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IMPACT OF PERITONEAL SOLUTE TRANSPORT
RATE ON NUTRITIONAL STATUS
AND CLINICAL OUTCOME
IN PERITONEAL DIALYSIS PATIENTS

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To the memory of my father

ABSTRACT

The transport characteristics of the peritoneal membrane may be influenced by inflammation and various comorbid diseases (CMD) in peritoneal dialysis (PD) patients. On the other hand, the peritoneal solute transport rate (PSTR) may influence patient characteristics such as nutritional status as well as the clinical outcome of PD patients. The aim of the present investigation was to elucidate the impact of PSTR on nutritional status and clinical outcome in PD patients.

I. Malnutrition (MN) as assessed by subjective global assessment was common in Korean patients at initiation of PD. Initial MN and initial lean body mass calculated from creatinine kinetics (LBM) were independent predictors of mortality. Initial nutritional status, therefore, appears to exert a powerful influence on PD patient survival.

II. At the start of PD, 49% of the patients with CMD had MN and 78% of patients with MN had CMD. MN alone was associated with a statistically insignificant increase in mortality but the combined presence of MN and CMD was associated with significantly higher mortality. This underlines the importance of CMD as a cause of poor clinical outcome in malnourished PD patients.

III. At the start of PD, high transporters had a higher proportion of patients with CMD. High PSTR had a significant impact on patient survival. However, high PSTR did not affect patient survival in patients without CMD. Thus, the association between initial high PSTR and high mortality may be in part due to an increased prevalence of CMD in high transporters.

IV. Patients with low residual renal function (RRF) had more often high C-reactive protein (CRP≥10mg/L). PTR correlated negatively with serum albumin concentrations and positively with serum CRP levels. Patient survival was significantly lower in the patients with low RRF, with high CRP, and with more than two of the following: low RRF, high CRP, and high PTR. In contrast, patients with high PSTR had high mortality only during the initial year on PD. These results indicate the importance of RRF and inflammation as predictors of mortality in PD patients whereas the predictive power of PSTR as such may loose its significance if these two parameters are taken into consideration.

V. In patients who were assessed after on average 10.8 months of PD treatment, nutritional variables, 24-h total fluid removal (TFR), Kt/V_{urea}, and creatinine clearance (CCr) were not different between the different transport groups. TFR correlated with D/P Cr, serum albumin, protein intake, LBM, Kt/V_{urea}, and CCr. Patients with high CRP had a higher proportion of patients with reduced (<1000 ml) TFR compared to patients with normal CRP (38% vs. 16%, p=0.04). Two-year patient survival rates from the time of the assessment were not different between the different transport groups. Inflammation was an independent predictor of mortality. These results indicate that a high PSTR as such should not be regarded as a relative contraindication for PD. Instead, the results suggest that more attention should be given to inflammation and inadequate fluid removal as predictors of mortality in PD patients

VI. During the 1st year on PD, patients with increased PSTR had a low RRF and more often high CRP compared to patients with decreased or unchanged PSTR. Patients with a decrease in RRF>1.9 ml/min during the 1st year on PD had more often high CRP, higher D/P Cr, and higher changes in D/P Cr compared to the patients with a decrease in RRF≤1.9 ml/min. High CRP and low RRF were independent factors associated with PSTR during the 1st year on PD. Thus, it is possible that inflammation may cause both an increase in PSTR and a decline in RRF, or that the decline in RRF and the increase in PSTR may induce or aggravate inflammation.

Key words; adequacy of dialysis, comorbid diseases, fluid removal, inflammation, mortality, malnutrition, peritoneal dialysis, peritoneal transport rate, residual renal function

LIST OF PUBLICATIONS

This thesis is based on the following studies, which will be referred to by their Roman numerals.

I. Chung SH, Lindholm B, Lee HB.
   Influence of initial nutritional status on continuous ambulatory peritoneal dialysis patient survival. Perit Dial Int 20(1): 19-26, 2000

II. Chung SH, Lindholm B, Lee HB.
   Is malnutrition an independent predictor of mortality in peritoneal dialysis patients? (Submitted for publication 2003)

III. Chung SH, Chu WS, Lee HA, Kim YH, Lee IS, Lindholm B, Lee HB.
   Peritoneal transport characteristics, comorbid diseases, and patient survival in CAPD patients. Perit Dial Int 20(5): 541-547, 2000

IV. Chung SH, Heimbürger O, Stenvinkel P, Qureshi AR, Lindholm B.
   Association between residual renal function, inflammation, and patient survival in new peritoneal dialysis patients. Nephrol Dial Transplant 18:590-597, 2003

V. Chung SH, Heimbürger O, Stenvinkel P, Wang T, Lindholm B.
   Influence of peritoneal transport rate, inflammation, and fluid removal on nutritional status and clinical outcome in prevalent peritoneal dialysis patients. Perit Dial Int 23:??-??, 2003

VI. Chung SH, Heimbürger O, Stenvinkel P, Bergström J, Lindholm B.
   Association between inflammation and changes in residual renal function and peritoneal transport rate during the first year of dialysis. Nephrol Dial Transplant 16: 2240-2245, 2001

CONTENTS

LIST OF ABBREVIATIONS

APD	Automated peritoneal dialysis
BMI	Body mass index
CAPD	Continuous ambulatory peritoneal dialysis
CCr	Creatinine clearance
CMD	Cormobid diseases
CRF	Chronic renal failure
CRP	C-reactive protein
CVD	Cardiovascular disease
D/P Cr	Dialysate to plasma creatinine concentration ratio
ESRD	End-stage renal disease
HD	Hemodialysis
LBM	Lean body mass
MN	Malnutrition
NN	Normal nutrition
NO	Nitric oxide
NOS	Nitric oxide synthase
nPNA	Normalized protein equivalent of total nitrogen appearance
PD	Peritoneal dialysis
PET	Peritoneal equilibration test
PSTR	Peritoneal solute transport rate
RRF	Residual renal function
sAlb	Serum albumin
sCr	Serum creatinine
SD	Standard deviation
SGA	Subjective global assessment
TFR	Total fluid removal
VEGF	Vascular endothelial growth factor
Δ	Change

1 INTRODUCTION

1.1 GENERAL INTRODUCTION

Since Popovich and Moncrief first introduced the concept of continuous ambulatory peritoneal dialysis (CAPD) [1], peritoneal dialysis (PD) has been established as a successful renal replacement therapy in the management of end-stage renal disease (ESRD) patients. Currently, there are more than 130,000 patients on PD worldwide, representing approximately 15% of the total world population requiring dialysis [2]. It is now well established that PD preserves residual renal function better than hemodialysis (HD) [3-7] and offers equal [8-10] or better [11-13] patient survival within the first 2 years of therapy compared to HD.

However, the mortality rate in ESRD and dialysis patients is still very high and this may be due to variety of factors. The ADEMEX study [14] shows that in PD patients dialysis adequacy as determined by small solute clearance is not as critical for patient survival as previously thought. On the other hand, there has been an increasing focus in recent years on the roles of high peritoneal solute transport rate [15-21], malnutrition [22-25], inflammation [26-28], residual renal function [29-33], and fluid overload [34] as predictors of mortality in PD patients.

Although the relative importance of these factors for patient survival and the relationships between these factors are not clearly established, the transport characteristics of the peritoneal membrane may be influenced by inflammation [35-39] and various comorbid diseases [20, 21, 40]. On the other hand, the peritoneal transport rate of solutes may influence patient characteristics such as nutritional status [41, 42], fluid status [16, 43], as well as the clinical outcome of PD patients [15-21].

During PD, the excess water and waste products, which normally are excreted in the urine, are removed from the capillaries to the intraperitoneal dialysate using the peritoneum as a dialysis membrane. Although residual renal function is the strongest determinant of small solute clearance [44, 45], as residual renal function decreases, small solute clearances will largely depend upon the peritoneal membrane transport status. However, membrane transport characteristics does not only differ between different patients but may also change over time on the PD therapy [19, 46-48].

Despite an increased solute transport rate in so-called high transporters (see below), the actual solute mass removed may be lower [16] due to impaired ultrafiltration and also due to peritoneal fluid absorption, which plays an important role in fluid and solute removal during long time dwell [49].

The aim of the present investigation was to elucidate the impact of peritoneal solute transport rate on nutritional status and clinical outcome in PD patients.

2 REVIEW OF THE LITERATURE

2.1 HISTORY OF PERITONEAL DIALYSIS

The first clinical application of PD was done in 1923 by Ganter who treated a uremic patient by instilling 1.5 liters of physiological solution into the peritoneal cavity and then draining the solution [50]. However, a distinct point in the history of PD is the description of the concept of CAPD, "a novel portable/wearable equilibrium peritoneal dialysis technique", by Popovich and Moncrief in 1976 [51]. There was a major improvement in the CAPD technique with reduced peritonitis rates when Oreopoulos et al. [52] introduced the Toronto Western Hospital spike system with flexible dialysate containers of polyvinylchloride in 1977. A further improvement of the PD technique was the introduction of the Y-shaped disconnect line [53], which overcomes the problem of the spike system and has been shown to reduce the incidence of peritonitis [54-56]. Another variant of PD therapy was the automated peritoneal dialysis (APD) and the introduction of continuous cyclic peritoneal dialysis described by Nakagawa et al. [57] in 1981. These modified techniques have provided the patients improved convenience [58] and decreased peritonitis rates [58-62] as well as more individualized dialysis regimens [63, 64].

In recent years, the importance of improving clinical outcomes for PD patients has led to investments in research for better understanding and management of nutrition, adequacy of dialysis, and preservation of peritoneal membrane viability. Thereafter, there has been an increasing focus on the role of PD solutions. In contrast to conventional PD solutions, new PD solutions have been shown to have positive effects on several aspects of the therapy. The amino acid-based solution can improve nutritional status [65-68] as well as peritoneal membrane viability [69]. The bicarbonate/lactate buffered solution may ameliorate the local and systemic effects caused by the low pH [70, 71], high lactate [71, 72], and high glucose degradation products [73] in conventional dialysis fluid. The icodextrin-based solution may not only improve hypertension and cardiovascular problems [74] but also extend the time of therapy in patients with loss of ultrafiltration capacity [75, 76]. Thus, the new biocompatible PD solutions represent an entirely new era in the evolution of the PD therapy, which is likely to have markedly positive effects on both PD technique and PD patient survival in the coming years.

2.2 PERITONEAL MEMBRANE AND SOLUTE TRANSPORT

The peritoneum is a large, intricately arranged serous membrane, which lines the abdominal wall (parietal peritoneum) and visceral organs of the abdominal cavity (visceral peritoneum) [77]. The parietal peritoneum represents about 10% of the total peritoneal surface area and receives its blood supply from the vasculature of the abdominal wall. The visceral peritoneum represents 90% of the total peritoneal surface area and receives its blood supply via the mesenteric vessels [77]. The peritoneal membrane consists of at least two distinct anatomical layers, mesothelium and interstitial tissue.

The surface of the peritoneal membrane is a single layer of mesothelial cells, which are covered with a thick mantle of microvilli, which are 2-3 μ in length and 0.08 μ in diameter [78] and a thin (5 μm) film of peritoneal fluid. The basal mesothelial cell surface is separated from the adjacent connective tissue by a membrane consisting of an inner and outer dense line separated by a lighter area, the three structures measuring about 50 nm in width. In some cases, small vesicles or granules are associated with this membrane.

Beneath the mesothelium lies the interstitial tissue, comprising of an amorphous ground substance or gel-like matrix interlaced with collagenous, reticular and elastic fibers, adipocytes, fibroblasts, and granular material, and containing blood capillaries, nerves, and lymphatic vessels. The interstitial ground substance is a mucopolysaccharide hydrogel, which may be subdivided into a colloid-rich and a water-rich phase. It contains several different glycosaminoglycans (including hyaluronic acid, chondroitin sulphate, and dermatan sulphate), which has low isoelectric points, and consequently the interstitial ground substance has a high density of negative colloidal charge at physiological pH [79].

The total surface area of the peritoneum in adults approximates the surface area of the skin (1-2m^2) [80]. However, the effective surface area, actually participating in solute transport is smaller than the anatomic surface area and relates to the capillary density and the arrangements of capillaries in the peritoneal interstitium [81]. Furthermore, the relationship between body surface area and peritoneal transport rate seems to be controversial. In a cross-sectional study, Tzamaloukas et al. [82] reported that there was

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no evidence of influence of body size on the dialysate to plasma solute concentration (D/P) ratio of small solutes. Davies et al. [46, 83] showed significant correlations between body surface area and peritoneal small solute transport rate at 6 months and 12 months but no correlation after commencing treatment and lack of correlation also later during treatment. In contrast, Diaz-Alvarenga et al. [84] reported that the peritoneal solute transport rate was significantly correlated with body surface area.

For the transport of solutes from blood to peritoneal cavity, at least three anatomical barriers have to be passed: (1) capillary wall, (2) interstitium, and (3) mesothelial cells. The surface area of the capillaries (diameter 5-6 μm) and the so-called post capillary venules (diameter 7-20 μm) are the most important determinants of the peritoneal exchange of solutes [81]. Several properties of the capillary circulation are important to the mass transport of solutes through the capillary wall such as the capillary perfusion rate, capillary surface area, and diffusive permeability characteristics of the capillary wall.

2.3 EFFECT OF COMORBID DISEASES ON PERITONEAL SOLUTE TRANSPORT RATE

Cardiovascular disease

Although little has been reported on the relationship between cardiovascular disease and peritoneal solute transport rate, inflammatory mechanisms are involved in the pathophysiology of cardiovascular disease and may affect the microcirculation [85, 86]. At the level of the myocardial microcirculation, reperfusion injury manifests itself as endothelial dysfunction and increased capillary permeability [87], suggesting that cardiovascular disease might affect peritoneal solute transport characteristics.

In a preliminary report, Heimbürger et al. [88] reported that high peritoneal solute transport rate, assessed by the peritoneal equilibration test within 1 month after start of PD, was associated with cardiovascular disease. Similarly, we have found that Korean patients with high peritoneal solute transport rate have a higher proportion of patients with cardiovascular disease [21].

Diabetes mellitus

Diabetic patients with ESRD have widespread vascular complications [89-92] and may, therefore, have significant peritoneal microvascular disease, which may alter the peritoneal membrane permeability.

Conflicting results have been reported regarding the relationship between peritoneal solute transport characteristics and diabetes mellitus [15, 20, 93-100]. Lamb et al. [95] reported that diabetics had higher D/P for creatinine (Cr) than non-diabetics. The CANUSA study group [15] and Cueto-Manzano et al. [20] showed that a greater proportion of patients with higher peritoneal solute transport rate had diabetes mellitus. In contrast, Lee et al. [96] reported no difference in peritoneal clearances of urea and creatinine, drained protein concentrations, or fractional glucose absorption between diabetic and non-diabetic patients. In addition, Serlie et al. [97] found no differences in solute transport or protein between diabetic and non-diabetic patients when matched for sex, age, and duration of CAPD after the onset of CAPD treatment.

Chronic hepatic disease

An increase in the peritoneal surface area related to portal hypertension may increase solute transport. In a study of 5 CAPD patients with liver cirrhosis, Bajo et al. [101] observed increased peritoneal mass transfer coefficients for urea and creatinine in patients at the start of CAPD. In a cross-sectional study, Dadone et al. [102] showed that patients with chronic hepatic disease had an increased transport of small solutes compared to patients without chronic hepatic disease. Yoon et al. [103] found that patients with liver cirrhosis and ascites had increased solute transport rate. We have recently reported that patients with high peritoneal solute transport rate have a higher proportion of chronic hepatic disease [21].

2.4 CHANGES IN PERITONEAL SOLUTE TRANSPORT RATE DURING PD

Peritoneal solute transport rate often changes after initiation of PD. Some studies have shown that in most patients peritoneal solute transport rate increases with time on PD [19, 37, 46, 47, 104], while others have found that peritoneal solute transport rate may decrease in a few patients with time [47, 48]. Finally, after initial early

changes in peritoneal solute transport rate, the membrane function often is stable up to three years [47, 83]. Table 1 shows changes in peritoneal solute transport with time on PD in different studies.

Table 1. Changes in peritoneal solute transport with time on PD

Study	n	Time (Months)	D/P or K_{BD} creatinine	Ultrafiltration
Blake et al 1989 [47]	49	24	Increased	Constant
Kush et al 1990 [105]	43	60	Increased	Constant
Selgas et al 1994 [38]	56	84	Increased	Decreased
Struijk et al 1994 [106]	61	24	Increased	Decreased
Faller et al 1994 [107]	23	84	Constant	Decreased or constant
Davies et al 1996 [46]	166	48	Increased	Decreased
Hung et al 2000 [108]	32	29	Decreased	Constant
Chung et al 2001 [37]	76	12	Increased	Decreased

Abbreviations; D/P, dialysate to plasma concentration ratio; K_{BD}, diffusive mass transport coefficient

2.5 FACTORS AFFECTING CHANGES IN PERITONEAL MEMBRANE

Glucose

The conventional PD solutions contain glucose at supraphysiological concentrations (75-214 mmol/L) as an osmotic agent and the peritoneal membrane is continuously exposed to these solutions. Moreover, approximately 75% of the initial intraperitoneal glucose amount is absorbed during a 6-hour dwell [109]. Thus, not surprisingly, pathophysiological alterations in peritoneal membrane of long-term PD patients are similar to those seen in diabetic angiopathy. Several studies showed glucose-induced diabetic alterations in the peritoneal microvasculature, such as reduplications of the capillary basement membrane [110] and a marked increase in the number of microvessels [111] with deposition of collagen IV [111, 112].

The high glucose concentration in the dialysis fluid is associated with stimulation of growth factors, such as transforming growth factor β1 [113-116] and vascular

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endothelial growth factor (VEGF) [117-119], leading to peritoneal neoangiogenesis with deposition of extracellular matrix [116, 120]. Furthermore, glucose reacts nonenzymatically with amino groups to produce cross linking moieties, advanced glycation end-products (AGEs) [121, 122], which act to produce complex vascular alterations closely resembling diabetic vasculopathy [123-125]. In addition, the nitric oxide synthase (NOS) expression and the nitric oxide (NO) production may increase in the peritoneal microcirculation in response to uremia *per se*, the exposure to glucose, glucose degradation products (GDPs) and AGEs, and the elevated levels of VEGF [126-128].

Although it is difficult to separate the effect of glucose and GDPs, which are generated during heat sterilization and storage of PD solutions, are considered to contribute to alterations in peritoneal membrane by different mechanisms [119, 129-133]. Single GDPs or combinations of GDPs not only have significant cytotoxic effects on peritoneal cell function [130-132] but may also markedly accelerate the formation of AGEs [131, 134].

Inflammation

Peritoneal inflammation plays a major role in peritoneal membrane alterations. One of the challenges to peritoneal membrane viability is peritonitis [38, 46, 135, 136].

An acute episode of peritonitis results in increased peritoneal solute transport rate but there are conflicting results regarding the relationship between peritonitis and long-term peritoneal membrane transport alterations [38, 46, 135-138]. Selgas et al. [38] reported that a high rate of accumulated days of peritonitis was related to significant functional changes in the peritoneum. Other investigators found that severe and multiple peritonitis episodes caused changes in peritoneal function [46] whereas a single peritonitis episode did not [46, 135]. Selgas et al. [136] also demonstrated that late mild peritonitis had distinct peritoneal function consequences relative to early peritonitis. In contrast, Fussholler et al. [137] reported that peritonitis incidence did not have a significant influence on small solute transport or fluid kinetics.

Although it is difficult to determine to what extent peritonitis is involved in peritoneal membrane alterations (apart from the acute effects), local release of cytokines due to

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various stimulations such as infection or bioincompatible PD solutions, is associated with peritoneal membrane alterations [36, 139-141]. We also found that factors associated with an increase in D/P Cr were high serum CRP and a low residual renal function [37]. In addition, uremia *per se* has been reported to be associated with alterations in the structure and function of the peritoneal membrane [142-145].

Therefore, it follows from the aforementioned findings that peritoneal membrane alterations may be linked to the bioincompatible nature of PD as such and the exposure to PD solutions with high concentration of glucose and GDPs, and other factors stimulating the release and accumulation of cytokines, such as peritonitis and low residual renal function. However, it should be noted that the important pathogenetic roles of glucose, GDPs, and inflammation do not exclude an important additive contribution of low pH, hyperosmolarity, and high lactate concentration in the "old" PD solutions as reviewed earlier [146, 147]. Possible relationships between high peritoneal solute transport rate, glucose exposure, and inflammation are shown in Figure 1.
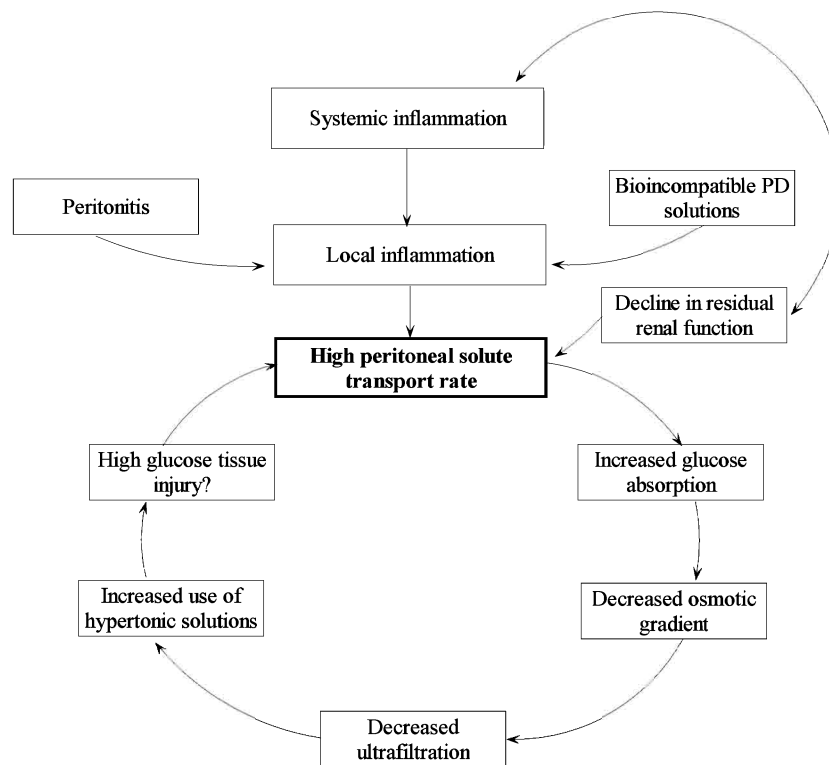
Figure 1. Possible relationships between high peritoneal solute transport rate, glucose exposure, and inflammation.

2.6 EFFECT OF PSTR ON NUTRITION, INFLAMMATION, AND MORTALITY

Peritoneal solute transport rate and nutrition

It has been suggested that a high peritoneal solute transport rate may be a risk factor for malnutrition and this may be due to several reasons.

Firstly, peritoneal protein loss has been suggested to be associated with malnutrition in CAPD patients [35, 148]. In CAPD, the average loss of protein into the dialysate reportedly ranges from 5 to 15 grams per 24 hours in various studies with large interindividual differences although in most patients the losses are about 5 to 10 grams for 24 hours [149]. Several reports using cross sectional data in CAPD patients [41, 42, 84, 150-153] have shown that there is an inverse correlation between D/P Cr and serum albumin. On the other hand, serum albumin is not an ideal nutritional marker as it is influenced also by many non-nutritional factors, and several previous studies [15, 150, 152-154] did not demonstrate an effect of peritoneal protein loss as such on nutritional status.

Secondly, a large influx of glucose absorbed from the dialysate may suppress appetite [41, 155]. There is a positive correlation between D/P Cr and the absorbed amount of glucose [109]. Hypophagia induced by PD solutions because of the utilization of absorbed nutrients from the solutions have been emphasized by our group [156] and others [157], using appetite models in animals. More recently, Zheng et al. [158] found that the degree of appetite inhibition was higher with a higher concentration of glucose.

Thirdly, fluid removal may affect nutritional status. The removal of small solutes, which correlate also with protein intake [159, 160], is dependent not only on the diffusive transport rate but also on the peritoneal fluid removal during PD [161, 162]. Thus, increased fluid removal results in increased small solute clearance and this in turn may influence nutritional status. On the other hand, fluid overload has been reported to be associated with inflammation [163-165], which may be one of the most important causes of malnutrition [166-172]. Freeman et al. [163] have reported that proinflammatory cytokines, generated in response to factors such as reduced tissue perfusion, altered gut permeability and congestion, may play an important role in

anorexia and the loss of lean body mass. Furthermore, Niebauer et al. [164] showed that diuretic treatment controlling volume status in chronic non-renal heart failure patients was associated with a significant decrease in systemic endotoxin levels. Konings et al. [165] recently reported that fluid status was positively correlated with CRP in CAPD patients. In general, high transporters may be at risk as they have difficulty controlling their volume status [43, 173] using standard PD prescriptions.

However, the relationship between peritoneal solute transport rate and nutritional status in PD patients is controversial [15, 41, 42, 152, 153]. The CANUSA study [15] showed that the serum albumin concentration decreased in the increased transport category but that there was no difference in other estimates of nutritional status such as subjective global assessment, % lean body mass, and normalized protein catabolic rate. In a cross sectional study, Harty et al. [153] found that increased peritoneal transport rate did not adversely affect somatic fat and protein status. Likewise, Szeto et al. [152] did not find any correlation between peritoneal solute transport status in new and prevalent patients and no relationship with longitudinal changes of nutritional status.

In contrast, Nolph et al. [41] reported significantly lower protein catabolic rate and lean body mass obtained from creatinine kinetics in high transporters. Cueto-Manzano et al [150] showed significantly lower serum creatinine levels in high transporters which may indicate reduced lean body mass in these patients. Kang et al. [42] observed that peritoneal solute transport characteristics correlated with the overall nutritional index of PD patients.
Nevertheless, protein-energy malnutrition with muscle wasting is present in a large proportion of PD patients [22, 174-177] and is a strong predictor of morbidity and mortality in maintenance dialysis patients [22-25, 178-181].

Peritoneal solute transport rate and inflammation

It is generally accepted that peritoneal solute transport rate depends on both effective peritoneal surface area and permeability [139]. Many of the mediators produced in the inflammatory process can affect microvascular permeability and vascular tone [77]. Such mediators include proinflammatory cytokines such as interleukin (IL)-6, VEGF, NO, and AGEs [36, 87, 182-184].

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Furthermore, high peritoneal solute transport rate has been shown to correlate with low serum albumin concentration assessed *before* the start of dialysis [185], at the start of dialysis [15, 17], and during the course of dialysis therapy [17, 41, 150]. Since low serum albumin concentration is also a marker of inflammation or infection [186-188] and underlying comorbid diseases [189-191], it is conceivable that a high peritoneal solute transport rate may be associated with inflammation. The CANUSA study [15] showed that an increased solute transport rate was associated with low serum albumin, perhaps reflecting a negative acute phase response. Recently, Pecoits-Filho et al. [36] reported that plasma and dialysate IL-6 levels correlated with a high peritoneal solute transport rate. Likewise, we have shown that an increase in peritoneal solute transport rate during the first year on PD was associated with high serum CRP [37]. In contrast, Wang et al. [192] found no relationship between peritoneal solute transport rate and inflammatory parameters such as serum IL-1β, tumor necrosis factor-α, CRP, and hyaluronan concentration in a cross-sectional study of patients who had been on PD for more than 3 months.

High peritoneal solute transport rate and mortality

It has been reported that PD patients with increased peritoneal solute transport rate have higher mortality rates [15-21]. The reason(s) for this is, however, not clear. As discussed above, a possible explanation may be that that high peritoneal solute transport rate may be a risk factor for malnutrition and this in turn may lead to a poor prognosis [178-180, 193, 194].

It should be noted however that the association between high peritoneal solute transport rate and high mortality may be due primarily to inflammation and/or comorbid diseases. As aforementioned, inflammation and comorbid diseases may contribute to high peritoneal solute transport rate. Furthermore, various markers of inflammation such as CRP [26, 28, 195-197], proinflammatory cytokines [27, 166, 198], and hyaluronan [167] and comorbid diseases [21, 22, 40, 180, 190] have shown to be strong predictors of mortality in ESRD patients. We previously reported that a high peritoneal solute transport rate in patients with comorbid diseases had a significant impact on patient survival while a high peritoneal solute transport rate did not affect patient survival in patients without comorbid diseases [21]. Thus, the association between high

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peritoneal solute transport rate and high mortality may be in part due to inflammation and/or comorbid diseases.

Furthermore, the high mortality in high transporters may also reflect an adverse effect of fluid overload on underlying cardiovascular disease, considering that cardiovascular disease is the most common cause of mortality in the PD patients [199] and that fluid removal is a predictor of mortality in these patients [34]. Fluid overload may be associated with both low serum albumin concentrations [200-202] and inflammation [163, 164], which could be risk factors for cardiac disease [35, 203-208]. For example, hypoalbuminemia may promote a hypercoagulable state, which could predispose to cardiovascular morbidity [35, 204] and a high CRP has been shown to be related to endothelial dysfunction in patients with cardiac disease [206]. Foley et al. reported that among dialysis patients, a 10-g/L fall in mean serum albumin level was independently associated with the development of *de novo* ischemic heart disease and cardiac failure [205].

It is thus tempting to speculate that a high peritoneal solute transport rate may be associated with malnutrition, inflammation, and cardiovascular disease, contributing to premature deaths in CRF patients [167, 209]. However, further studies are needed to verify this hypothesis.

3   AIMS OF THE PRESENT STUDY

The general aim of the present study was to analyze the impact of peritoneal solute transport rate on nutritional status and clinical outcome in PD patients. The specific aims of the present study were:

1. To evaluate the influence of initial nutritional status on CAPD patient survival and to identify factors affecting initial nutritional status and patient death. (Paper I)

2. To elucidate the impact of comorbid diseases on mortality in malnourished PD patients. (Paper II)

3. To evaluate the relationship between initial peritoneal solute transport rate and comorbid diseases on CAPD patient survival. (Paper III)

4. To identify the relationships between residual renal function, inflammation, and initial peritoneal solute transport rate in patients starting PD and the impact of these factors, alone or in combination, on patient survival. (Paper IV)

5. To evaluate the possible associations between peritoneal solute transport rate, fluid removal, inflammation, and nutritional status in patients who had been treated with PD for more than 6 months, and the impact of these factors on subsequent patient survival. (Paper V)

6. To elucidate the relationship between changes in peritoneal solute transport rate during patients' 1st year on PD, inflammation, and declining residual renal function. (Paper VI)

4 PATIENTS AND METHODS

4.1 PATIENTS

The patients in Study I, II, and III were recruited from the Dialysis Center at Soon Chun Hyang University Hospital in Seoul, Korea while those in Study IV, V, and VI were recruited from the Home Dialysis Unit at the Renal Medicine, Huddinge University Hospital, Stockholm, Sweden. Briefly, the patients were studied as follows:

In study I, 91 CAPD patients (48 males, aged 54 years), who underwent initial nutritional assessment and peritoneal equilibration test (PET), were included in this study. Nutritional status was assessed at a mean of 7 days after beginning CAPD by subjective global assessment (SGA), biochemical and anthropometric measurements, lean body mass calculated by creatinine kinetics, and calculation of the normalized protein equivalent of total nitrogen appearance from urea kinetic studies. Of 91 patients included in the analysis, 28 patients were on conservative therapy, 43 were on temporary HD for 6-8 weeks after the PD catheter was inserted subcutaneously, and the remaining 20 were transferred from long-term HD.

In study II, 153 PD patients (88 males, aged 53 years), who underwent initial assessment of nutrition, comorbid diseases survey, and PET at a mean of 7 days (range 3 - 24 days) after beginning PD, were included in this study. Based on the nutritional status as assessed by SGA and presence of comorbid diseases, patients were divided into four groups; malnutrition with (n=50) or without comorbid diseases (n=14), normal nutrition with (n=53) or without comorbid diseases (n=36). Of 153 patients included in the analysis, 32 patients were on conservative therapy, 100 were on temporary HD for 6-8 weeks after the PD catheter was inserted subcutaneously, and the remaining 21 were transferred from long-term HD.

In study III, 213 CAPD patients (120 males, aged 50 years) were included in this study. A modified PET was performed using 4.25% glucose dialysis solution at a mean of 7 days after beginning CAPD. Based on the dialysate to plasma creatinine concentration ratio at 4-h dwell (D/P Cr, mean +1SD) the patients were divided into high (H; n = 36), high average (HA; n = 65), low average (LA; n =78), or low (L; n = 34) transporters. Comorbid diseases were surveyed.

In study IV, 117 patients (70 males, aged 57 years) with initial assessments for residual renal function, serum CRP, and PET at a mean period of 0.4 ± 0.2 months (range: 0.1-1.0 month) after start of PD were included in this study. Based on residual renal function (cut-off point, 4 ml/min/1.73m^2), serum CRP (cut-off point, 10mg/L), and the D/P Cr, the patients were divided into different groups: low residual renal function (n = 54) and high residual renal function group (n = 63), high CRP (n =36) and normal CRP group (n =81), and high peritoneal solute transport rate (n = 17) and other peritoneal solute transport rate (n =100) groups, respectively.

In study V, 82 PD patients (48 males, aged 58 years) who underwent PET, evaluation of adequacy of dialysis and nutritional status, and biochemical analyses at 10.8 ± 2.8 months after start of PD were included in this study. Based on the D/P Cr, the patients were classified as H and HA (H/HA; n = 46) and LA and L (L/LA; n = 36) peritoneal solute transport rate.

In study VI, 76 PD patients (40 males, aged 57 years) were enrolled in the study. A standard PET was performed at a mean of 0.4 months and 1 year after beginning PD. Based on the change in D/P Cr during first year on PD, the patients were divided into two groups with 1) decreased or unchanged (n = 22) and 2) increased (n = 54) groups.

The clinical characteristics of the patients are presented in Table 3.

4.2 METHODS AND CALCULATION

Comorbid diseases

The following comorbid diseases were recognized and were defined as follows: *CVD* was defined as previous or present history of congestive heart failure, myocardial infarction, angina, peripheral vascular disease, or cerebrovascular disease. *Respiratory disease* included recent active tuberculosis, chronic lung disease, or recurrent asthmatic attacks. *Liver disease* was defined as chronic liver disease proved on biopsy or by persistently elevated serum glutamic-pyruvic transaminase and serum glutamic-oxaloacetic transaminase. *Diabetes mellitus* included both types I and II.

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Table 3. Summary of clinical characteristics of the patients

Study	I	II	III	IV	V	VI
Number	91	153	213	117	82	76
Nationality	Korean	Korean	Korean	Swedish	Swedish	Swedish
Gender, F/M	43/48	65/88	93/120	47/70	34/48	36/40
Age, years	54±12	53±12	50±14	57±15	58±14	57±14
Months on PD at assessment	0.2±0.1	0.2 0.1	0.3±0.2	0.4±0.2	10.8±2.8	12.0±3.1
Diabetes, n (%)	50 (55%)	84 (55%)	86 (40%)	42 (36%)	24 (29%)	20 (26%)
CVD, n (%)	-	33 (22%)	29 (14%)	28 (24%)	22 (27%)	16 (21%)
Body wt, kg						
Male	60±8	62±9	-	76±12	77±137	77±12
Female	49 ± 9	51±9	-	62±11	61±13	62±12
BMI, kg/m^2	219±3	22±3	-	24±3	24±4	24±3
S-albumin, g/L	37±6	36±6	36±7	33±5	32±5	32±5
RRF, ml/min	1.3±1.8	1.6±1.8	-	4.1±2.1	2.5±2.4	2.4±2.4

Abbreviations; CVD=cardiovascular disease, wt=weight, BMI=body mass index, RRF = residual renal function

Subjective global assessment

Subjective global assessment (SGA) was used for evaluation of the overall nutritional status (study I and II). The SGA includes six subjective assessments, three based on the patient's history of weight loss, incidence of anorexia and vomiting, and three based on the nurse's grading of muscle wasting, presence of edema, and subcutaneous fat loss. Each item was graded as 1 for severe malnutrition, 3 for moderate malnutrition, and 5 for normal nutrition (study I). A seven-point Likard-type scale of four items, i.e. weight loss, anorexia, subcutaneous fat loss, and muscle wasting was also used in study II. Each item was given a score to produce a global assessment. Scores of 1 to 2 represent severe malnutrition; 3 to 5, moderate to mild malnutrition; and 6 to 7, normal nutrition.

Biochemical measurements

A fasting venous blood sample was taken before the morning exchange. All patients were asked to refrain from taking foods and medications for 8 hours before the tests. Blood chemistry was measured by standard techniques. Serum albumin was

determined by the bromcresol purple in Stockholm and bromcresol green in Seoul. Serum CRP was measured by using an immunonephelometric method (only CRP values above 10 mg/L were reported).

Anthropometric measurements

Actual body weight was recorded in the morning (after drainage of dialysate). The mid-arm muscle circumference (MAMC) was derived from triceps skin fold thickness (TSF) and mid-arm circumference (MAC) as follows: MAMC = MAC − (π × TSF). The measurements were repeated three times and the highest score was recorded. Hand-grip strength was measured using the Harpenden dynamometer. The body mass index was calculated as weigh (in kilograms)/[height (in meters)]^2.

Lean body mass

Lean body mass was estimated by creatinine kinetics [210]. Total daily creatinine excretion, measured as the amount of creatinine excreted in dialysate and urine plus the estimated creatinine lost via the gut [211], were used to calculate lean body mass. Lean body mass in kilograms was computed by the following equation [210, 212]: Lean body mass (kg) = 0.029 × total creatinine production in mg/day + 7.38.

Estimated protein intake

Dietary protein intake was estimated from the protein equivalent of nitrogen appearance (PNA) using the Bergström equation PNA = 15.1+6.95 UNA (g/24hr) + protein loss (g/24hr) [213]. Urea nitrogen appearance (UNA) and protein losses were determined from the measured urea and protein excretion in dialysate and urine. PNA was normalized to desirable body weight obtained from the Metropolitan height and weight table [214].

Peritoneal equilibration test (PET)

The PET was performed as described by Twardowski et al. [215]. Briefly, a standard 4-h dwell period was used, using a 4.25% (Korean patients) or 2.27% (Swedish patients) glucose concentration for a 2-liter volume exchange. As glucose interferes with the assay for creatinine, the corrected value for creatinine was obtained by subtracting the glucose concentration multiplied by a correction factor; 0.00027 for

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Korean patients and 0.35 for Swedish patients. Note that mg/dL was used as units of glucose and creatinine in Korea and that mmol/L was used as a unit of glucose and μmol/L was used as a unit of creatinine in Sweden.

Residual renal function (RRF)

RRF was estimated by calculating the average residual renal clearance of urea and creatinine from a 24-h urine collection [45].

4.3   STATISTICAL ANALYSIS

Data are presented as mean ± SD. Student's t-test, ANOVA, or Kruskal-Wallis test was used to compare the difference between different subgroups. Chi-square test or Fisher's exact test was used to compare the nominal variables between different subgroups. Spearman's rank correlation was used to determine correlations between variables. Stepwise multiple regression analysis was applied to identify the factors independently affecting nutritional status (I), inflammation (IV), and changes in peritoneal transport rate (VI). Actuarial survival was performed using the Kaplan-Meier method and the log-rank test was used to compare survival between subgroups. Cox proportional hazards model was used to identify the factors predicting patient mortality. The difference was considered significant when the p-value was less than 0.05.

5 METHODOLOGICAL CONSIDERATIONS

5.1 PERITONEAL EQUILIBRATION TEST (PET)

In studies I-VI, PET was used to assess peritoneal transport characteristics. A standardized peritoneal equilibration test was developed by Twardowski et al. [215] as a simple alternative to the assessment of the diffusive mass transport coefficient. Heimbürger et al. [216] reported that D/P Cr and the ratio of dialysate glucose at time to dialysate glucose at dwell time 0 (D/D_0), provided a good estimate of the corresponding diffusive mass transport coefficients for Cr and glucose, respectively. However, although D/P Cr reflects mainly diffusive transport, it also includes some convective transport [216]. The D/D_0 ratio for glucose represents mainly diffusive transport, but it is also dependent on the initial dissipation of the glucose gradient within the interstitial compartment [81].

In studies III-V, mean D/P Cr ±1 SD was used to classify the patients into four peritoneal solute transport rate groups instead of using published classifications criteria [217], which may not be applicable for patients investigated in Korea and Sweden. In consequence, the number of patients with high transport rate was smaller compared to patients with HA or LA solute transport rate. Furthermore, transplantation and technique failure were censored observations for patient survival analysis in the present studies. Thus, the statistical power is weak in the high transport group because of the small number of patients and events.

In study V, value of D/P Cr was considerably higher (mean D/P Cr: 0.81 ± 0.13, range 0.47-1.11) than that reported by Twardowski et al. [217]. The discrepancy is probably due to differences between the studies both as regards laboratory methods and patient characteristics.

5.2 NUTRITIONAL ASSESSMENT

The incidence of malnutrition in dialysis patients may vary with the assessment method used.

Subjective global assessment (SGA)

The SGA is a valid clinical estimate of nutritional status for dialysis patients [218] and this estimate was strongly associated with PD patient survival [22]. However, the main limitation of SGA is that it is a subjective method. In the same patients, assessment results can differ between different examiners.

Lean body mass calculated by creatinine kinetics

The lean body mass (LBM) was calculated by creatinine kinetics which has been proposed for assessment of skeletal muscle protein mass in maintenance dialysis patients [210, 219] and correlated with patient survival [220]. However, creatinine kinetics gives estimates of LBM that are systematically lower (by about 6-8kg) compared to estimates of lean body mass by dual energy x-ray absorptiometry, bioelectrical impedance analysis, anthropometry, and total body potassium [221-224]. The results obtained with this method are influenced by mathematical coupling with creatinine kinetics. Furthermore, it is affected by creatinine intake mainly in the form of meat, and by the creatinine metabolism which is not well studied in patients with CRF. The variability in individual patients is large.

Estimated protein intake

The protein equivalent of total nitrogen (PNA) is an indirect estimate of dietary protein intake [225] and is a key measure of nutritional status in dialysis patients [226]. However, this method is influenced by mathematical coupling with urea kinetics and the correlation between PNA and dietary protein intake is far from perfect due to various factors that influence metabolism, such as dietary protein and energy intake, acidosis, inflammation/infection, and other forms of comorbidity. Furthermore, the fecal nitrogen excretion may vary considerably between different patients, although it tends to be constant in the individual patient [225] and unmeasured losses of nitrogen by other routes, such as respiration, sweat, skin desquamation, nails, hair, ejaculates, blood sampling, and other blood losses are not taken into account. Finally, normalized PNA (nPNA) by actual weight tends to be high in malnourished, underweight PD patients [227]. In the present studies, PNA was normalized to desirable body weight obtained from the Metropolitan height and weight table [214].

5.3   SERUM C-REACTIVE PROTEIN (CRP)

In the present studies, we relied on a single measurement of inflammation, which cannot take into account any variation of inflammation that may have occurred over time. Furthermore, the limit for reported values of CRP at the Department of Clinical Chemistry, Huddinge Hospital was 10 mg/L and this value, which is generally thought to indicate inflammation, was chosen as the cut-off point classification of high CRP. However, the normal level of CRP is much lower and the use of 10 mg/L as "cut-off" level makes it impossible to distinguish between patients with normal and slightly elevated CRP.

5.4   RESIDUAL RENAL FUNCTION (RRF)

The accuracy of the measurements of RRF is dependent on a complete urine collection, and the recording of the exact duration of the collection time period. This may also affect the calculation of creatinine and urea kinetics.

6 RESULTS AND DISCUSSION

6.1 PREVALENCE OF MALNUTRITION IN PD (I-II)

Protein-energy malnutrition and wasting are present in a large proportion of patients with chronic renal failure [174-177, 220]. By using SGA, we found malnutrition in 42-45% of the Korean patients at the start of PD (in studies I-II). These results are similar to those of Fenton et al. [174] who found malnutrition in 41.6% of Canadian patients who had been on CAPD for less than three months.

6.2 DIFFERENT TYPES OF MALNUTRITION IN PD (II)

It has been suggested that there may be different types of malnutrition in dialysis patients [228, 229]. Stenvinkel et al. [172] proposed two types of malnutrition; one that is associated with poor nutritional intake due to uremic syndrome *per se* while the other type is associated with significant comorbidity and inflammation.

We found that 78.1 % of malnourished patients had comorbid diseases and that 48.5% of patients with comorbid diseases had malnutrition (Figure 2). A high prevalence of comorbid diseases in the malnourished patients in the study II suggests that malnutrition may be related to comorbid diseases. This is in agreement with previous studies [189, 230], which suggested that comorbid conditions may influence the nutritional status either by reduced nutritional intake or by increased catabolism, resulting in depleted energy stores, loss of somatic protein, and decreased visceral protein. Indeed, in study II, malnourished patients with comorbid diseases had lower initial serum albumin, lower serum creatinine, lower lean body mass, and lower % lean body mass compared to all other study groups (Table 3).

Furthermore, it is well appreciated that serum albumin is more closely related to inflammation than to nutritional status [200] and that the serum albumin level may reflect the presence of systemic disease [190]. Our finding of significantly lower serum albumin concentrations in malnourished patients with comorbid diseases compared to malnourished patients without comorbid diseases is in line with previous reports [172, 188]. Heimbürger et al. [188] reported that the serum albumin level did not differ significantly between well-nourished and malnourished predialysis patients whereas the presence of inflammation was associated with lower serum albumin levels. Thus, the

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subgroup of patients with low serum albumin concentrations, comorbid diseases, and malnutrition in this study may represent the second type of malnutrition.

	Malnutrition	Normal nutrition	
With comorbid disease	50 (32.8%)	53 (34.6%)	103 (67.3%)
Without comorbid disease	14 (9.1%)	36 (23.5%)	50 (32.7%)
	64 (41.8%)	89 (58.2%)	

Figure 2. Distribution of 153 patients according to presence of malnutrition and comorbid diseases. Data from II.

Table 3. Comparison of initial variables among different study groups

	Malnutrition		Normal nutrition		ANOVA
	With CMD	Without CMD	With CMD	Without CMD	P value
	(n = 50)	(n = 14)	(n = 53)	(n = 36)	
Age (years)	55.7 ± 10.1	51.8 ± 17.5	55.7 ± 10.2	47.0 ± 13.6	0.003
sAlb (g/dL)	3.3 ± 0.5	3.9 ± 0.4	3.7 ± 0.5	3.9 ± 0.5	<0.0001
sCr (mg/dL)	7.9 ± 2.3	9.2 ± 3.3	8.2 ± 2.2	9.8 ± 3.1	0.004
nPNA (g/kg/day)	0.99 ± 0.17	0.93 ± 0.20	1.07 ± 0.25	1.13 ± 0.23	0.01
LBM (kg): male	36.6 ±10.4	40.0 ± 4.8	40.0 ± 9.3	48.8 ± 13.6	0.004
female	25.2 ± 6.1	26.6 ± 6.4	31.2 ± 6.8	33.7 ± 6.8	0.0006
% LBM	54.9 ±14.5	56.7 ± 11.2	61.9 ±13.5	67.9 ± 14.8	0.001
RRF (mL/min)	1.1 ± 1.6	0.8 ± 1.3	2.1 ± 2.1	1.8 ± 1.6	0.002

Abbreviations: CMD = comorbid diseases; sAlb = serum albumin; sCr = serum creatinine; nPNA = normalized protein equivalent of total nitrogen appearance; LBM = lean body mass; RRF = residual renal function. Data from study II.

6.3 ASSOCIATION BETWEEN MALNUTRITION AND PATIENT SURVIVAL (I-II)

Malnutrition has been reported to be associated with increased mortality [22-25]. The CANUSA study [22] showed that mortality increased with low serum albumin concentration and poor nutritional status. Perez et al. [25] reported that high creatinine excretion ratio predicted a good outcome in PD patients. We also found that malnutrition as assessed by SGA (studies I and II) and lean body mass were independent risk factors for mortality (study I).

However, it should be noted that the confounding effect of comorbid diseases on mortality was not dissociated from that of malnutrition in the CANUSA study [22] or in study I. Furthermore, several lines of evidence suggest that nutritional status alone does not predict morbidity and mortality [231-233] and therefore a better nutritional intake or improved nutritional status will not necessarily reduce morbidity and mortality [233]. On the other hand, comorbid diseases are strongly associated with poor clinical outcome [40].

Different mortality in the combination of comorbid diseases and malnutrition is shown in Figure 3 and Table 4. We found that comorbid diseases exert a powerful influence on mortality in both malnourished and normally nourished PD patients. The risks for mortality in patients with malnutrition and comorbid diseases and in patients with normal nutrition and comorbid diseases were nearly 9 and 5 times, respectively, that of patients with normal nutrition but without comorbid diseases. The risk in patients with malnutrition but without comorbid diseases was 2.7 fold higher than that of patients with normal nutrition without comorbid diseases but the difference did not reach statistical significance. Thus, our observation suggests the importance of comorbid diseases as a cause of poor clinical outcome in malnourished PD patients.
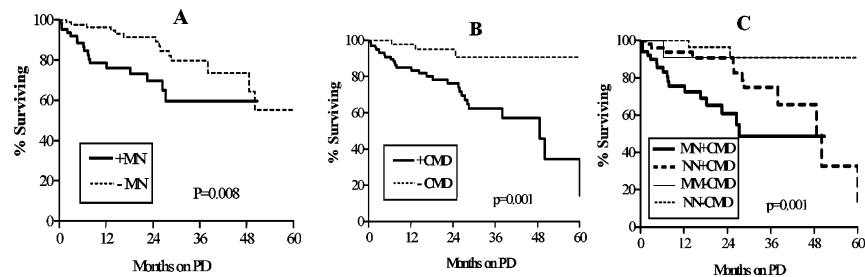
Figure 3. Probability of patient survival in different study groups. Patients with malnutrition (A), comorbid diseases (B), and both malnutrition and comorbid diseases (C) had significantly lower patient survival compared to patients in other groups (by log rank test). Data from study III.

Table 4. Adjusted* risk ratios for mortality in different study groups (Cox proportional hazards multivariate analysis)

| Variable	Risk ratio	χ^2	P value
Malnutrition with comorbid diseases	9.01	7.57	0.006
Malnutrition without comorbid diseases	2.72	0.64	NS
Normal nutrition with comorbid diseases	5.07	4.28	0.04
Normal nutrition without comorbid diseases	1.00		

* Adjusted for age, gender, serum albumin, residual renal function, and D_4/P_4 creatinine. Data from study II.

6.4 ASSOCIATION BETWEEN PERITONEAL SOLUTE TRANSPORT RATE AND MORTALITY (III-V)

Comorbid diseases and mortality in high transporters (III)

Although increased peritoneal solute transport rate has been reported to predict mortality in PD patients [15, 16, 19, 234], it is controversial whether increased peritoneal solute transport rate predicts patient survival independently. Both the CANUSA study [15] and the Stoke PD study [19] reported that the peritoneal solute transport rate predicted patient survival independently. However, Wang et al. [16] found a high mortality rate with increased peritoneal permeability in patients that also

had impaired fluid and small solute removal. Blake [35] suggested that the most likely mechanism underlying the high mortality in high transporters is its effect on cardiovascular status, which is further impaired by fluid overload. In the study III, we found that at the start of PD, high transporters had a higher proportion of patients with comorbid diseases and that high peritoneal solute transport rate had a significant impact on patient survival; however, it did not affect patient survival in patients without comorbid diseases (Figure 4 and Table 5). Therefore, it is likely that high peritoneal solute transport rate is in some way associated with an increased risk of death due to comorbid diseases. However, it should be noted that there was a non-significant increase in mortality in high transporters without comorbidity compared to other transporters without comorbidity (Figure 4B). Therefore, it is possible that the lack of significance is due to the small sample size (Type 2 error).
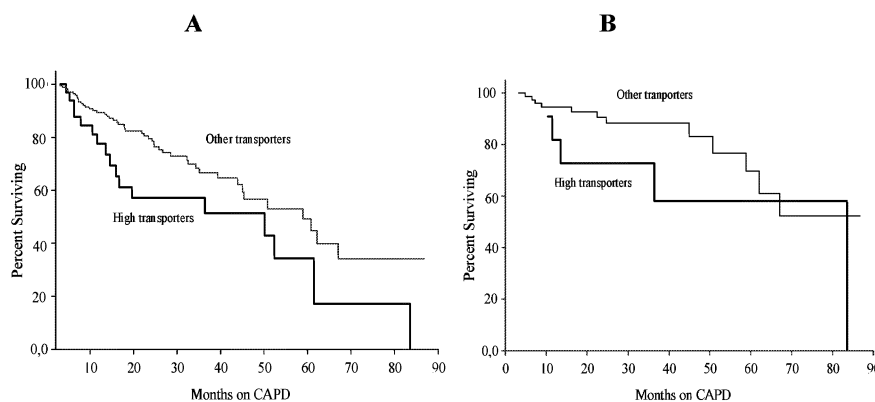
Figure 4. The 2-year patient survival was **57.1%** and **79.5%** for high and other transporters in all 213 patients (A) while in 97 patients without comorbid diseases, the 2-year patient survival was **72.7%** and **90.6%** for high and other transporter (B). Data from study III.

Table 5. Risk factors for mortality (Cox proportional hazards multivariate analysis)

Variable	All (n=213)		Without comorbid diseases (n=97)	
	RR (95% CI)	P value	RR (95% CI)	P value
Comorbid diseases	1.49 (1.07-2.18)	0.02		
Age (per year)	1.06 (1.04-1.09)	<0.0001	1.12 (1.06-1.21)	<0.0001
S-albumin (per g/L)	0.95 (0.90-0.99)	0.02	1.03 (0.92-1.16)	0.63
D/P Cr (per 0.1 unit)	1.23 (1.02-1.49)	0.03	1.13 (0.75-1.70)	0.55

Abbreviations: RR = relative risk, CI = confidence interval. Data from study III.

Residual renal function, inflammation, and mortality in high transporters (IV)

Residual renal function (RRF) [29-33], inflammation [26, 27], and a high peritoneal solute transport rate [15-21] have been reported to predict mortality in PD patients. In the study IV, we confirmed that both initial RRF and initial serum CRP had an impact on overall patient survival whereas a high peritoneal solute transport rate was associated with increased mortality only during the initial year on PD.

It has been reported that a high peritoneal solute transport rate at the start of PD is associated with inflammation [88] and that inflammation predicts mortality in PD patients [26, 27]. Although a significant relationship between an initial high peritoneal solute transport rate and inflammation was not found in the study IV, Figure 5 shows that the initial peritoneal solute transport rate correlated significantly with initial serum albumin concentrations and initial serum CRP levels in the thirty-six patients with CRP$\geq$10 mg/L, i.e. the only group for which individual quantitative CRP values were available. Furthermore, three of the five high transporters with high CRP died within the first year of PD whereas 2 of the twelve high transporters with normal CRP died during the follow-up period although there was a small number of deceased patients. These findings underline the possible importance of inflammation as a contributing factor for the decreased patient survival in high transporters during the initial year on PD.

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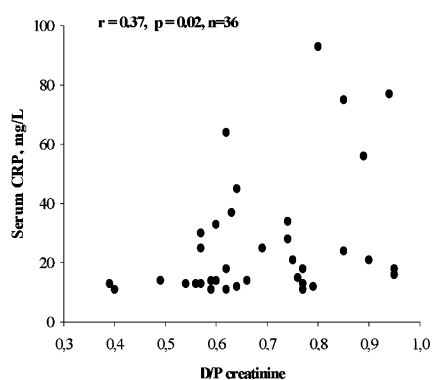
Figure 5-a. Correlation between serum CRP and D/P CR. Data from study IV.
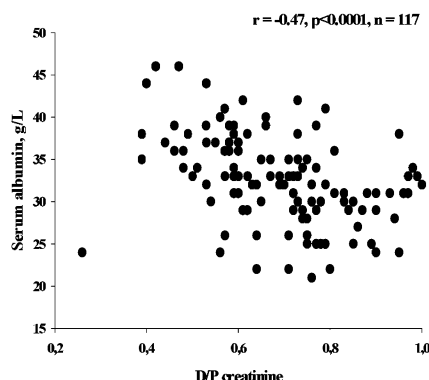
Figure 5-b. Correlation between serum albumin and D/P CR. Data from study IV.

However, in study IV, a confounding factor was that patients with high peritoneal solute transport rate had higher initial RRF than the other patients. An important finding of study IV is that a low RRF is a factor affecting inflammation (Table 5). It is likely that the high RRF in this group may have lessened the impact of high peritoneal solute transport rate on patient survival. On the other hand, high RRF in high transporters is associated with a decrease in peritoneal solute transport rate during the first year of PD [37] and this change in the peritoneal solute transport rate may have reduced the impact of the predictive role of a high initial peritoneal solute transport rate on mortality during the subsequent years of PD.

Table 5. Factors associated with inflammation (Logistic regression analysis)

Variable	Estimated coefficient	Standard error	χ^2	P value
Age	0.046	0.019	5.89	0.02
Cardiovascular disease	0.103	0.269	0.15	NS
Gender (male)	0.444	0.262	0.26	NS
Serum albumin	-0.093	0.050	3.47	0.06
Residual renal function	-0.263	0.120	4.63	0.03
D/P creatinine	-1.489	0.880	0.63	NS

Data from study IV.

The combined effect of two or more of the three characteristics low RRF, inflammation, and high peritoneal transport rate is seen in Figure 6. Although any conclusion is limited by the low number of patients, one may speculate that high transporters with no inflammation and well-maintained RRF may not represent a high risk group. Figure 6 shows that in the patients (n = 40) who had none of these characteristics, the 5-year survival was 100% whereas the 5-year survival was only 17.5% in patients with two or more of these characteristics.
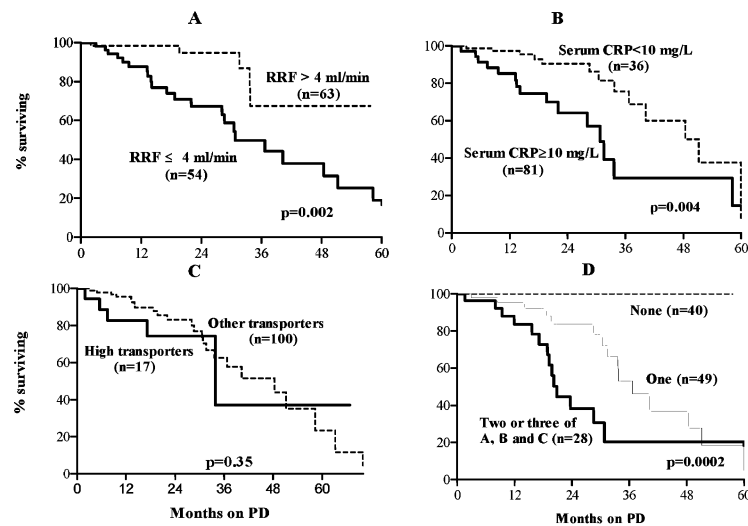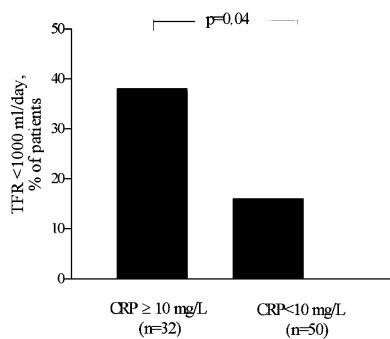

Figure 6. Probability of patient survival according to RRF (**A**), serum CRP (**B**), PSTR (**C**), and presence of A, B and C (low RRF, high CRP, and high PTR) (**D**) at the start of PD. Patient survival was significantly lower in the patients with low RRF, high serum CRP, and more than two of these discriminators (low RRF, high CRP and high PSTR). However, in the high PSTR group, patient survival rates were significantly lower only at one year of PD (82.6% versus 95.6% for high PTR and other PTR, respectively, p=0.03) but not for subsequent years of PD (p>0.05). Data from study IV.

Fluid removal, inflammation, and mortality in high transporters (V)

High peritoneal solute transport rate in patients undergoing CAPD is associated with decreased peritoneal fluid removal and this may result in decreased small solute removal [161, 235], which may lead to malnutrition. Furthermore, fluid overload has been reported to be associated with inflammation [163, 164], which is one of the most important causes of malnutrition [166-172]. In general, high transporters are at risk of fluid overload as they have difficulty controlling their volume status due to less efficient fluid removal, especially when residual renal function is marginal or poor [49].

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Thus, it is possible that these factors in high transporters may contribute to malnutrition and this in turn may lead to high mortality.

However, in study V, despite positive correlations between total fluid removal and serum albumin concentrations, nPNA, %lean body mass, total Kt/Vurea, and total CCr, there were no significant differences in total fluid removal and nutritional variables between the different transport groups. In addition, peritoneal solute transport status was not associated with subsequent patient survival whereas inflammation predicted mortality in these patients.


In study V, we also found that patients with high serum CRP had a higher proportion of patients with reduced (<1000 ml) total fluid removal compared to patients with normal serum CRP (38% vs. 16%, p=0.04, Figure 7). However, the prevalence of high CRP did not differ between the different transport groups. Thus, our findings suggest that patient survival at least in part could be related to fluid removal and inflammation, and not to peritoneal solute transport rate.

Figure 7. Association between serum CRP and total fluid removal. Patients with high serum CRP($\geq$10 mg/L) had a higher proportion of the patients with reduced total fluid removal (<1000 ml) (black bar) compared to patients with normal serum CRP (<10 mg/L) (38% versus 16%, p = 0.04). Data from study V.
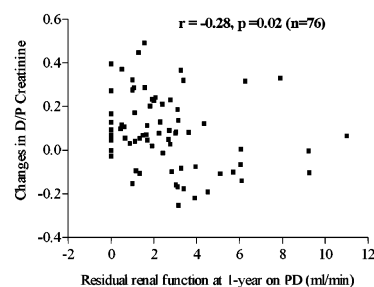
6.5 CHANGES IN PERITONEAL SOLUTE TRANSPORT RATE DURING THE FIRST YEAR ON PD (VI)

Although the factors contributing to changes in the peritoneal solute transport rate during the first year on PD are not clear, Figure 8 shows that changes in the peritoneal solute transport rate were strongly correlated with a high initial serum CRP, and patients with increased peritoneal solute transport rate had decreased serum albumin. It is generally accepted that the peritoneal solute transport rate depends on both effective peritoneal surface area and permeability [139]. Many of the mediators

produced in the inflammatory process can affect microvascular permeability and vascular tone [77]. Thus, our finding of a strong relationship between changes in peritoneal solute transport rates and serum inflammatory markers suggests that a state of inflammation may affect changes in the peritoneal solute transport rates during the first year of PD.
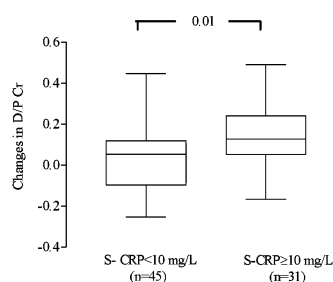
Figure 8. Relationship between changes in D/P Cr and serum CRP. Patients with high CRP had significantly increased D/P Cr (0.14 ± 0.16 versus 0.05 ± 0.16, p=0.01). Data from study VI.

Figure 9. Relationship between changes in D/P Cr and RRF. RRF was inversely correlated with changes in D/P Cr. Data from study VI.

In addition to this relationship, Figure 9 reveals that changes in the peritoneal solute transport rate were correlated with RRF. Patients with an increased peritoneal solute transport rate had lower RRF as well as a marked decline of RRF during the first year of PD. Similar findings have been described by Davies et al. [83, 138], who reported that solute transport was stable in patients with stable RRF, resulting in a lesser requirement of hypertonic glucose exchanges in these patients. This may suggest that changes in the peritoneal solute transport rate could be related to intraperitoneal glucose or other components in the dialysis fluid. However, in study VI, we found no significant relationship between changes in the peritoneal solute transport rate, amount of dialysate glucose used, and glucose absorption amount. In the patients with changes in RRF >1.9 ml, three patients used icodextrin solution and seven patients were treated with APD whereas in the patients with changes in RRF ≤1.9 ml, five patients were treated with APD. This may explain why there was no major difference in the amount of dialysate glucose used and glucose absorption amount between the two groups.

On the other hand, there may also be an association between renal function and inflammatory mediators [236-239]. It has been suggested that renal failure *per se* may

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contribute to the inflammatory response with elevated serum levels of pro-inflammatory cytokines [236, 240]. We also found that the patients who had changes in RRF >1.9 ml during the first year on PD had more often at the 1-year test a high serum CRP compared with patients who had changes in RRF ≤1.9 ml. Therefore, our finding of a negative correlation between changes in peritoneal solute transport rate and RRF and a significant correlation between low RRF and high CRP may suggest that a reduction in renal function may aggravate an inflammatory state due to decreased renal clearance of cytokines and that this may increase the peritoneal solute transport rate.

From our findings, the possible relationships between high peritoneal solute transport rate and various related factors and mortality are summarized in Figure 10.
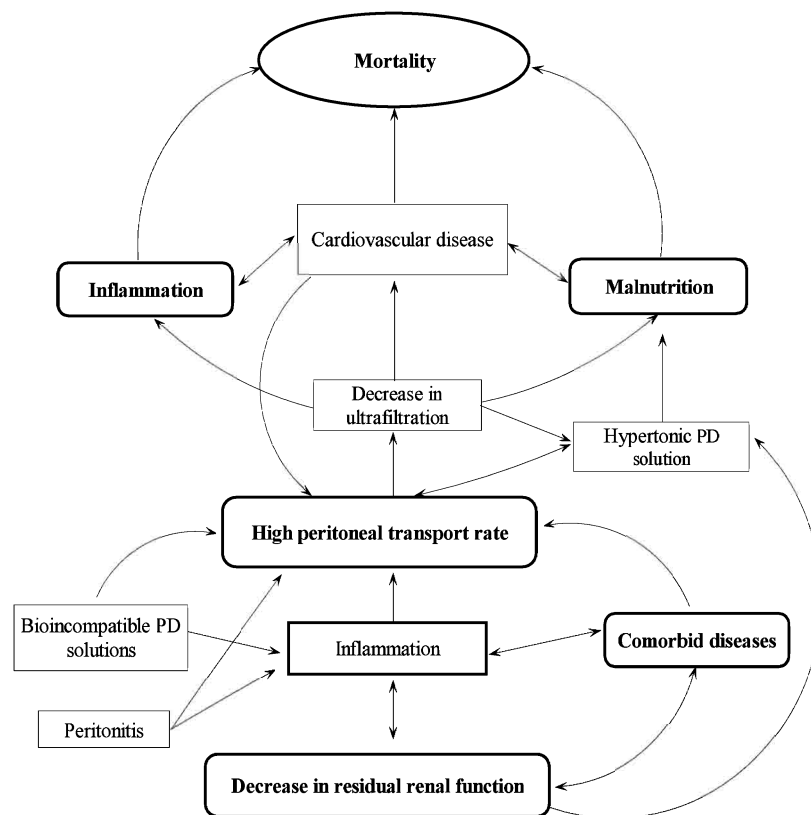
Figure 10. Possible relationships between high peritoneal solute transport rate and mortality in PD patients.

7 SUMMARY AND CONCLUSIONS

I. Malnutrition as assessed by SGA was common in Korean CAPD patients at initiation of dialysis. Initial malnutrition as assessed by initial SGA and initial lean body mass were independent factors of death. Initial nutritional status, therefore, appears to exert a powerful influence on CAPD patient survival.

II. There is a high prevalence of malnutrition and comorbid diseases at the start of PD and the combined presence of these conditions is associated with high mortality. Malnutrition in the absence of comorbid diseases was associated with a statistically insignificant increase in mortality. High mortality in the malnourished PD patients is, therefore, to a large extent related to comorbid diseases rather than to malnutrition as such.

III. These data suggest that a high peritoneal solute transport rate at initial PET is associated with high mortality and that this is in part due to an increased prevalence of comorbid disease in high transporters. The high transporters with comorbid diseases represent a subset of patients with especially poor prognosis.

IV. In patients starting PD, a low initial RRF is associated with inflammation, and a low RRF and inflammation are both associated with high mortality. A high peritoneal solute transport rate was associated with increased mortality, but only during the initial year on PD. These results underline the importance of residual renal function and inflammation as predictors of mortality in PD patients whereas the predictive power of peritoneal solute transport rate as such may loose its significance if these two parameters are taken into consideration.

V. In this group of prevalent PD patients who were assessed after on average 10.8 months of PD treatment 1) inflammation was an independent predictor for mortality; 2) reduced total fluid removal was associated with impaired nutritional status and decreased small solute clearance as well as with inflammation; 3) peritoneal solute transport status however was *not* significantly associated with nutritional status after 6 months treatment with PD and was *not* associated with subsequent patient survival. These results from a selected group of patients indicate that high peritoneal solute transport status as such in prevalent patients may represent less of a clinical problem

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than previously thought compared with the impact of inflammation and inadequate fluid removal.

VI. Our data suggest that changes in peritoneal solute transport rate during patients' 1st year on PD may be linked with inflammation and declining residual renal function. Inflammation and residual renal function were identified as independent factors affecting peritoneal solute transport rate during the 1st year on PD. It is possible that inflammation may cause both an increase in peritoneal solute transport rate and a decline in residual renal function, or that the decline in residual renal function further aggravates inflammation due to less efficient removal of cytokines. On the other hand, it cannot be ruled out that solute transport rate may result in changes (fluid overload or increased use of hypertonic glucose solutions) that might aggravate inflammation.

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