observation reflecting a "regression-to-mean" phenomenon with no physiologic relevance. An inverse correlation between ΔD/Pcr and baseline D/Pcr, normal distribution of ΔD/Pcr and insignificant change of D/Pcr values all point to this possibility.

Another possibility for this result is the timing of baseline PET. In this report, baseline PET was performed within three months after initiation of CAPD. Previous studies reported a decrease in D/Pcr in the first few months after initiation of CAPD [27,31]. This suggested that a larger peritoneal surface area with an increased peritoneal permeability were present on initiation of dialysis. This phenomenon is probably caused by the effect of dialysis solution on the number of perfused peritoneal capillaries, leading to an initial increase in blood flow and blood volume [32]. After a few months, the peritoneum adapted to the vasoactive effect of the dialysate. Struijk et al [27] has suggested that baseline values for evaluation of the peritoneal membrane function should not be obtained before three months after start of CAPD. A PET performed in the early phase of CAPD, as in our report, may overestimate the peritoneal solute transfer. Thus, periodic assessment of the peritoneal solute transfer with PET, especially in the initial period of PD, may give more detail information on the longitudinal change of peritoneal transport.

VI (b). Diabetes Mellitus and Peritoneal Transport

Diabetic nephropathy is the single most common cause of end stage renal disease (ESRD), accounting for approximately 30% of patients undergoing dialysis in Western Europe and United States [33]. Only a small number of PD patients with diabetes have extended follow-up, as in our report, which may be related to the lower survival rate in this subgroup of patients. The reported four-year survival rate of diabetic patients on CAPD varies from 17-72% (mean value 39%). Diabetic patients represented 26.6% (17/ 64) of the study group. The under-representation of diabetes may bias the result of diabetic status on longitudinal change of peritoneal transport.

No difference in the baseline and Δ D/Pcr was observed in diabetic and non-diabetic patients. The issue of whether diabetes mellitus will have potential effect on the peritoneal membrane is controversial. All forms of diabetes are characterized by microvascular changes including endothelial dysfunction, increased microvascular permeability, and vascular proliferation. The molecular mechanisms underlying these microvascular changes include accumulation of advanced glycosylation end products (AGEs), release of growth factors such as the vascular endothelial growth factor (VEGF), and modifications of the L-arginine: nitric oxide (NO) pathway [34]. As mentioned before, the peritoneal membrane alteration that occurs with time on PD has similar pathophysiological features. Thus it is tempting to hypothesize that diabetes mellitus may have potential effect on the structure and function of the peritoneal membrane.

Nevertheless, the clinical studies of the effect of diabetes mellitus on peritoneal membrane yielded conflicting results. The CANUSA prospective study showed a greater proportion of diabetic patients among PD patients characterized as

high transporters [21]. Nolph et al [35] reported lower peritoneal urea and creatinine clearance values in patients with advanced diabetes during intermittent PD than in the control group. No effect on peritoneal solute transport was reported in other studies [36,37]. In contrast, a higher permeability for creatinine and lower transcapillary UF [38] in diabetic patients has been observed. The duration of peritoneal dialysis, before peritoneal transport being studied, is the most probable cause for this discrepancy. Long-term exposure to glucose containing dialysis solutions will induce diabetiform changes in peritoneal tissues, thereby obscuring the initial differences in diabetic and non-diabetic peritoneal membranes. Serlie et al [38] compared the peritoneal transport between 11 diabetic and 11 non-diabetic matched controls for the first six months of PD. The only difference between the two groups was the lower transcapillary UF rate in the diabetic patients, which disappeared after one year of CAPD. Thus, if the effect of diabetes mellitus alone on the peritoneal transport needs to be investigated, it should be performed before the initiation of CAPD, as continuous exposure to the glucose containing dialysis solution may mask the effect of diabetes mellitus.

Another probable cause for this discrepancy is the difference in glycemic control prior to PD initiation. As hyperglycemia has a central role in diabetic complications, it might be a critical factor for peritoneal membrane alterations. Stoenoiu et al [39] has reported that uncontrolled diabetes with hyperglycemia was able to induce significant alterations in the peritoneal membrane in a rat model and the alterations were prevented by chronic insulin treatment. Thus the variability in intrinsic peritoneal permeability may actually reflect the control of diabetes prior to the onset of PD.

VI (c). Peritonitis and Peritoneal Transport

Contrary to the current belief, the present report failed to find a correlation between peritonitis rate and longitudinal change in peritoneal transport. Most peritonitis episodes had no long-term effect on peritoneal transport. The introduction of twin bag system in CAPD resulted in a decline in peritonitis rate [40]. Currently, most of the patients on CAPD in our dialysis center are using the twin bag system. Only sixty-three episodes of peritonitis were reported in the study group, and thirty-three patients were peritonitis free. This low peritonitis rate may lead to results that differ from those of previous studies where peritonitis has been more frequent [31]. Peritonitis episode is associated with several alterations in peritoneal transport, such as an increase in D/P ratios and MTACs of low molecular weight solutes, an increase in peritoneal clearances of serum proteins and a decrease in net UF [31,41]. These alterations in peritoneal transport during peritonitis return to normal value within two weeks after recovery from the infection [41]. Davis et al [31] reported that single isolated episode of infection did not have significant long-term effects on peritoneal kinetics. They tried to quantify the severity of peritonitis by counting the cumulated white cell count from the peritoneal dialysate effluent. A correlation between the changes in solute transfer, net UF, and the dialysate leukocyte counts was observed, suggesting that the intensity of inflammation as well as the number of infectious episodes were important.

It has been reported that recurrent peritonitis was a major cause of morphological alterations in peritoneal membrane [42]. The peritoneal macrophages form the first line of defense. These macrophages provide triggering signals for the initiation and amplification of the cytokine network, which result in the recruitment of

leukocytes [43]. The mesothelial cells lining the peritoneal cavity are also involved in the local host defense. The mesothelium contributes directly to leukocyte recruitment and transmigration through the secretion of chemokines and adhesion molecules. The majority of these leukocytes are neutrophils that influx rapidly into the peritoneal cavity, releasing reactive oxygen metabolites and enzymes such as elastase in proportion to the dialysate neutrophil count, which are able to initiate peritoneal damage. Lai et al [44] demonstrated the persistent release of sclerogenic cytokines, transforming growth factor-β (TGF-β) and basic fibroblast growth factor (bFGF) for a prolonged period even after resolution of peritonitis. It is apparent that the stimulatory effect of both growth factors on the peritoneum may favor fibroblast proliferation, leading to peritoneal fibrosis and subsequently, UF failure in CAPD.

VI (d). Dialysate Protein Loss and Peritoneal Transport

Higher dialysate total protein loss in patients with higher D/Pcr is in agreement with previous studies [45,46]. Although the serum albumin level was not studied in the present report, it has been observed from previous study that patients with a high peritoneal transport rate have increased dialysate protein loss and decreased serum albumin level [45]. The lower serum albumin level in high transporters is partly due to increased dialysate protein loss, which is related to the intrinsic permeability of the peritoneal membrane to macromolecules and the surface area of the peritoneal membrane. Higher mortality rate was observed in patients with high transporter status, which may be partly due to the higher dialysate protein loss with resulting hypoalbuminemia. We have also observed a trend of higher dialysate

protein loss in diabetic patients in the present study, which may explain the inferior outcome of diabetic patients on CAPD.

VI (e). Morphological Change of Peritoneal Membrane

Morphological changes of the dialysed peritoneal cavity in response to glucose-containing dialysis solution has been extensively examined [20,47] and data for correlation between functional and morphological changes are emerging. The normal parietal peritoneal membrane is lined by a continuous sheet of flat mesothelial cells, which have a surface area vastly increased by the presence of microvilli. The mesothelial monolayer lies on a discontinuous basement membrane composed entirely of Type IV collagen. The submesothelial compact collagenous zone consists of bundles of collagen fibers loosely arranged and interwoven with occasional elastin fibers. The vascular bed is maximal at the junction of the compact zone with the underlying adipose tissue [47]. The Peritoneal Biopsy Registry studied the morphology of the parietal peritoneal membrane in patients on PD and compared these with the peritoneal membrane of normal individuals, uremic pre-dialysis patients and patients on hemodialysis [20]. They found that the median thickness of the submesothelial compact collagenous zone in PD patients increased significantly with the duration of therapy. Vascular change comprised of progressive endothelial hyalinization with luminal narrowing or obliteration. Vessel numbers were only significantly higher in patients with membrane failure and correlated with the degree of fibrosis and denudation of the protective mesothelial monolayer. Morphological changes were more commonly observed in patients experiencing clinical problem with PD. A positive, but weak correlation between the total number of peritonitis

episodes and the thickness of the submesothelial compact zone was demonstrated [47]. The accumulation of clinical data, together with peritoneal biopsies, will make a comprehensive analysis of structure-function relationships in PD possible.

VI (f). Molecular Mechanism for Changes in Peritoneal Membrane

The functional and morphological changes of peritoneal membrane appear to be related to total glucose exposure. Continuous exposure to non-physiologic dialysis solution is an important factor in membrane failure. The commonly used dialysis solutions are not biocompatible because of their low pH (5.5), type of buffer (lactate), glucose concentration (75-200 mmol/liter), and hypertonicity (osmolarity, 334-486 mOsm/liter) [48]. High glucose concentration, in combination with a low pH and lactate, has shown to be toxic to the cultured mesothelial cells. Chronic exposure of peritoneal membrane to high glucose concentrations is associated with enhanced glycation of proteins, with formation of AGEs in the peritoneum. Nonenzymatic glycation is supported by the presence of high concentrations of glycated albumin and IgG in the peritoneal effluent of CAPD patients [49] and by the demonstration of AGEs in the peritoneal tissue of non-diabetic CAPD patients as soon as three months after the initiation of CAPD [50].

Reactive carbonyl compounds (RCOs) induce advanced glycation of proteins. Several RCOs, including glyoxal (GO), methylglyoxal (MGO), and 3-deoxyglucose (3-DG), have been identified. These compounds lead to the formation of AGE epitotes such as pentosidine and carboxymethyllysine (CML) in the dialyzed peritoneal cavity [51]. These compounds (GO, MGO, 3-DG) are formed during heat sterilization of PD fluid. Plasma RCO precursors of AGEs also contribute to the

invasion of the peritoneal cavity during the dwell time. They are derived from carbohydrates and lipids, accumulating in the uremic plasma ("carbonyl stress") and lead to the formation of AGEs and ALEs (advanced lipoxidation end products) in the body [51]. Both PD fluid and serum-derived RCOs contribute to the genesis of peritoneal AGEs. These proteins initiate a range of cellular responses including the stimulation of monocytes, secretion of inflammatory cytokines, proliferation of vascular smooth muscle cells, stimulation of growth factors and secretion of matrix protein [52]. In addition, RCOs may also interfere with various cellular functions and induce both structural and functional alterations of proteins. In cultured mesothelial and endothelial cells, exposure to MGO is associated with increased expression of mRNA and protein synthesis of VEGF.

VEGF is a potent regulator of angiogensis and vascular permeability. The binding of VEGF to tyrosine-kinase receptors located in endothelial cells initiates a cascade responsible for endothelial proliferation and migration, activation of plasminogen and collagenase, and vasodilatation, resulting in physiological angiogenesis [53]. VEGF is expressed in the endothelium lining peritoneal capillaries. Its expression is up regulated in long-term PD patients [18]. Zweers et al [54] has demonstrated the presence of VEGF in the dialysate, where its abundance correlated with the permeability of small solutes and the loss of UF. By analogy with other angiogenic disease, such as tumor angiogenesis and ischemic heart disease, upregulation of VEGF may trigger vascular proliferation in the peritoneal membrane in long-term PD.

Nitric oxide (NO) plays a role in the regulation of vascular tone and permeability and interacts with angiogenic growth factors [53]. NO is synthesized from L-arginine by a family of NO synthase (NOS) isoforms that are expressed in a

large variety of tissues and cells. The neuronal and endothelial NOS (nNOS and eNOS, respectively) are constitutive isoforms and their activities depend on intracellular concentration of calcium. Inducible NOS (iNOS) is regulated at a transcriptional level and its activity is independent of calcium level [55]. In long-term PD, peritoneal NOS activity increases fivefold above levels observed in control and uremic subjects prior to the onset of PD. The increased NOS activity correlates positively with PD duration and is solely due to the up-regulation of eNOS [18]. A major increase in NOS activity, due to both eNOS and iNOS, has been observed in a rat model of acute peritonitis. Addition of the NOS inhibitor to the dialysate restored the UF in this model [55].

Devuyst et al [53] proposed a hypothetical framework for molecular mechanisms of peritoneal membrane dysfunction in long-term PD. Chronic uremia is associated with high levels of circulating RCOs, which initiate AGE protein modifications in the peritoneal membrane, and it is further amplified by the RCOs contained in the glucose containing dialysis fluids. RCOs and AGEs initiate a number of cellular responses, including stimulation of VEGF expression. In turn, VEGF interacts with endothelial cells and, together with NO and eNOS, stimulates angiogenesis and increases vascular permeability. These modifications increase EPSA, and eventually impair UF (Figure 4).

Peritoneal fibrosis is also involved in peritoneal membrane dysfunction. Peritoneal fibrosis is associated with exaggerated synthesis of pro-fibrotic peptides such as TGF-β1, bFGF and VEGF. TGF-β1 is an important growth factor involved in extracellular matrix (ECM) modulation and can increase many protein syntheses and decrease their degradation [56]. It is a growth factor vital to tissue repair but excessive production can lead to tissue fibrosis. The production of TGF-β1 is increased in

patients maintained on PD, especially during episodes of peritonitis [44]. In vitro studies demonstrated that high glucose concentrations could activate protein kinase C (PKC) and induce the synthesis of TGF-β1 in peritoneal mesothelial cells, which can modulate cell proliferation and up-regulate matrix protein synthesis [57]. Thus, TGF-β1 may have a key role in peritoneal fibrosis in CAPD patients.
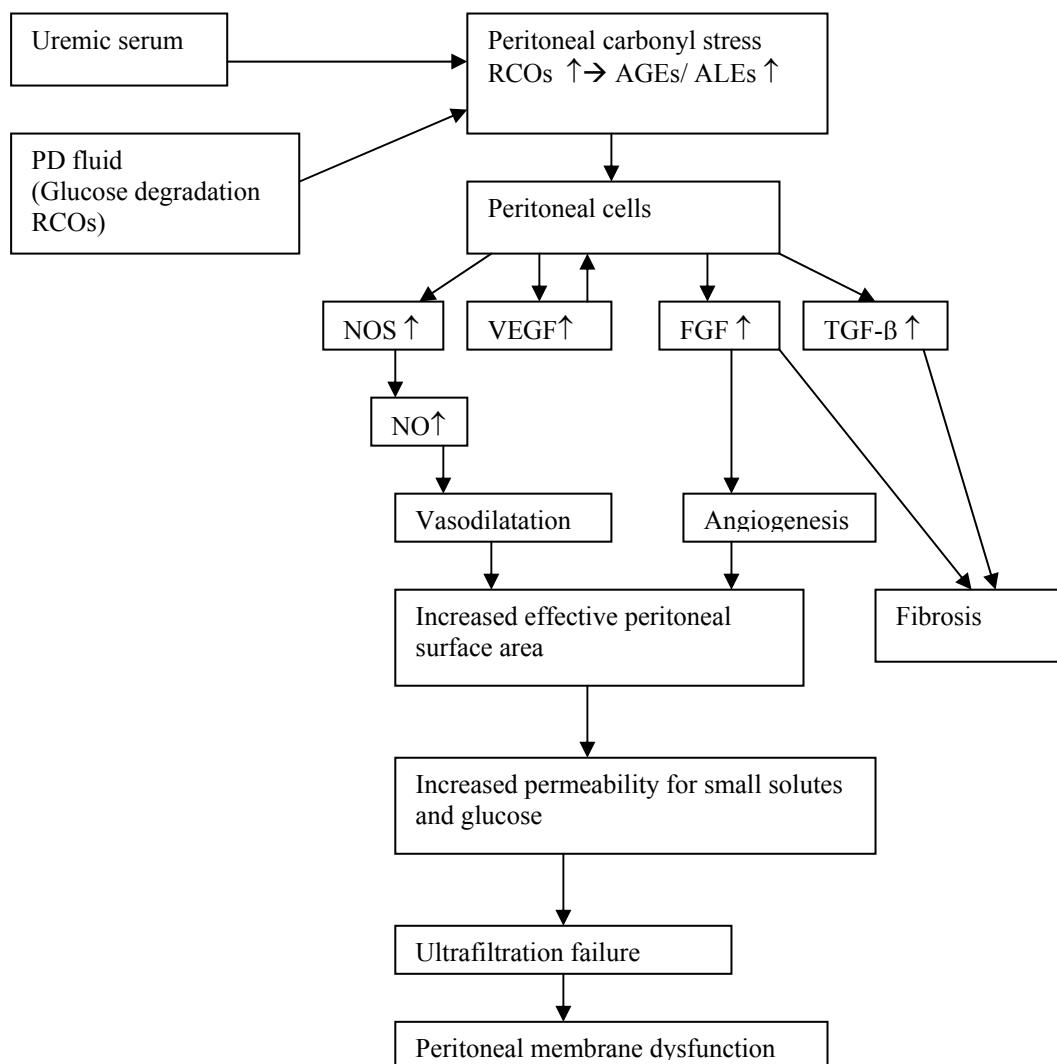
Figure 4. A model for the different molecular mechanisms involved in the peritoneal membrane dysfunction in long-term peritoneal dialysis.

VI (g). Therapy of Peritoneal Membrane Failure

With the increase in understanding of the molecular events in the peritoneal membrane in long-term PD patients, therapeutic approaches that might protect the peritoneal membrane were investigated. Peritoneal resting for four weeks has been tried in CAPD patients with UF failure [58]. An increase in UF (from 500ml/ 24 hours to 800ml/ 24 hours), accompanied by a decrease in MTAC of creatinine (from 16.7 ml/min to 13.6 ml/min) was reported.

The use of alternative osmotic agents in peritoneal dialysis solutions

Reducing the exposure of the peritoneal membrane to glucose is another emerging method. Alternative osmotic agents that can replace glucose include glycerol, icodextrin (glucose polymer), and amino acids. The advantage of these newer solutions accrues from their lower RCO content. Glycerol was generally well tolerated and is associated with stable clinical and biochemical control. However, the development of a hyperosmolar syndrome was recognized as a potential hazard [59]. Icodextrin sustains UF profile that is beneficial for long dwells by employing colloidal, rather than crystalloid, osmotic pressure, whereas amino acid fluid improves nitrogen balance in patients with malnutrition and avoids the glucose load, an advantage in diabetes and obese patients. Amino acids and icodextrin-based solutions can only be given once daily in the commonly used concentrations, because of the nitrogen load and the accumulation of maltose in the extracellular volume [60]. However, the clinical benefits these fluids in the preservation of the peritoneal membrane remain to be documented in long-term studies.

Multi-compartment bag

Another approach in lowering the RCO content of glucose containing PD fluid is the use of multi-compartment bag system [61]. In this system, glucose is kept at a low pH, separated from the electrolyte buffer (bicarbonate-based) solution, which is stored at a neutral pH. When both bags are mixed, the final solution has a physiologic concentration of bicarbonate, a reduced concentration of lactate, and a physiologic pH. In addition to an improved in vitro biocompatability profile, these dialysis solution might also improve the host defense status, membrane transport characteristics, UF capacity, and effluent markers of peritoneal membrane integrity [61]. It is safe and effective in correcting uremic acidosis and providing relief of inflow pain. Although encouraging, longer study period are required to reveal the changes of characteristics of the peritoneal membrane.

Inhibition of AGE formation

Compounds, such as aminoguanidine, OPB-9195, contain a hydrazine nitrogen atom that reacts with the carbonyl groups to form hydrazone. Trapping of RCOs by these compounds thus should inhibit the RCO modification of proteins. Miyata et al [62] has demonstrated that adding OPB-9195 or aminoguanidine to commercial glucose PD fluids could reduce the formation of AGE and ALE. However, the use of these compounds in diabetic patients has been hampered by their neurotoxicity due to the trapping of pyridoxal. Less toxic and more specific carbonyl stress inhibitors need to be developed.

RCOs detoxification

RCOs are partly detoxified by the glyoxalase pathway. Detoxification of RCOs by glyoxalase I is markedly impaired by a decreased thiol concentration. Thiol compounds such as glutathione, cysteine or N-acetylcysteine added to mixtures of GO, MGO, and 3-DG decreases their levels. Use of glutathione alone is less effective than aminoguanidine. However, addition of glyoxalase I to glutathione dramatically accelerate and intensify the in vitro lowering of GO and MGO in glucose containing PD fluid [63]. These results open the exciting prospect of lowering the peritoneal carbonyl stress in humans by raising glyoxalase I activity by genetic engineering or by the concomitant administration of recombinant glyoxalases I with glutathione.

Inhibition of the L-arginine-NO pathway

Modulation of the activity of NO may have considerable therapeutic value. L-arginine analogs interfere competitively with the binding of L-arginine to NOS. L-arginine analogs, such as N-monomethyl-L-arginine (L-NMMA) and its prodrug N-nitro-L-arginine methyl ester (L-NAME), are non-selective NOS inhibitors. The use of these compounds has been studied in animal models with variable results. Thus, the usefulness of NOS inhibition in patients on long-term PD remains to be characterized [64]. Current efforts aim at improving the selectivity of NOS inhibitors, taking into account differences in expression levels, cofactor utilization and location.

Prevention of peritoneal fibrosis

The pivotal role of TGF-β1 in peritoneal fibrosis prompted the study of various agents in abrogating its upregulation. Fang et al [65] showed that pentoxifylline, a xanthine derivative, inhibited TGF-β-stimulated human peritoneal

mesothelial cell (HPMC) growth and collagen synthesis in a dose dependent manner. The mechanism of these effects might be due to the phosphodiesterase inhibitory property of pentoxifylline. Dipyridamole is a widely used anti-platelet agent and acts as a phosphodiesterase inhibitor that increases intracellular cAMP. It acts similarly to pentoxifylline and was demonstrated to inhibit TGF-β-induced collagen gene expression in HPMC through the extracellular signal-regulated protein kinase (ERK) pathway [66].

Emodin (3-methyl-1,6,8 trihydroxyanthraquinone), a natural anthrquinone extracted from *Rheum*, had been studied as an antifibrotic agent. Chan et al [57], in an in vitro study, demonstrated that emodin could effectively ameliorate the detrimental effects of concentrated D-glucose on HPMC, namely the induction of TGF-β1 bioactivity and matrix synthesis, through the inhibition of PKC activation and consensus cAMP response element binding protein (CREB) phosphorylation. Further studies in animal models of peritoneal fibrosis are needed to confirm these in vitro findings.

Gene therapy

Gene therapy is employed in modification of some of the structural and functional changes associated with long-term PD. Clinical application of gene therapy for PD has focused on the peritoneal mesothelial cells. Mesothelial cells are identified as the primary target of gene transfer to the peritoneal cavity because of their location and large population of cells. In an animal model, the genetically modified cells had been demonstrated to produce anti-inflammatory and anti-oxidant proteins in experimentally denuded peritoneal membrane [67]. Decorin is a small leucine-rich dermatan sulphate proteoglycan that is found in the interstitial ECM. It has been

demonstrated to bind to TGF-β1 and blocked its biological action, thus ameliorating TGF-β-induced matrix synthesis [68]. Gene therapy can deliver the complementary DNA (cDNA) of decorin to the mesothelial cells by employing the adenovirus system. Thus it is possible that decorin can be used as an anti-fibrotic agent in the peritoneum during PD. However, local changes resulting from inflammatory and immune responses limit its use in vivo.

VII. Conclusion

The longitudinal change of peritoneal transport follows a centripetal pattern, which may be due to the "regression-to-mean" phenomenon. This change is not associated with duration of dialysis, diabetes mellitus, peritonitis or dialysate protein loss. The lack of effect of diabetes mellitus status and peritonitis on peritoneal transport may be due to the inadequate power of the study. A trend of higher daily dialysate protein loss in diabetes patients was observed, which warrants further study. Previous studies revealed that several mediators were involved in the pathogenesis of peritoneal membrane failure. Therapeutic approaches have been developed to target at each component of pathogenic mechanism to maintain the integrity of the peritoneal membrane. Future studies should focus on application these therapeutic modalities in animal models and CAPD patients.

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