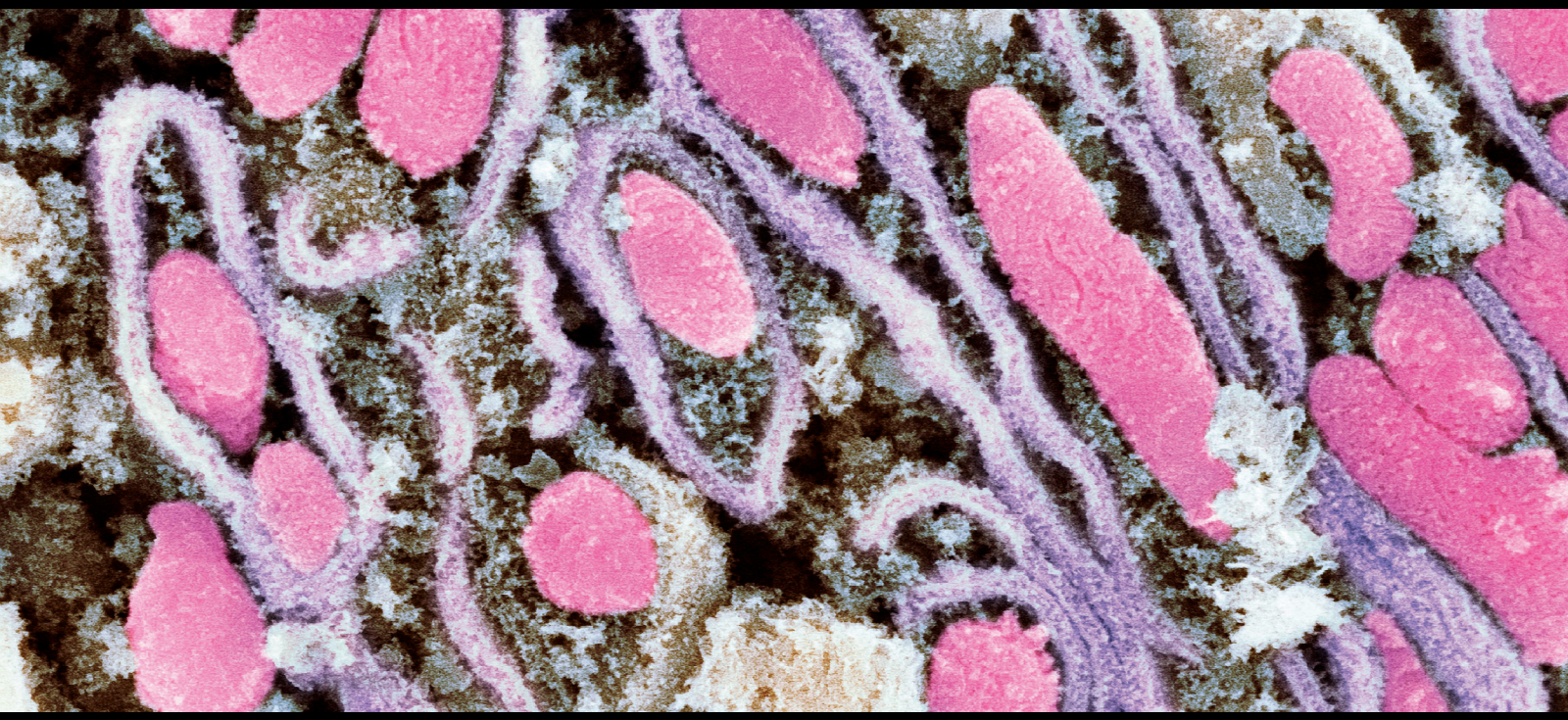
International Journal of Nephrology

Peritoneal Dialysis—Moving from Current Status to the Future

Guest Editors: Kook-Hwan Oh, Yong-Lim Kim, Wai-Kei Lo, and Peter J. Margetts



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Editorial Board

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Editorial

Peritoneal Dialysis—Moving from Current Status to the Future

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Peritoneal dialysis (PD) has been widely used as one of the major renal replacement therapies (RRT) for end-stage renal disease (ESRD) patients. Although PD therapy has witnessed remarkable technical advances, and the patient's survival early after starting PD is comparable, or superior, to that of hemodialysis, it is currently faced with many challenges. Long-term PD is associated with progressive loss of UF capacity, resulting in increased cardiovascular morbidity or ultimate discontinuation of PD. This is related to inflammation, new vessel formation (angiogenesis), and fibrotic thickening of the peritoneal membrane (PM). Bioincompatible PD fluid, along with peritonitis, is the major contributor to the PM change. In order to establish PD as a more general and longstanding renal replacement therapy, clinicians and scientists need to investigate the pivotal issues such as adequate volume control and long-term preservation of the peritoneal membrane and the prevention from devastating conditions such as encapsulating peritoneal sclerosis.

In this special issue, we have compiled elegant reviews and clinical studies with a special interest in the above-mentioned "*Contemporary issues of PD therapy*." This special issue deals with many of the current issues such as PD catheter implantation by nephrologists, clinical benefits of the newer biocompatible PD fluid, peritonitis, and how to cope with low ultrafiltration volume with bimodal and twice-daily icodextrin use and several others. It is the hope of our editorial committee that this special issue will contribute to an improved patient care and serve as a stimulus to seek a new knowledge in renal replacement therapy.

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Clinical Study

Transperitoneal Calcium Balance in Anuric Continuous Ambulatory Peritoneal Dialysis and Automated Peritoneal Dialysis Patients

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Backgrounds. Calcium (Ca) and bone metabolism in continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD) patients show a remarkable difference depending on dialysis modalities. The levels of serum Ca and phosphate (P) in HD patients fluctuate contributing to the intermittent and rapid removal of plasma solute unlike in CAPD. Characteristics of plasma solute transport in automated peritoneal dialysis (APD) patients are resembled with that in HD. The purpose of the present study was to examine the difference of transperitoneal Ca removal between APD and CAPD anuric patients. *Subjects and Methods*. Twenty-three APD anuric patients were enrolled in this study. Biochemical parameters responsible for transperitoneal Ca removal in 24-hour and 4-hour peritoneal effluents were analyzed on CAPD and APD. *Results*. Transperitoneal Ca removal on APD was smaller compared with that on CAPD. The Ca removal was related to the ultrafiltration during short-time dwell. Decrease of the Ca removal during NPD induced by short-time dialysate dwell caused negative or small Ca removal in APD patients. The levels of intact PTH were increased at the end of PET. *Conclusion*. It appears that short-time dwell and frequent dialysate exchanging might suppress the transperitoneal Ca removal in anuric APD patients.

1. Introduction

Bone disease is one of the serious complications in chronic dialysis patients. Adynamic bone disease and secondary hyperparathyroidism are associated with not only viability and quality of life (QOL) but also mortality in long-term dialysis patients. It is generally considered that Ca and bone metabolism between peritoneal dialysis (PD) and hemodialysis (HD) patients provided remarkable differences according to dialysis modalities. Hemodialysis patients undergo rapid and intermittent removal of phosphate, uremic toxins and excess body fluid from sera, and influx or efflux of Ca influent in such metabolism [1–3]. Higher serum Ca levels and continuous glucose loading occur, which may lead to a higher incidence of adynamic bone in CAPD patients compared with that in HD patients [4, 5]. Patients with very low parathyroid hormone (PTH) level had a higher mortality rate after adjustment for age, gender, diabetes, and dialysis vintage [6]. The turnover of bone remodeling in PD patients is lower than that in HD patients [4, 5]. Using 3.5 mEq/L Ca dialysate in HD, Ca removal demonstrated a negative balance [7, 8]. It is recognized that Ca mass transport in CAPD patients depends on the following factors: Ca concentration in the dialysis fluid, starting plasma Ca and P concentrations, and ultrafiltration, which removes the nonprotein bound diffusible calcium [9–12]. Characteristics of plasma solute transport in patients with automated peritoneal dialysis (APD) are resembled with that of HD. Effects of APD on residual urinary volume compared with that in CAPD were reported [13, 14]. It is postulated that a short-time dwell of peritoneal dialysate may lead to differences in the transperitoneal Ca balance and PTH secretion between APD and CAPD patients.

The objective of the present study was to evaluate differences of transperitoneal Ca balance between APD and CAPD patients without residual renal function.

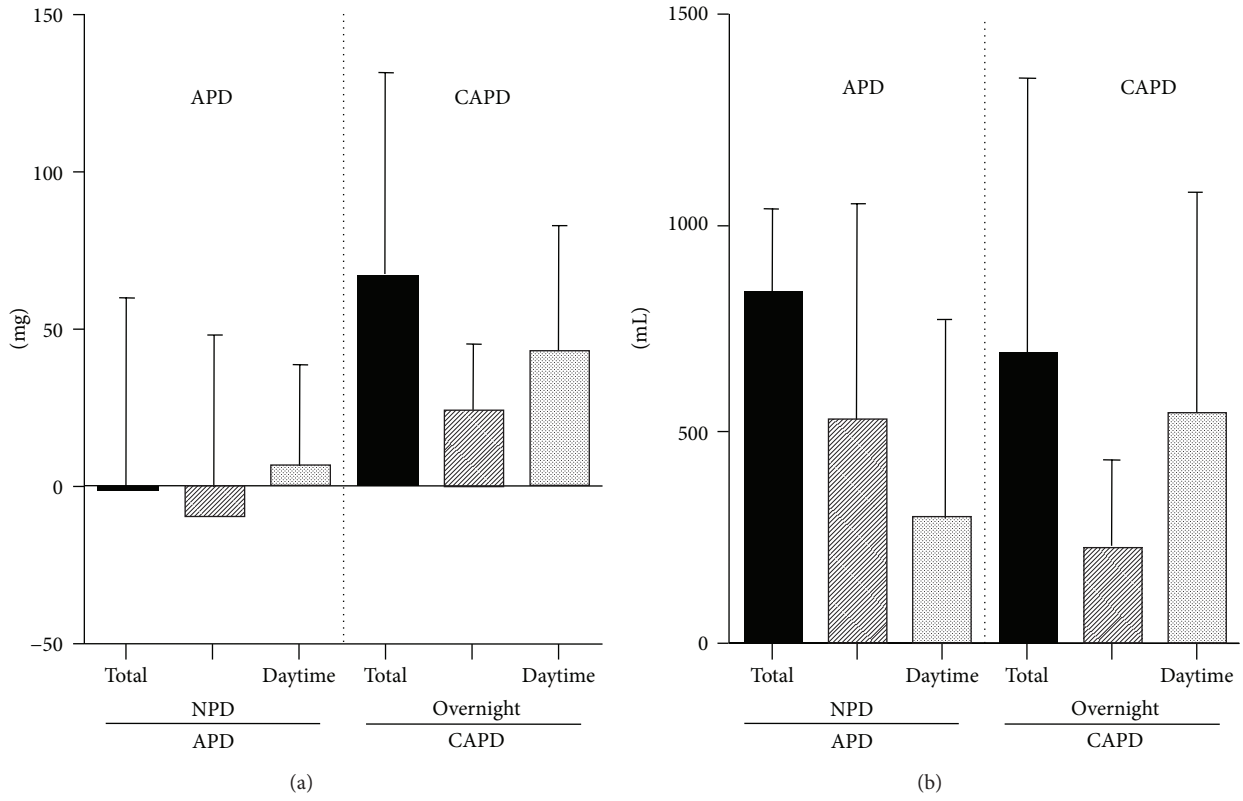

Figure 1: (a) Transperitoneal Ca balance and (b) ultrafiltration on APD and CAPD in same PD patients. Black bars show total Ca balance in 24 hours. Diagonal bars show transperitoneal Ca removal in NPD or overnight dwell. Dots bars show transperitoneal Ca removal in daytime dwells.

2. Subjects and Methods

2.1. Patients. Twenty-three patients (15 males and 8 females) took a standard peritoneal equilibrium test (PET), and 24-hour peritoneal effluents (PE) were collected on CAPD for the determination of solute kinetics every year. Transperitoneal balance studies of calcium (Ca) were examined for these anuric patients treated by PD. All PD patients provided informed consent to participate in this study. Most of the measurements are performed in the routine of our hospital laboratory. The transperitoneal Ca balance was calculated according to the formula for peritoneal mass transfer as follows:

$$\begin{aligned}&\text{Concentration of Ca} \times \text{Drained volume}\\ &-\text{Concentration of Ca} \times \text{Infused volume.}\end{aligned} \quad (1)$$

A routine peritoneal equilibration test (PET) using 2.5% dextrose PD solution was performed after the initiation of PD in new patients and every 12 months thereafter. PET results were used for the patients in order to choose the optimized PD prescriptions. PD effluents were obtained just before the PET and at 4 hours as the long-time and short-time dwell samples. In uremic patients and non-CKD patients, family members gave their consent in writing. The Ethics Committee of Juntendo University Faculty of Medicine approved this study including evaluation of peritoneal morphology and peritoneal function.

Statistical analysis consisted of both simple and multiple linear regressions. Comparisons between the two groups were made using Mann-Whitney test. Relationships between ultrafiltration and transperitoneal Ca removal were analyzed with Spearman's correlation coefficient test. A value of $P < 0.05$ was regarded as significant. Data were expressed as mean ± standard deviation (SD).

3. Results

3.1. Characteristics of CAPD and APD Patients. Basic characteristics of participants are shown in Table 1. Mean age of patients was 51.1 ± 14.9 years old. Mean duration of PD was 78.7 ± 35.9 months. Noncalcium-based phosphate binders were not administered in all participants. The D/P ratio of creatinine in APD patients was 0.68 ± 0.13. Dairy average dosage of $CaCO_3$ was 3.44 ± 2.57 g. Average dialysate Ca concentration in APD patients was 6.10 ± 0.94. Eleven APD patients used low-calcium PD solution in order to suppress elevation of serum Ca. Icodextrin PD solution was not used.

3.2. Calcium Balance in 24-Hour Collected Peritoneal Effluents. Eleven peritoneal effluents (PE) for 24 hours on APD and 23 PEs on CAPD were collected in the same patients

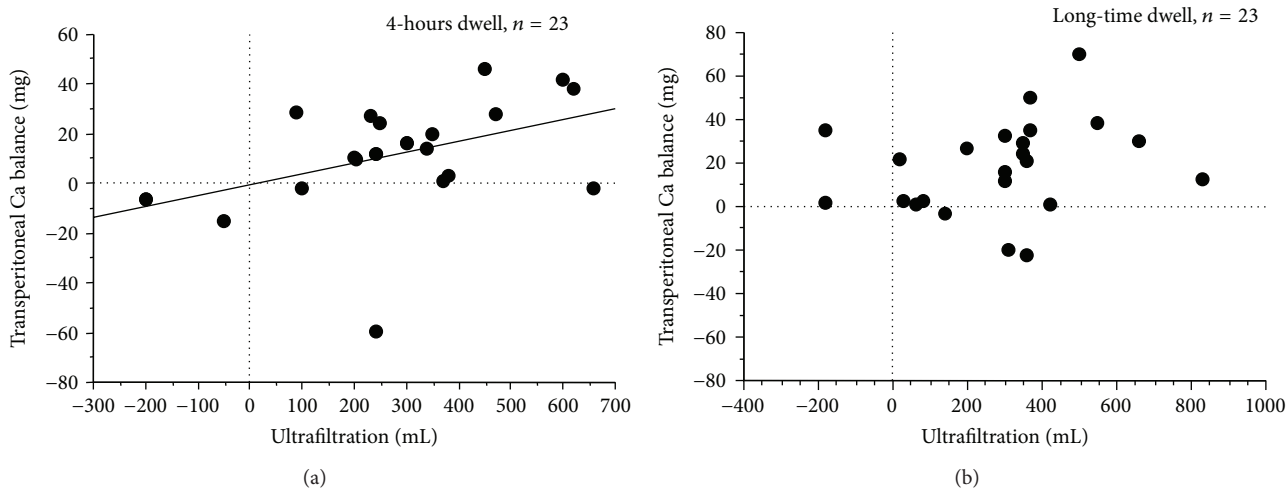

Figure 2: Relationship between transperitoneal Ca removal and ultrafiltration in short-time dwell and long-time dwell. (a) In 4-hour dwell. (b) In long-time dwell.

Table 1: Characteristics of participants.

Number of patients	23
Age (years)	51.5 ± 14.9
PD duration (months)	78.7 ± 35.9
Serum creatinine (mg/dL)	11.7 ± 2.48
Serum calcium (mg/dL)	10.0 ± 0.66
Serum phosphate (mg/dL)	5.07 ± 1.11
Intact PTH (pg/mL)	178.3 ± 180.4
Weekly Ccr (L/week)	51.9 ± 7.48
D4/P cre	0.68 ± 0.13
$CaCO_3$ (g/day)	3.44 ± 2.57
Vitamin D3 (μg/day)	0.03 ± 0.07
Dialysate Ca concentration (mg/L)	6.10 ± 0.94

Mean ± SD, Cre: creatinine, PET: peritoneal equilibration test, PTH: parathyroid hormone, and Ccre: creatinine clearance.

(Table 2). There was no significant difference in the Ca concentration of PD solution between APD and CAPD. Ca removal on APD was significantly smaller than that in CAPD. Small molecule substance removal quantities were independent on the PD option and dwell volume. We obtained 24-hour collected PE on APD and CAPD on consecutive days in 23 PD patients. 1.37 ± 63.18 mg of Ca was absorbed from PD solution on APD, whereas 67.1 ± 58.6 mg of Ca was removed on CAPD (Table 3). Calcium was removed on CAPD; however, the Ca removal indicated zero on APD, using the same Ca concentration PD solution and removing the same amount of body fluid, respectively, ($P < 0.01$, Figure 1(a)). During night peritoneal dialysis (NPD), Ca was absorbed from PD solution (Figures 1(a) and 1(b)).

3.3. Relationship between Ultrafiltration and Intact PTH on PET. Calcium removal in PD patients using 2.5% dextrose dialysate containing 7.0 mg/dL of Ca is shown in Table 4. The ultrafiltration was 311.9 ± 137.7 mL. Calcium concentration in peritoneal effluent was markedly decreased at 4 hours. There was no significant change in the levels of serum Ca. The levels of intact PTH were remarkably increased at 4 hours of PET (from 170.2 ± 161.5 pg/mL to 201.1 ± 181.3 pg/mL, $P < 0.002$).

3.4. Relationship between Transperitoneal Ca Removal in PE and Ultrafiltration in Short-Time Dwell and Long-Time Dwell. Transperitoneal Ca removal and ultrafiltration showed a significant positive relationship both in short-time and long-time dwell (Figure 2, coefficient value = 0.367, $P < 0.02$). Calcium removal was related to ultrafiltration in short-time dwell. Meanwhile, there was no relationship between Ca removal and ultrafiltration in long-time dwell.

4. Discussion

We demonstrated that transperitoneal Ca removal in APD patients without residual renal function was smaller, compared with that in CAPD patients. The transperitoneal Ca removal was dependent on the PD modality. In the same patients, the Ca removal in APD was significantly lower than that in APD. The solute and body fluid kinetics have been shown to be quite different between CAPD and HD [2, 3]. Factors influencing calcium removal during dialysis are as follows: (1) ultrafiltration rate, (2) concentration of serum ionized calcium at starting of dialysis session, (3) concentration of serum inorganic phosphate at the start, and (4) concentration of dialysate calcium [9–12, 15, 16]. The levels of serum Ca and phosphorous in HD patients fluctuated, contributing to intermittent and rapid removal of solute and body fluid; meanwhile, constant solute and body fluid kinetics were major characteristics of CAPD therapy. Exchanges and removal of minerals and small molecule solutes were rather drastic during NPD and steady during day-time dwell

Table 2: Twenty-four-hour collected peritoneal effluent on APD and CAPD in same PD patients.

	Dwell volume (mL)	Drain volume (mL)	Ca of PDS (mg/dL)	24-hour collected PE				
				UN (mg)	Cre (mg)	TP (mg)	Ca (mg)	iP (mg)
APD $n = 11$ samples	14222.2 ± 1371.8	15101.0 ± 1356.5	5.9 ± 0.7	4911.7 ± 1280.8	869.4 ± 264.7	4.5 ± 2.1	9.9 ± 38.7	378.2 ± 75.0
CAPD $n = 23$ samples	8200.0 ± 462.6*	9190.0 ± 698.0*	6.0 ± 1.8	4783.4 ± 1263.2	927.7 ± 268.0	7.0 ± 3.2*	111.3 ± 107.2*	355.0 ± 126.8

Mean ± SD, $^{*}P < 0.001$, $^{**}P < 0.02$ versus APD.
PDS: peritoneal dialysis solution, UN: urea nitrogen, Cre: creatinine, TP: total protein, and iP: inorganic phosphate.

Table 3: Transperitoneal Ca balance and ultrafiltration on successive PD treatment in the same patients.

	Ca concentration of dialysate (mg/L)	Ultrafiltration (mL)	Transperitoneal Ca balance (mg)
APD	5.84 ± 0.72	832.44 ± 225.66	−1.37 ± 63.18
CAPD	6.00 ± 0.90	773.75 ± 595.03	67.12 ± 58.63*

Mean ± SD, $^{*}P < 0.05$ versus APD, $n = 23$ patients.

Table 4: Effluent and serum Ca and parathyroid hormone on PET.

		At the start	At 4 hours
PE volume	(mL)	2116.7 ± 65.8	2428.6 ± 137.7*
Ca concentration of PE	(mg/dL)	3.90 ± 0.14	3.36 ± 0.21#
Ca concentration in sera	(mg/dL)	9.44 ± 0.70	9.41 ± 0.60
Intact PTH	(pg/mL)	170.2 ± 161.5	201.1 ± 181.3**

Mean ± SD, $^{*}P < 0.01$ versus at the start, $^{**}P < 0.002$ versus at the start, $^{\#}P < 0.0001$ versus at the start, $n = 23$.
PET: peritoneal equilibrium, PE: peritoneal effluent, Ca: calcium, and PTH: parathyroid hormone.

in continuous cyclic PD (CCPD) patients. Since dialysate Ca concentration influences Ca balance during HD and CAPD, active vitamin D and calcium-containing phosphate binders regulating serum Ca concentration require a reduction in dose, from 1.75 to the more physiological dialysate Ca concentration [1, 7, 8, 17–19].

The present study showed that the dwell time and ultrafiltration played crucial roles in transperitoneal Ca removal in PD patients. Ca removal in long-time dwell was independent on ultrafiltration, whereas ultrafiltration increased Ca removal in short-time dwell. According to the results, it appears that smaller amount of Ca-containing phosphate binder in APD patients can be administrated compared with that in CAPD patients. The average concentration of dialysate Ca was 6.1 mg/dL, and all participants used low-calcium dialysate at least one or two bags to prevent the elevation of serum Ca. The level of PTH markedly increased during PET, but not the elevation of PTH (data not shown) in this study. However, the slight Ca change contributing to ultrafiltration might be a stimuli of PTH secretion.

5. Conclusions

This study showed the characteristics of the Ca removal in anuric APD patients as being somewhere between that of CAPD and HD. Short-time dwell and frequent dialysate exchanges during NPD suppressed the transperitoneal Ca removal in APD patients; it appears that the levels of serum Ca increase easily in anuric APD patients using calcium-containing phosphate binder.

Disclosure

This study is an experimental investigation on human subjects according to The Ethics Committee of Juntendo University Hospital approval.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Review Article

Are the Mesothelial-to-Mesenchymal Transition, Sclerotic Peritonitis Syndromes, and Encapsulating Peritoneal Sclerosis Part of the Same Process?

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Mesothelial-to-mesenchymal transition (MMT) is an autoregulated physiological process of tissue repair that in uncontrolled conditions, such as peritoneal dialysis (PD), can lead to peritoneal fibrosis. The maximum expression of sclerotic peritoneal syndromes (SPS) is the encapsulating peritoneal sclerosis (EPS) for which no specific treatment exists. The SPS includes a wide range of peritoneal fibrosis that appears progressively and is considered as a reversible process, while EPS does not. EPS is a serious complication of PD characterized by a progressive intra-abdominal inflammatory process that results in bridles and severe fibrous tissue formation which cover and constrict the viscera. Recent studies show that transdifferentiated mesothelial cells isolated from the PD effluent correlate very well with the clinical events such as the number of hemoperitoneum and peritonitis, as well as with PD function (lower ultrafiltration and high Cr-MTC). In addition, in peritoneal biopsies from PD patients, the MMT correlates very well with anatomical changes (fibrosis and angiogenesis). However, the pathway to reach EPS from SPS has not been fully and completely established. Herein, we present important evidence pointing to the MMT that is present in the initial peritoneal fibrosis stages and it is perpetual over time, with at least theoretical possibility that MMT initiated the fibrosing process to reach EPS.

1. Introduction

Peritoneal dialysis (PD) is a form of renal replacement therapy that uses the peritoneal membrane (PM) as semipermeable barrier for the exchange of toxic substances and water. This technique has increased during the last years, in parallel to its complications. Currently, prolonged survival on PD has been reached due to technological advances, prevention, and early diagnosis of uremic complications. The basic objective of DP is the long-term preservation of the PM function. The PM is lined by a monolayer of MCs that have characteristics of epithelial cells and act as a permeability barrier across which ultrafiltration and diffusion take place. The long-term exposure to hyperosmotic, hyperglycaemic, and low pH of dialysis solutions and repeated episodes of peritonitis or hemoperitoneum cause injury of the peritoneum, which progressively becomes denuded of MCs and undergoes fibrosis and neovascularization [1]. Such structural alterations are considered the major cause of ultrafiltration failure [1, 2]. In this context, it has been proposed that local production of vascular endothelial growth factor (VEGF), a potent proangiogenic cytokine, during PD plays a central role in processes leading to peritoneal angiogenesis and functional decline [2–5]. Recently, it has recognized the role of transdifferentiation of mesothelial cells (MMT) in peritoneal fibrosis, angiogenesis, lymphangiogenesis, and PM

failure. The process is governed by the transforming growth factor-β (TGF-β) and the representative cell form is the myofibroblast. TGF-β synthesis may be stimulated by glucose, and infections, via peritoneal leucocyte-derived factors and it is considered the master molecule of tissue fibrosis [6, 7]. The maximum expression of peritoneal fibrosis or sclerotic peritoneal syndromes (SPS) induced by PD fluids is the encapsulating peritoneal sclerosis (EPS) which is a serious complication of PD [8, 9]. The SPS is traditionally considered as a reversible process, while EPS is not. Emerging evidences have indicated that MMT is persistently present in initial and end stages of peritoneal fibrosis [10–12]. Moreover, its significant blockade decreases the peritoneal damage induced by PD fluids, including fibrosis and angiogenesis [13, 14]. These findings suggest that there is a chain between MMT and SPS. But the jump from SPS to EPS has not yet been fully established. Here we review current data regarding a possible connection between MMT, SPS, and EPS, considering the MMT as a new process in PD presumably involved in the deterioration phases of PM.

2. The Peritoneal Membrane Fibrosis in PD

Peritoneal fibrosis (or sclerosis) is a term that comprises a wide spectrum of peritoneal structural alterations, ranging from mild inflammation to severe sclerosing peritonitis and its most complicated manifestation, encapsulating peritonitis sclerosis (EPS) [8, 9, 15]. Simple sclerosis (SS), an intermediate stage of peritoneal fibrosis, is the most common peritoneal lesion found in the patients after few months on PD and could represent the initial phase of sclerosing peritonitis syndrome (SPS). Rubin et al. [16] described a normal thickness of the peritoneum of 20 μm, which after a few months on PD could reach up to 40 μm (SS). The SPS is a progressive sclerosis that is characterized by a dramatic thickening of the peritoneum (up to 4000 μm) and is accompanied by inflammatory infiltrates, calcification, neovascularization, and dilatation of blood and lymphatic vessels, being the most thickening commonly used pathological criterion for differential diagnosis [17–19]. In some instances, granulated tissue is observed to immerse in exudates containing fibrin and giant cells, probably reflecting chronic inflammation. Peritoneal fibrosis consists in the accumulation of ECM proteins (collagen I, III, V, VI, fibronectin, tenascin) in the interstitium, with augmented number of fibroblasts, some of them with myofibroblastic features, and mononuclear cell infiltration. In the basement membrane there is usually accumulation of collagen IV and laminin and proteoglycans, and polysaccharides and glycoproteins are also present extracellularly [8, 9, 15]. In 2003, our group discovered that MCs undergoes a process of transdifferentiation that is so-called epithelial to mesenchymal transition (EMT) or mesothelial to mesenchymal transition (MMT) by the negative effects of PD liquids [10].

2.1. Mesothelial-to-Mesenchymal Transition (MMT). MMT is a complex and generally reversible process that starts with the disruption of intercellular junctions and loss of apical-basolateral polarity, typical of epithelial cells, which are then transformed into fibroblast-like cells with increased migratory, invasive, and fibrogenic features. The objective of this process is to repair tissue wounds by promoting the recovery of ancestor capabilities of epithelial cells. Cell migration, production of extracellular matrix, and induction of neoangiogenesis are the main activities [20]. The process is conducted by the transforming growth factor-β (TGF-β).

2.2. TGF-β Is the Master Molecule in MMT and Peritoneal Fibrosis Pathway. TGF-β is a growth factor implicated as the causal agent in fibrosis of different tissues and organs [7]. This exists in tissues, generally in a latent and inactive form, bound to the latency-associated peptide (LAP), and it is activated through proteolytic cleavage by thrombospondin, plasmin, cathepsin D, furin, and glycosidases when exposed to PD solutions [21]. Its synthesis may be stimulated by glucose, acid pH, and infections, via peritoneal leucocyte-derived factors and its overexpression has been correlated to worse PD outcomes [22–25].

Four different intracellular signal pathways are triggered upon engagement of TGF-β to its receptors, being the most important as the Smads cascade [26–30]. Clinically, the factors involved in the stimulation of TGF-β and the initiation of SPS include the following.

(1) Peritonitis is one of the most commonly invoked pathogenic factors for SPS [8, 9]. Some etiological agents have been identified including the bacteria *Staphylococcus aureus, Pseudomona* sp., and *Haemophilus influenza*. These pathogens promote conversion of fibrinogen by coagulase to a molecular form of fibrin particularly resistant to break down by plasmin [31]. The mechanism by which peritonitis promotes progression to SP may start by the denudation of the mesothelium, which facilitates the peritoneal damage by the bioincompatible compounds from PD solutions, increases peritoneal permeability to glucose, and favours nonenzymatic glycosylation of submesothelial structural proteins and decrease in fibrinolytic capacity. Furthermore, peritonitis is associated with the increased intraperitoneal. Expression of TGF-β and other cytokines and growth factors that may accelerate the fibrotic process of the peritoneum [32].

(2) Time on PD: some authors [17–19], but not others [8, 9], have found a relationship between months on PD and the incidence of SPS. The main factor appears to be the prolonged exposure to glucose from PD solution [33], which is able to stimulate TGF-β and fibroblast growth factor (FGF) productions by MC [22, 34]. In addition, we have observed a correlation between the time on PD and the progression MMT [10].

(3) Poor biocompatibility of dialysis fluids: high glucose concentration, glucose degradation products (GDPs), advanced glycation end-products (AGEs), low pH, and lactate buffer in current PD solutions are all factors that have been implicated in peritoneal fibrosis [32, 35, 36]. These compounds have been associated to diminished production of phospholipids by MC, impaired phagocytosis capacity of macrophages, decreased activation of neutrophils [37] and lymphocytes [38], and direct toxicity of fibroblasts. Although the PD fluid components are risk factors for SP [37, 38], it is not always possible to identify the triggering agents for the progression of SP. Chlorhexidine and povidone iodine,

Table 1: Implication of TGF-β in peritoneal fibrosis.

(i) Activates quiescent fibroblasts into myofibroblasts
(ii) Increases fibronectin production by fibroblast and MC
(iii) Induces the expression of connective tissue growth factor (CTGF) by MC
(iv) Stimulates the synthesis of PAI, the natural inhibitor of tPA, contributing to the generation of an antifibrinolytic environment
(v) Increases matrix synthesis and inhibits matrix degradation by decreasing the ratio MMPs/TIMPs
(vi) Induces MMT of MC

employed to sterilize PD connections and preparation of surgeries, have been also implicated in the progression of SP [39, 40]. The peritoneal catheter as well as bags and tubes for dialysis are other risk factors that may cause reactive fibrosis [9]. Low pH, GDPs, and AGEs are shown to have a great capacity for stimulating the production of TGF-β [41].

(4) On the other hand, evidence for genetic predisposition to SPS has also been proposed. In fact the Japanese population in PD seems to be more prone to develop EPS [42]. Similar to other diseases, the genetic factors may predispose certain PD patients to develop EPS. In this case, the genetic polymorphisms of genes related to fibrosis and inflammatory processes may get a great importance in triggering the EPS. This is the case of single nucleotide polymorphisms (SNPs) in the promoter region of the interleukin-6 (IL-6), which has been related to transporter status [43]. However, there are few studies about the polymorphisms and their association with EPS, due to the large number of patients that are needed to do these studies and the low frequency of this pathology. In this regard, there is a study that associated RAGE polymorphisms with EPS; however, due to the low number of patients studied this relationship does not reach statistical significance [44].

There are a number of genes candidate to be studied which may have polymorphisms as toll-like receptors, inflammatory cytokines, chemokines, and several growth factors. Currently it is known around 2.4 million SNPs in the human genome and it is estimated that there may be millions more. In the future, it will be known which of these variants may be related with the development of EPS or in the perpetuation of SPS in EPS so that patients may have an individualized treatment trying to prevent its development.

Table 1 summarizes the effects of TGF-β into the peritoneum. We have recently demonstrated that TGF-β is definitively one of the most important molecules in the initiation and perpetuation of peritoneal damage in PD. Experimentally, we used [14] strategies to identify the leading roles of TGF-β in peritoneal damage. First, in our mouse model we induced PD MMT, fibrosis, and type-I PM failure injecting daily glucose-rich PD liquid for 5 weeks. Two more groups received the same stimulus and a cotreatment with inhibitors of TGF-β two peptides (P17 and P144). Fibrosis, angiogenesis, and MMT decreased at the end of treatment also the PM function was preserved. Second, mice were infected with adenovirus encoding active TGF-β by intraperitoneal injection, and animals were killed on day 4 after infection. We reply all anatomical and functional changes induced by PD fluids but also find evidence of local endothelial cells (CD31+) conversion to fibroblasts, reinforcing the hypothesis that TGF-β and MMT are keys in the damage induced by PD liquids in PD.

2.3. From MMT to SPS. The importance of establishing a connection between MMT, SPS, and EPS is the potential therapeutic and preventive effect of blocking this axis. Also emerging evidence suggests that partial or total blockage of the MMT prevents early stages of PM fibrosis and angiogenesis and preserves the PM function [14]. Moreover, current studies show that TGF-β is probably the most important molecule in the PM failure development and so acts on a single molecule, the TGF-β, and facilitates therapeutic approach [14, 45]. In fact we have shown that blockade of TGF-β significantly attenuated PM failure induced by PD fluids [14].

One of the biggest problems to establish the definitive connection between SPS and EPS is that the EPS animal model has not been fully and properly developed. While in our mice PD model in 4 or more weeks reaches the typical changes induced by PD fluids on humans, the peritoneal fibrosis model with chlorhexidine results too much artificial and extremely aggressive for PM. The experimental development of an appropriate EPS model is mandatory. Possibly the most appropriate EPS mice model would be to maintain long term (months) in PD according to our model of SPS. Once accepted this limitation, the current data suggest that MMT and SPS are part of the process. We have analyzed serially PM pieces of mice in PD at baseline, 15, and 30 days and we found a linear correlation between time on PD, the thickness of the PM, and the number of MCs cytokeratin (+) and FSP-1 (+) in the submesothelial area (unpublished data by us). This phenomenon was accompanied by local progressive loss of the mesothelial monolayer which indicates an important participation of the MMT in the development of peritoneal fibrosis and MCs migration to submesothelial area (unpublished data by us). Using a TGF-β adenovirus model, we found early MMT at day 4 after stimuli intraperitoneal injection that was correlated with PM fibrosis [14]. Similar finding was found by others [45]. Clinically, in MCs serially isolated and cultured from PD effluents, the MMT was present progressively over time in PD and is associated with solute transport disorders and ultrafiltration failure [46]. In PM biopsies from 35 PD stable patients performed during the first 2 years on PD, we demonstrated that the first morphological change in peritoneum that appears as a consequence of PD is submesothelial thickening partially caused by the MMT. This phenotype change is associated with an increase in peritoneal solute transport independent of the number of

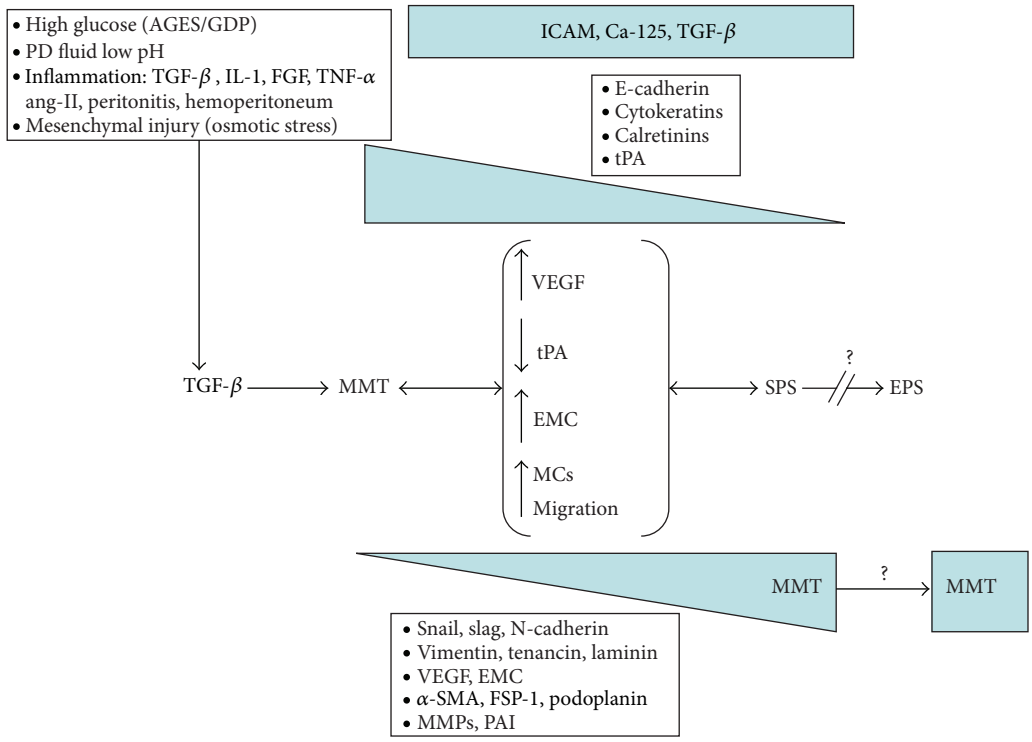

Figure 1: Mechanism for MMT, SPS, and EPS induction as a single process. The PD fluids bioincompatibility induces overproduction of TGF-β that initiates and perpetuates the MMT. MMT includes angiogenesis (VEGF), decreased in fibrinolytic capacity by decrease in tPA, increased in extracellular matrix component production (collagen-1, fibronectin, etc.), and migration mediated by MMPs. MCs lost their gene expression of E-cadherin, cytokeratins, and other and gain the expression of snail, slag, N-cadherin, and so forth. All of these changes become to peritoneal fibrosis and sclerotic peritoneal syndromes (SPS) which are originally reversible. MMT increases in parallel to fibrosis but its role in EPS pathogenesis is unknown. EPS is considered as irreversible process. ICAM, TGF-β, and Ca-125 expression remains stables.

capillaries present in the tissue [11]. Reached this point the following questions arise, could have peritoneal fibrosis without MMT? or more specifically, could have MMT without the participation of TGF-β? Experimental data by us [13, 14] and others [47] indicate that blocking MMT in different degrees result in a significantly attenuation of structural and functional changes of PM. Using the adenovirus (TGF-β) and our PD mice model, the double submesothelial staining for cytokeratin (+) and FSP1 (+) was positive in approximately 37% of activated fibroblasts, indicating its epithelial origin [14]. However, the peritoneal fibrosis is inhibited in more than 50% indicating that direct inhibition of TGF-β with anti-TGF-β peptides inhibited other effects of this molecule as the activation of regional fibroblasts. Promising results have been also obtained acting on immune system [48], on AGEs accumulation, or on renin-angiotensin system (ACE, AR-II, Paricalcitol) [49] and BMP-7 which also modulate directly or indirectly the TGF-β [13]. These arguments lead us to conclude that TGF-β is a key in the initiation and possibly perpetuation of an uncontrolled MMT, which leads to fibrosis and SPS (Figure 1).

2.4. From SPS to EPS. The next question is as follows: at which point the SPS becomes an irreversible process to become EPS? The "two-hit" hypothesis explains the EPS as the result of the PD injury. Two factors are required for the onset of EPS: a predisposing factor, such as peritoneal deterioration from persistent injury caused by peritoneal dialysis (the first "hit"), and an initiating factor, such as inflammatory stimuli superimposed on the chronically injured peritoneum (the second "hit"). Peritoneal deterioration (consisting of mesothelial denudation, interstitial fibrosis, vasculopathy, and angiogenesis) leads to an increased tendency toward plasma exudations that contain fibrin and coagulation factors. The fibrins in the exudates contribute to the intestinal adhesions and formation of fibrin capsule. Inflammatory stimuli caused by infectious peritonitis are superimposed on the damaged peritoneum and act as an initiating factor to trigger the onset of EPS. Inflammatory cytokines also induce activation and proliferation of the peritoneal fibroblasts, promoting peritoneal fibrosis and intestinal adhesions. The relationship between the extent of the first and second "hits" can be demonstrated. The extent of peritoneal damage (the first "hit") increases with the duration of peritoneal dialysis. The onset of EPS depends on the total intensity of both lesions: peritoneal damage and inflammatory stimuli. For the onset of EPS, the total intensity must be greater than a given threshold. The extent of the inflammatory stimuli (the second "hit") required for the onset of EPS therefore decreases as the duration of peritoneal dialysis increases [42, 50].

In both cases (acute and chronic peritoneal injury), the TGF-β is activated with subsequent initiation and perpetuation of MMT and its deleterious effects (fibrosis, angiogenesis, etc.). However, it is very difficult to establish the point of no return in peritoneal lesions clinically because patients with type-I PM failure usually recover functionality and possibly tissue damage with rest peritoneal [51]. In experimental animals, data about fibrosis reversibility are not available. Unfortunately, the initial degree of PM fibrosis has been determined in very few cases (peritoneal biopsies not available). Finally a genetic component cannot be ruled [43, 44].

2.5. From MMT to EPS. In both, experimental animals [14, 45] and human peritoneal biopsies from patients within 2 years in PD [11], it seems clear that MMT is an early phenomenon able to determine the degree of peritoneal fibrosis and the future of the PM. But no information about MMT in patients with long term in PD or diagnosis of EPS is available. It is possible that MMT may be an initial phenomenon and few signs of it are in severe stages of fibrosis (Figure 1). However, in bridles and postsurgical adhesions, we have found MMT signs (unpublished data by us), and Bowel adherences may represent an intermediate degree between the SPS and EPS (our unpublished data by us), which encourages to conduct studies aimed to find MMT peritoneum with EPS. These findings represent important evidence linking both processes, but indirect evidence may also be marked. In human studies [10] and in experimental animals (unpublished data), our studies demonstrated a direct relationship between MMT and time on PD. Similarly, the several studies showed a parallel between EPS and time on PD [52, 53]. Another important fact is that peritoneal function studies also show a parallel between high frequency of MMT of MCs, high Cr-MTC, and low ultrafiltration. Indeed we observed a higher frequency of mesothelial fibroblastoid phenotype in patients with type Cr-MTC >11 mL/min [54]. Furthermore, as is well known, patients with EPS even displayed these with SPS showed similar functional PM deterioration [9, 55, 56]. Another indirect association between these two events is peritonitis. Yáñez-Mo and coworkers [10] found that the frequency of nonepithelioid MC was associated with episodes of peritonitis, this means that peritonitis leads to the MMT. In the case of the EPS, there are some studies in the literature that correlate it with peritonitis events. Previous studies suggest that peritonitis may predispose to EPS, especially if this is caused by *Staphylococcus aureus*, fungi, and/or *Pseudomonas* [9, 57]. There is also an association between persistent infections such as tuberculosis peritonitis and EPS [58]. Although peritonitis and EPS are highly associated in several studies it is also known that, especially in a long-term case, EPS may occur without peritonitis. Moreover, patients that have suffered from more events of peritonitis have a higher incidence of MMT and EPS, which suggest again that these processes are related. Finally, we have analyzed more than 10 peritoneal biopsies from patients with EPS where we had found a significant amount of mesothelial cells (CK +) in the peritoneal submesothelial area, which indicates that despite the significant denudation of the peritoneal MCs monolayer persists and important migration of MCs to compact zone (Figure 2).

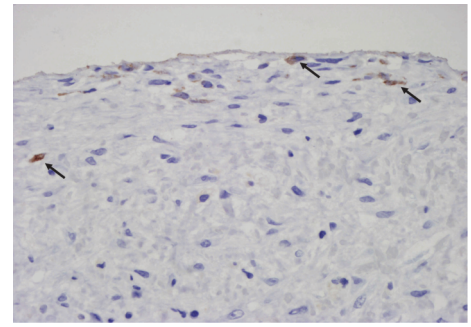

Figure 2: Evidence of MMT in EPS. Light microscopy analysis of a parietal peritoneal biopsy from a patient with EPS. Despite significant denudation of the peritoneal membrane, a submesothelial cytokeratin staining (brown) in submesothelial area is observed. This cytokeratin staining suggests the superficial precedence of these cells (arrows). Magnification ×200.

3. Conclusion

TGF-β appears to be the most important molecule in the initiation of MMT and peritoneal fibrosis. MMT is present from early stages of peritoneal fibrosis and is perpetuated over time. Current data support a connection between MMT and SPS. However, the jump from SPS to EPS and the connection between MMT and EPS have not been fully established. We concluded that the MMT can be a therapeutic target, the blockade of which could be a benefit especially in initial stages of the process.

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Review Article

The Choice of Peritoneal Dialysis Catheter Implantation Technique by Nephrologists

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Peritoneal dialysis catheter (PDC) is the lifeline of peritoneal dialysis (PD) patients. One of the critical issues for successful PD is a well-functioning PDC which is timely inserted. It is the implantation technique rather than the catheter design that determines the outcome of the catheter. Dedication in acquiring the appropriate technique is vital to the success of a PD program. In this paper, we discuss the pros and cons of various techniques used for PDC implantation. A detailed description of PDC implantation by using the minilaparotomy method is presented. We strongly recommend mini-laparotomy as the method of choice for PDC implantation by nephrologists.

Peritoneal dialysis (PD) is a well-established technique of renal replacement therapy in patients with end-stage renal disease (ESRD). The advantages of PD include preservation of residual renal function, better patient survival in the first few years, better quality of life and cost-effectiveness over hemodialysis [1–4]. Thus, PD is well suited to act as a first-line renal replacement therapy in an integrated approach to end-stage renal failure care. In Hong Kong, "PD-first" policy has been adopted since mid-1980s. Currently, up to 80% of ESRD patients on maintenance dialysis are on PD. It has provided a successful model for the PD first policy.

For a PD program to succeed, access to peritoneal dialysis catheter (PDC) implantation must be timely and the procedure must be performed by an experienced operator with low catheter failure rates and complications. PDC can be implanted percutaneously or by open surgery (Table 1). The standard percutaneous placement includes the "trocar and cannula" method and the Seldinger technique, with variations like fluoroscopy-assisted or peritoneoscopy-assisted placement. Open surgical approach includes minilaparotomy and laparoscopic placement.

In many centers, PDC is implanted by surgeons, either by minilaparotomy or laparoscopic approach. However, referral to surgeons usually causes delay in initiating PD therapy, for both the waiting time to see a surgeon and the time required to arrange the operation afterwards. The date of implantation is often not under the control of nephrologists and this may make timely implantation of a PDC an impossible dream. Some patients may be forced to remain on hemodialysis with a central venous catheter, which is associated with an accelerated decrease in residual renal function and high rates of bacteremia and mortality. Survival data from the United States consistently showed a higher mortality in patients started with hemodialysis in the first three months [5–7]. Together with the large PD patient load, nephrologists in Hong Kong are obliged to insert PDCs by themselves. In fact, the success of PD access procedures performed by nephrologists using various techniques has been well documented [8–12]. Catheter insertion by nephrologists has been shown to improve PD utilization and increase the PD population growth rate in other parts of the world [9, 11, 13, 14].

Conventionally, nephrologists prefer the percutaneous approach. The percutaneous techniques are relatively simple to perform. They require a short learning period and can be performed in a clean side-room under local anesthesia. The "trocar and cannula" technique is the first method adopted by nephrologists for the implantation of PDCs. With this technique, the trocar's sharp pointed stylet is pushed through the linea alba into the lower abdomen. After entry into the peritoneal cavity, the stylet is removed and the PDC is passed

Table 1: Comparison of different methods of peritoneal dialysis catheter implantation.

Method	Trocar and cannula	Seldinger technique	Minilaparotomy	Laparoscopic
Done by	Nephrologist	Nephrologist	Nephrologist/surgeon	Surgeon
Setting	Clean side-room	Clean side-room	Operating theater	Operating theater
Anesthesia	Local anesthesia	Local anesthesia	Local/general anesthesia	General anesthesia
Pros	Short learning time	(i) Short learning time (ii) Low complication rates	(i) Direct visualization of peritoneum (ii) Allow purse-string suture of peritoneum (iii) Low leakage rates	(i) Visualization of intra-abdominal structures (ii) Allow adjunctive procedures for example Adhesiolysis, omentopexy
Cons	High complication rates	Relatively high early leakage rates	Long learning time	(i) Very long learning time (ii) High cost (iii) Specialized equipment needed

with a stiffening stylet into the peritoneal cavity toward the pelvis. The side pieces of the trocar are removed with the internal cuff of the catheter situated above the linea alba. This technique is easy to perform but due to its blind entry into the peritoneal cavity with the sharp and thick trocar, complications are common. Serious complications, such as perforation of the bladder or bowel, jejunal mesenteric artery laceration, and even laceration of the spleen, have been reported [15–17]. Risk of subsequent incisional hernia development is high [17]. In our opinion, the trocar and cannula method should not be used for PDC insertion because the blind insertion of the sharp and thick trocar is inherently associated with the risk of viscera perforation or damage, no matter how careful and experienced the operator is [18]. The Seldinger technique was developed to improve the results of bedside PDC implantation. With the Seldinger approach, a guidewire is inserted through a priming needle. An introducer, dilators, and a peel-away sheath are then inserted along the guidewire. The guidewire is removed and the PDC is inserted with a stiffening stylet through the sheath, as in the trocar and cannula technique. The peel-away sheath is then separated and removed. The subcutaneous tunnel is created in the usual way. It requires priming the peritoneal cavity with 2 liters of peritoneal dialysate to prevent visceral injury from the blind puncture of the priming needle. In contrast to the trocar and cannula technique, this technique is less traumatic. Although it is also a blind procedure, reported complication rates are much lower compared to the trocar and cannula technique [12, 19]. In some centers using the Seldinger technique, the catheter survival rates were even better than that implanted by open surgical method in selected groups of patients without prior abdominal surgery [20, 21]. In the recent years, there has been an increase in the utilization of peritoneoscopic implantation of PDC with the Y-TEC system by nephrologists. This method adopts the Seldinger technique for catheter placement but allows direct visualization of the peritoneal cavity after air insufflation, thus avoiding placing the catheter under bowel loops, omentum, or against adhesions. Good results have been reported [8, 22]. Although peritoneoscopic implantation of PDC provides direct visualization, the introduction of the peritoneoscope still involves blind insertion through the abdominal wall. Therefore, bowel perforation remains a potential serious complication [13]. Pneumoperitoneum and pneumomediastinum are the rare complications caused by the air insufflation. The major limitation of this approach is the high cost of the peritoneoscope system and the disposable consumables.

The safety of the percutaneous technique is further improved by using ultrasound and fluoroscopic guidance. Ultrasound helps the operator to identify and avoid damaging blood vessels like the inferior epigastric artery and vein, during abdominal puncture. In the fluoroscopic guided insertion, contrast may be used after the puncture needle has entered the peritoneum to ensure that the needle has not entered the bowel. The guidewire and the PDC can be visualized during the advancement into the pelvis. However, the danger of bowel perforation and organ damage still exists because the peritoneum is not punctured and entered under direct visualization and this is the main limitation of all percutaneous methods. The percutaneous approach is, therefore, relatively contraindicated in patients with previous abdominal surgery or peritonitis. Furthermore, the peritoneum opening cannot be sutured, causing a relatively high incidence of early leakage. Pericatheter leaks predispose to catheter exit site infection and peritonitis. Persistent leak calls for catheter removal. Reported early leakage rates range from 5% to 20% [21, 23–26]. To decrease the incidence of leakage, it is recommended to have a break-in period of 7 to 14 days for commencement of PD [27, 28]. However, patients often are reluctant to start dialysis without uremic symptoms, and the onset of uremic symptoms is relatively sudden among those with low glomerular filtration rate. To allow immediate PD after catheter implantation with low early leakage rates and other complications, open surgical implantation by minilaparotomy is the best solution.

Nephrologists can be trained to perform open surgery with minilaparotomy for PDC implantation. We have been using surgical approach by minilaparotomy for PDC insertion in our center for more than 20 years. Several nephrologists have been trained to perform the procedure competently. Patients with previous uncomplicated abdominal operations other than colectomy like hysterectomy and cholecystectomy are not excluded. Preoperatively, the beltline of the patient is identified in the standing and sitting positions. The main wound, the tunnel, and the exit site are marked

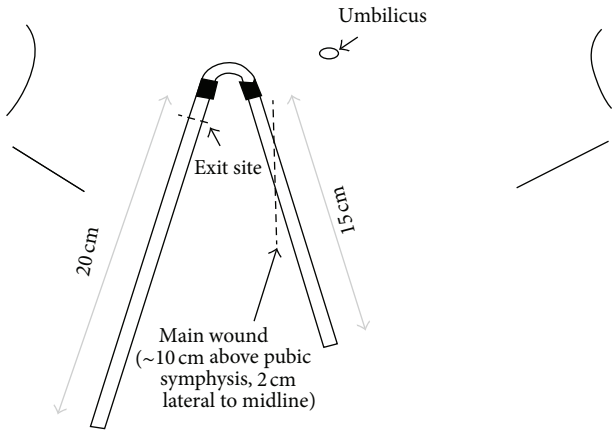

Figure 1: Location of main wound and exit site.

in such a way that the position of the future exit site is few centimeter away from the beltline. The location of the main wound is around 10 cm above the pubic symphysis and 2 cm lateral to the midline (Figure 1). We usually use the conventional straight Tenckhoff catheter which is 42 cm in length. Longer catheter is chosen when the positions of the main wound and the exit site are higher. Patients are asked to empty their bladder before the procedure. We routinely performed bladder ultrasound scanning to exclude urinary retention after voiding. This prevents perforation of the urinary bladder during catheter insertion [29–31]. Prophylactic antibiotic is routinely given. The procedure is performed in a day-care operating room under local anesthesia without anesthetist support. 2% lignocaine is used as a local anesthetic agent, with intravenous midazolam when needed. After paramedian skin incision, the subcutaneous tissue is dissected till the reach of the anterior rectus sheath. Paramedian placement reduces the risk of pericatheter leak and hernia and enhances tissue ingrowth into the deep cuff with firm fixation of the catheter [32, 33]. The anterior rectus sheath is then opened, and the rectus muscle is bluntly split. The posterior rectus sheath and the peritoneum are then identified and cut open. Purse-string suture of the peritoneum together with the posterior rectus sheath is then applied. After the insertion of PDC with a malleable stylet, the peritoneum and posterior rectus sheath are closed with the purse-string suture. The internal cuff is tightly tied above the posterior rectus sheath and the peritoneum, secured within the rectus muscle. Free drainage is tested, followed by indwelling of PD fluid to test for pericatheter leakage. The tight purse string suture and direct visualization for leakage check greatly reduce the chance of leakage even with immediate commencement of PD. The anterior rectus sheath is then sutured with a part of the PDC tunneled between the anterior rectus sheath and the rectus muscle. This rectus sheath tunneling is an important adjunctive technique to keep the catheter positioned in the pelvis and to prevent catheter tip migration [34–36]. After the PDC is tunneled in the subcutaneous layer, a downward pointing exit site is created with the external cuff located at 2 cm from the exit site. No suture is placed at the skin exit. The wound and the exit site are covered with nonocclusive dressings. Adhesives are applied to fix the PDC on the abdominal wall. In our center, intermittent PD is performed in almost all patients immediately after implantation, and yet leakage is almost absent and catheter malfunction from other causes is also very uncommon [10, 37]. Excellent PDC outcomes have also been reported from other centers using minilaparotomy as the insertion technique by nephrologist [38–40]. To many nephrology services, the requirement of an operating room setting for minilaparotomy may be a limiting factor. However, in Hong Kong, it is still safely implanted in operating rooms converted from sidewards.

Compared to the percutaneous techniques, the learning time for minilaparotomy is longer. Apart from mastering the surgical steps, the nephrologist has to learn to handle potential intra-operative complications such as arterial bleeding. But once the skill is acquired, the nephrologist will find the satisfaction of freedom from postoperative troubles of blind implantations, and will have the control of arranging the catheter implantation procedures. Other PDC-related procedures including PDC removal, exteriorization and shaving of the external cuff, simultaneous removal, and reinsertion of PDC [41] are made possible after acquiring minilaparotomy techniques.

Laparoscopy is increasingly being used as a modality for establishing peritoneal access and various laparoscopic techniques have been described for catheter placement. Laparoscopy provides the ability to directly visualize placement of the catheter tip in pelvis and proactively address anatomic problems that may result in mechanical catheter dysfunction. Lysis of adhesions, omentopexy, peritoneal biopsy, and hernia repairs can be done at the time of catheter placement. However, laparoscopy requires longer duration of operation and is more costly than open surgical insertion because specialized equipment is required. Laparoscopy has an inherently steep learning curve. Experienced surgeons are required. In addition, general anesthesia is usually required and many ESRD patients are high-risk candidates for general anesthesia for their multiple comorbid conditions. Thus, laparoscopy approach should be reserved for the needy patients like those who are expected to have intra-abdominal adhesions rather as a routine first-line approach.

PDC is the lifeline of PD patients. One of the critical issues for successful PD is a well-functioning PDC which is timely inserted. PDC insertion must be regarded as an important procedure, demanding care and attention to detail. There is no PDC that is definitely better than the conventional double-cuffed Tenckhoff catheter [42, 43]. It is the implantation technique rather than the catheter design that determines the outcome of the catheter. Dedication in acquiring the appropriate technique is vital to the success of a PD program. We strongly recommend minilaparotomy as the method of choice for PDC insertion by a nephrologist providing that an operating room setting is available. The percutaneous approach by the Seldinger technique is a good alternative method of PDC implantation in selected patients without prior abdominal surgery. Most importantly, the operators should be well trained for the technique chosen and the outcome monitored regularly.

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Review Article

Bimodal Solutions or Twice-Daily Icodextrin to Enhance Ultrafiltration in Peritoneal Dialysis Patients

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The efficacy and safety of icodextrin has been well established. In this paper, we will discuss the pharmacokinetics and biocompatibility of icodextrin and its clinical effect on fluid management in peritoneal dialysis patients. Novel strategies for its prescription for peritoneal dialysis patients with inadequate ultrafiltration are reviewed.

1. Introduction

The use of icodextrin (ico) has been characterized as one of the major achievements in peritoneal dialysis (PD) [1]. Ico-based peritoneal dialysis solutions have been used successfully by PD practitioners for two decades.

Ico is an isoosmolar alternative osmotic agent that induces ultrafiltration (UF) in peritoneal dialysis by colloid osmosis. Peritoneal absorption of ico is limited and occurs by convection *via* the lymphatics of the peritoneum [2]. As a result, the net pressure gradient is relatively constant, sustaining UF for the long dwell. Many clinical benefits of ico have been described, such as a reduction in total glucose load [3], equivalent or higher UF than that provided by hypertonic glucose solutions [4], and better control of fluid balance [5]. Ico is recommended for patients with poor UF and those with a high or high/high-average pattern in the peritoneal equilibrium test (PET). It is well known that UF volume correlates with patient and technique survival [6].

Glucose degradation products (GDPs) and the products of advanced glycosylation end products (AGEs) induce inflammation and fibrosis of the peritoneal membrane [7]. Minimizing dextrose exposure by using ico for the long dwell may prevent long-term detrimental changes of the peritoneal membrane.

In addition, there is a growing concern about the total amount of absorbed glucose and so there is interest in the use of new alternative glucose-sparing osmotic agents.

The use of a "bimodal" solution composed of glucose and ico, in order to increase sodium and fluid removal, is a promising approach [8].

Ico was used initially during the long night dwell in continuous ambulatory peritoneal dialysis (CAPD) and during the day dwell in continuous cyclic peritoneal dialysis (CCPD). Recently, the daily use of two ico exchanges has been suggested in order to minimize the glucose load and/or to increase the UF rate [9–12].

The biocompatibility of ico has been investigated; however, it should be noted that there are data suggesting that those who use icodextrin are still vulnerable to develop encapsulating peritoneal sclerosis (EPS) [13].

2. Pharmacokinetics of Icodextrin

Ico consists of a complex mixture of starch-derived water-soluble glucose polymers, with varying chain lengths [14, 15].

Moberly et al. have observed that a median of 40% of the total administered dose of ico (2 L of 7.5%) was absorbed by lymphatics of peritoneal cavity during the 12 hours [15]. Thus the absorption of ico is slower than that of glucose, rendering

this osmotic agent unique due to the longer duration of the net pressure gradient.

Moreover, the plasma levels of ico and its metabolites increase during the dwell and decrease after drain as a result of absorption by the peritoneal lymphatics and their elimination by dialysis [15]. More than 20% of the absorbed icodextrin and metabolites are eliminated by renal excretion and dialysis [15].

The circulating enzyme α-amylase hydrolyzes the absorbed ico and its metabolites such as maltose, maltotriose, and maltotetraose, which can subsequently be metabolized to glucose by tissue maltases, or eliminated by urine and dialysis [16]. The intracellular metabolism of maltose and other similar metabolites into glucose does not result in hyperglycemia, because the major amount of glucose produced remains inside the cell.

Data from clinical studies in adults and children on PD that used 7.5% ico-based solutions for the long dwell demonstrate that the concentration of the metabolites increases initially, reaching a steady-state level after 7–10 days [17–21].

Rodríguez-Carmona et al. have investigated the total concentration of circulating ico metabolites in 12 PD patients, in which two ico exchanges were used during nocturnal automated peritoneal dialysis. The authors reported that the total concentrations of ico metabolites did not differ significantly compared to use of one daily ico exchange [22].

More recently, Gobin et al. used two ico exchanges daily and found a doubling of the total ico concentration in plasma within 3 months of treatment (345 ± 145 mg/dL to 615 ± 120 mg/dL), which remained stable after six months [9].

Moreover, Sav et al. observed that after using 3 for months two ico exchanges per day, there was a slight increase of blood levels of icodextrin and maltose, but was not statistically significant [10].

In a more recent retrospective study, it has been reported that six months after administration of twice-daily ico exchanges in 8 PD patients, the levels of icodextrin metabolites did not increase significantly [12]. The differences among these studies regarding the concentration of icodextrin and their metabolites could be explained by the limited number of patients enrolled in these studies, by the different duration of each study and by the total number of patients with residual renal function and their amount of urine output (which would serve to excrete the metabolites).

Posthuma et al. were the first to report that the ico metabolites may increase the serum osmolality [23]. Additionally, Ota et al. confirmed these findings and they reported that the increase of serum osmolality by the circulating ico metabolites had no effect on net UF [20].

3. Biocompatibility of Icodextrin

Four principal parameters of a PD solution may affect the degree of biocompatibility. These include the pH/buffer system, the osmolality, the concentration of glucose, and the glucose degradation products (GDPs).

All these parameters of a PD solution may activate the cells of the local immune system of the peritoneum. The activation of these cells leads to an increase of proinflammatory cytokines and chemokines resulting in an activation of the proinflammatory and profibrotic pathways [24].

It is well known that uremia, in combination with long-term exposure to bioincompatible solutions, induces structural peritoneal membrane changes, such as denudation of mesothelium, submesothelial thickening, neovascularization, and vascular hyalinization [25]. All these deleterious changes may be mediated by the presence of glucose in conventional PD solutions. GDPs may exert local toxicity leading to mesothelial cell injury [26]. In addition, AGEs increase the vascular permeability and may lead to peritoneal membrane injury [27].

Thus, there is an increasing awareness of glucotoxicity with an emphasis on the development of new more biocompatible PD solutions.

Ico-based solutions which use lactate as a buffer are isoosmolar (282 mOsm), contain low levels of GDPs, and are considered to be more biocompatible than glucose-based conventional solutions, which contain GDPs. The only parameter which is not corrected is the low pH (it is relatively acidic pH = 5.8).

There *ex vivo* and *in vitro* studies that suggest better biocompatibility for ico-based solutions compared to conventional PD solutions [24, 28, 29].

Bajo et al. have shown that ico effluent induces a greater proliferation of human mesothelial cells in comparison with glucose effluent [30]. This is assumed to be a beneficial effect, but is not proven.

However, there are conflicting data regarding ico and peritoneal inflammation [31–33]. In addition, there have been several reports that ico induces allergic responses such as exfoliative dermatitis and sterile peritonitis [34, 35].

There are data from large retrospective studies that implicate icodextrin in the development of EPS [13, 36, 37]. Indeed, although use of icodextrin can reduce the total amount of glucose exposure to the peritoneal membrane, in return the membrane is being exposed to a starch-derived solution that may not necessarily be any more protective of long-term membrane function.

The interpretation of these findings is difficult because the majority of patients had been using glucose-based solutions and ico in tandem. In addition, hypertonic glucose-based solutions were replaced by ico but there was a continuous exposure to glucose due to the use of glucose-based solution with lower tonicity.

The role of ico in the extension of technique survival, and the increase of UF rate in PD patients with UF failure is well established. Insofar as the use of ico can keep the patient on PD for a longer time, the association of ico with membrane failure may be the result of the longer duration of PD and nothing about the solution itself [38]. It is worth noting that the biocompatibility of bimodal solutions or the double dose of ico has not been yet investigated.

4. Effect of Icodextrin on Volume Status, Sodium Balance, and Blood Pressure

Volume overload is the major risk factor for hypertension and cardiovascular disease. Fluid overload, due to inadequate

UF and/or inadequate control of sodium balance, leads to hypertension, left ventricular hypertrophy, and associated increased mortality. The efficacy of ico on UF and fluid management has been demonstrated [17].

Finkelstein et al. reported that in patients on APD with high transport characteristics, ico is superior compared to hypertonic solutions for net UF [4].

Data from two randomized controlled studies reported a reduction in extracellular water (ECW) and total body water (TBW) with the use of ico [5, 19].

In addition, Konings et al. reported in a group of patients who used ico a decrease in left ventricular mass but not in the blood pressure [5]. Woodrow et al. observed a reduction in ECW and TBW with concomitant reduction in the systolic blood pressure in APD patients which switched from glucose-based solutions to ico [39].

Plum et al. reported that the use of ico increases the sodium removal in patients on APD [19]. The increased peritoneal sodium removal probably reflects both the enhanced UF obtained by colloid osmosis and a decreased sodium sieving. Ultrafiltration by crystalloid osmosis, as done with conventional PD solutions, removes water through both the small interendothelial pores and through aquaporins. Approximately half the water ultrafiltered is done so through the aquaporins. In contrast, the ultrafiltration with ico is through the small pores only, so that the ultrafiltrate is comprised of both water and sodium. Additionally, Fourtounas et al. reported that the use of ico enhances sodium removal in both continuous CAPD and CCPD [40].

More recently, data from a 12-month, multicenter, open-label controlled trial, reported that ico improves the metabolic control and the fluid management increasing the net UF in high and high-average diabetic patients on CAPD. The authors reported a statistically significant decrease of systolic and diastolic blood pressure in the group using ico [41].

There are controversial reports regarding the impact of ico on residual renal function [22, 42, 43]. A decline in urine volume which was reported in some studies reflecting the extracellular fluid volume depletion due to the increased UF obtained by ico. However, if ico is used to restore euvolemia in the fluid-overloaded patient, and not to induce volume depletion, residual kidney function is unchanged [44].

5. New Therapeutic Strategies to Prescribing Icodextrin

5.1. Combined Solutions with Icodextrin and Glucose. Peers was the first to introduce the concept of a mixed solution of ico and glucose [45].Theoretically, the advantages of this combination are sparing glucose and increasing UF, due to the combined effect of crystalloid and colloid osmosis during the same exchange.

Jenkins and Wilkie compared the UF profile of 1.36% glucose, 3.86% glucose, 7.5% ico and the combination solution of 1.36% glucose plus 7.5% ico in seven patients on CAPD and four patients on APD in a prospective open study [42]. The authors reported an improved UF profile for the combination solution, with similar UF compared to that obtained with the hypertonic 3.86% glucose-based solution. In addition, the combination of the two agents was well tolerated [42].

Dallas et al. in a 4-week, prospective randomized crossover study with five patients on CAPD and 3 patients on APD, reported that the use of the combination dialysate (7.5% ico plus 1.36% glucose) for the long dwell resulted in a 33% increase in long-dwell UF and a 29% increase in total drain volume in comparison with 7.5% ico alone [46]. Freida et al. have investigated the effect on net UF and sodium removal during a 15-hour single-dwell exchange using, alternatively, 3.86% glucose, 7.5% ico and a combination solution with 2.61% glucose, 6.8% ico with low sodium concentration (121 mmol/L) in seven stable patients on APD [47]. The authors reported that the major advantage of this approach was the enhanced UF (mean 990 mL) and the sodium removal (mean 158 mmol) during the 15 hour-long dwell exchange, obtained by the combination fluid [47].

The same investigators studied sodium and water removal obtained by the combined 6.8% ico, and 2.6% glucose solution in twenty-one patients on APD with high transport profile, in comparison with sodium and water removal obtained by 7.5% ico alone. All the patients enrolled in the study were on once-daily ico dwell for at least one month at baseline [8]. The authors reported that the estimated mean percent change from baseline in net UF for the combined solution was 150%, versus 18% for ico based solution ($P < 0.001$), and that the estimated mean percent change from baseline in sodium removal for the combined solution was 147% versus 23% for ico ($P < 0.001$) [8]. It should be noted that the reason for the change of estimated mean percent in net UF and in sodium removal with ico remain obscure in this study. However, the increase in sodium and fluid removal observed in the group using the combined solution was probably the result, in large part, of the low concentration in sodium of the dialysis fluid (121 mEq/L) resulting in greater diffusive flux of sodium into the dialysis solution.

In support of this hypothesis, Davies et al. reported a favorable effect of low-sodium PD solutions on sodium and water removal resulting in a decline in extracellular water [48].

Galach et al. reported that computer simulations in accordance with clinical data have shown an increase in UF and sodium removal in the group of combined solution with low sodium concentration in comparison with hypertonic solutions and ico-based solutions both with standard sodium concentrations [49]. In contrast, Akonour et al. used the same mathematical model and could not confirm the findings of Galach [49, 50].

However, the use of bimodal solutions with low sodium alternative concentration in PD patients with UF failure may represent an alternative option in order to enhance UF. A potential risk of this approach could be considered a concomitant hyponatremia due to increased sodium removal.

6. Twice-Daily Icodextrin Exchanges

For a long time, only one daily exchange with ico during the long dwell has been recommended, in order to increase UF in PD patients with inadequate UF.

The use of ico during the long dwell was based on the observation (derived from the use of computer simulation) that icodextrin did not produce sufficient UF during the early part of the dwell, whereas it leads to slow but steadily increasing net ultrafiltration after 8 hours.

Moreover, according to Rippe and Levin, UF obtained by ico continues linear and slightly even after a 15-hour dwell [51].

In contrast, Jeloka et al. reported that ico UF does not increase past a 10-hour dwell in APD patients. The authors reported that UF obtained by ico at 8 and 10 hours dwell time are similar and did not change significantly at 14 hours [52].

Since UF does not increase substantially with ico after 8–10 hours, the hypothesis in which this new approach was based is that the two 8-hour exchanges will provide more UF than one exchange over 16 hours.

Gobin et al. were the first to used two ico exchanges per day, in order to reduce glucose exposure in a group of nine patients on APD with high transport characteristics [9]. The authors observed at 6 months of treatment a significant decrease in the patient's glucose exposure from 410 ± 75 to 300 ± 75 g/day [9]. The authors did not observe an increase in UF due to the scheduled dwell of the two ico exchanges (one ico exchange for 4-5 hours and the other for 9-10 hours dwell time).

A recent prospective randomized study in 40 patients on CAPD with UF failure investigated the effect of two ico exchanges on body weight and left ventricular mass index [10]. Twenty patients were on one ico exchange for a 16 h dwell time and twenty patients were on two ico exchanges for 8 h each other dwell time. All the patients enrolled in the study were exposed to ico for the first time.

The authors reported in the group of two ico per day, a decrease in the body weight at the third month of treatment (68 ± 12.30 at baseline to 66.10 ± 11.90 at third month, $P < 0.05$). Moreover, significantly decreased left ventricular mass index was observed in the group with the two ico exchanges [10].

Recently, The PD Unit of the Toronto General Hospital reported its experience in nine PD patients with ultrafiltration failure and weight gain in whom two ico exchanges per day were prescribed [11]. Five CAPD patients received twice daily 7.5% ico-based solution, each with an 8 h dwell time. Each exchange with ico was alternated with dextrose based solution with 4 h dwell time. Four patients were on CCPD using dextrose-based solutions during the night for 8 h and two 7.5% ico-based solutions during the daytime. After six months of therapy, the authors observed a decrease in body weight in six patients by an average of 2.9 ± 1.2 kg. In addition, a decrease in the mean blood pressure was observed in all patients. The new regimen was well tolerated and none of the patients reported any side effects [11].

In another recent study, 28 patients with high transport profile and UF failure on CAPD were randomized to receive either one or two ico exchanges per day. Both groups experienced a decrease in serum brain natriuretic peptide, left ventricular mass, heart rate and cardiothoracic index [53]. Moreover, the authors reported an increase in ejection fraction at eight weeks in both groups. The percentage of change of all the parameters was enhanced in the group of patients who received twice-daily ico exchanges [53].

In a retrospective study, 8 PD patients with inadequate UF were switched from one ico exchange to twice daily ico exchanges. There was a significant increase in net UF from 452 ± 800.5 mL at 1 week before treatment, to 993.9 ± 553.1 mL at 3 months and 1078.1 ± 500.9 mL, observed after 6 months [12]. Moreover, osmolality and residual urinary output remained unchanged throughout the study [12].

There is a growing interest in the use of twice-daily ico exchanges either to reduce glucose load or to enhance UF. Recently, the Canadian Society of Nephrology work group suggested the use of two ico exchanges in PD patients with UF failure in order to enhance UF [54].

However, an important issue that must be addressed is whether the accumulated ico metabolites over the long term have an increased potential risk to peritoneal membrane function and systemic toxicity. More attention and further exploration are needed, given the findings regarding the doubling of the serum concentration of ico in the study of Gobin et al. [9]. At present, there is no reported systematic toxicity due to ico or its metabolites. After almost two decades of use, toxicity has become less of a concern for the PD community.

Twice-daily ico prescription has not been approved by the pharmaceutical agencies and more studies are needed to prove the safety and the efficacy of this new regimen. In addition, the increased cost of this regimen must be considered, although it should be compared to a transfer to hemodialysis [11].

In our opinion, use of bimodal solutions or twice-daily icodextrin exchanges may be warranted. It is imperative to provide adequate UF, especially in anuric PD patients, in order to maintain euvolemia and likely extend survival.

7. Conclusion

Ico is safe and effective in PD patients. Patients with UF failure may benefit from the use of combined solutions or from the use of two ico dwells daily. Further studies are needed to document the efficacy and safety of these new strategies.

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Review Article

Risk Factors Associated with Peritoneal-Dialysis-Related Peritonitis

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Background. Peritonitis represents a major complication of peritoneal dialysis (PD). The aim of this paper was to systematically collect data on patient-related risk factors for PD-associated peritonitis, to analyze the methodological quality of these studies, and to summarize published evidence on the particular risk factors. *Methods*. Studies were identified by searches of Pubmed (1990–2012) and assessed for methodological quality by using a modified form of the STROBE criteria. *Results*. Thirty-five methodologically acceptable studies were identified. The following nonmodifiable risk factors were considered valid and were associated with an increased risk of peritonitis: ethnicity, female gender, chronic lung disease, coronary artery disease, congestive heart failure, cardiovascular disease, hypertension, antihepatitis C virus antibody positivity, diabetes mellitus, lupus nephritis or glomerulonephritis as underlying renal disease, and no residual renal function. We also identified the following modifiable, valid risk factors for peritonitis: malnutrition, overweight, smoking, immunosuppression, no use of oral active vitamin D, psychosocial factors, low socioeconomic status, PD against patient's choice, and haemodialysis as former modality. *Discussion*. Modifiable and nonmodifiable risk factors analyzed in this paper might serve as a basis to improve patient care in peritoneal dialysis.

1. Introduction

Peritonitis still represents the main acute complication of peritoneal dialysis (PD) and is a leading cause of hospitalization [1], catheter loss, and technique failure [2]. It is also a common cause of death in PD patients [3] and has been described as one of the leading causes of transfer to hemodialysis (HD). The decline of peritonitis rates during the last decades has mostly been achieved by improvements in factors relating PD technique such as the change to plastic bags, the introduction of the Y-set-twin-bag connection system [4]. Despite the significant drop in the peritonitis rates since the 1980 from approximately 6 episodes/patient year [5], the peritonitis rate published in the literature remains constant at approximately 0.35 episodes/patient year.

To further reduce the risk of morbidity, mortality, and technique failure patient-specific risk factors, which one can divide into modifiable and nonmodifiable, gain more attention in PD patient care. The aim of this paper was to perform a comprehensive collection of published studies on modifiable and nonmodifiable risk factors for PD-associated peritonitis between 1990 and 2012, to assess the methodological quality of the identified studies and to offer an overview of evidence-based patient factors which are associated with an increased risk for peritonitis in PD patients.

2. Materials and Methods

Relevant studies were identified by searches of Pubmed in April 2012, with key words that included "peritonitis," "peritoneal dialysis," and "risk factor". The search was limited to studies with at least 40 patients in human adults in English language, published between 1990 and 2012. In order to provide an unbiased comparison, only studies reporting on peritonitis of any cause, that is, studies which reported data

Table 1: Assessment of methodological quality. Each statement scored with one point for the quality scoring.

(1)	Provide in the abstract an informative and balanced summary of what was done and what was found.
(2)	State specific objectives, including any prespecified hypotheses.
(3)	Describe the setting, location, type of data collection and relevant dates, including periods of recruitment.
(4)	Describe relevant data of follow-up time, including end of study period.
(5)	Give the eligibility criteria of participants, and the sources and methods of selection.
(6)	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria for episodes of peritonitis.
(7)	Explain how the study size was arrived at.
(8)	Describe all statistical methods, including those used to control for confounding.
(9)	Describe any methods used to examine subgroups and interactions.
(10)	Give demographic characteristics of study participants, at least gender and age.
(11)	Summarize follow-up time (average per patient and total amount).
(12)	Report numbers of peritonitis episodes or peritonitis rate over time.
(13)	Give unadjusted and confounder-adjusted estimates and their precision.
(14)	Discuss limitations of the study, taking into account sources of potential bias or imprecision.
(15)	Give a cautious overall interpretation of results considering objectives, multiplicity of analyses, results from similar studies, and other relevant evidence.

on all peritonitis episodes regardless of underlying germ were included. Hence, studies only reporting on risk factors for fungal or enteric peritonitis were excluded. The term "patient factor" was defined as a modifiable or nonmodifiable factor which is related to the individual. Data extraction was carried out by J. Kerschbaum and reviewed by M. Rudnicki. Studies were assessed for methodological quality using a modified checklist of the STROBE statement [6] (Table 1). For the purpose of this paper, we limited quality assessment to 15 relevant items. Study quality was considered as "acceptable" if the score was ≥ 10.

3. Results

The search identified 415 potentially relevant studies. First, 112 articles had to be excluded because they were no study on peritonitis of any cause. Then, 303 abstracts were screened and 3 articles were additionally identified through the references of the former identified articles. In a next step, 93 full-text articles were selected for detailed analysis, 49 articles had to be excluded due to the predefined exclusion criteria. Finally, 44 studies were assessed for methodological quality. Nine articles were excluded because of having low methodological scoring and finally, thirty-five studies were scored as having "acceptable" methodological quality. Selection process is depicted in Figure 1, characteristics of studies are shown in Table 2. Risk factors were divided into nonmodifiable and modifiable factors, a brief overview is shown in Figure 2.

3.1. Nonmodifiable Risk Factors (Table 3)

3.1.1. Ethnicity. Eleven studies found differences between ethnicities such as a higher risk in aboriginal ethnicity (IRR 1.93; 1.63–2.28) [13] and HR 1.78; 1.45–2.19 [39], Maoris (OR 1.64; 1.43–1.87) [13], First Nation Canadians ($P = 0.012$) [16], and black ethnicity in comparison to Caucasians (HR 1.255; 1.178–1.338, IRR 2.2; $P < 0.01$; HR 1.5; 1.2–1.8; IRR 1.629; $P = 0.004$; and IRR 1.37; 1.00–1.88) [14, 28, 30, 37, 40]. Lim et al. [15] reported not only an increased risk for peritonitis in indigenous people who lived far away from their treatment center ("remote"), but also a higher risk for technique failure, all-cause and peritonitis-related mortality. African Americans also had a higher risk for peritonitis (IRR 1.36; 1.04–1.77) [20]. A significantly shorter time to first episode of peritonitis has been observed in Native Canadians ($P < 0.01$) [34]. In contrast, Troidle et al. [32] showed that white people did not have a significantly decreased risk for peritonitis compared to other ethnicities (HR 0.90; 0.39–2.35). Furthermore, Nessim et al. [40] did not detect an increased risk for Asian people (IRR 0.89; 0.74–1.08).

Although these studies adjusted for some psychosocial factors and/or socioeconomic status in multivariable analyses, residual confounding might also account for these findings. Furthermore, it is possible that this association reflects a lower ability of receiving social support or health care service in these patient groups. Whether social assistance might decrease the risk for peritonitis in certain ethnicities remains unknown.

3.1.2. Age. Results on age as a risk factor were inconsistent. Four studies found an increased risk for peritonitis in older patients defined as >65 or >70 years [8, 12, 13, 17] whereas two studies which were both conducted in almost the same patient cohort could not confirm this association [7, 10] as well as three other studies did not detect an association between age and the risk for peritonitis [23, 32, 39]. Interestingly, one study conducted in a large patient cohort of 11975 subjects even found a higher risk in patients

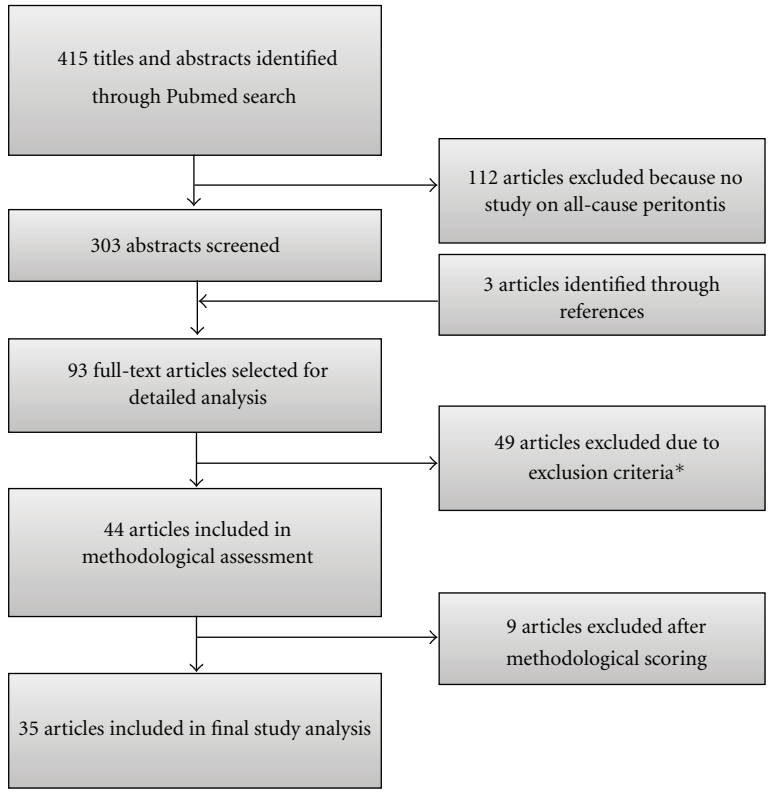

Figure 1: Process of identification of eligible studies. *16 studies: not on all-cause peritonitis; 21 studies: no patient risk factors, 6 studies: cohorts including children; 5 studies: cohorts < 40 patients; 1 study: single event report.

under the age of 65 [14] as well as the study by Zent et al. did [28].

3.1.3. Gender. Kotsanas et al. [12] found a significant increased risk for peritonitis in females (OR 1.91; 95% CI 1.20–3.01), whereas the large study register study by Oo et al. [14], including 11975 patients from the United States Renal Data System Database, did not find an increased risk in females. Furthermore, neither in the studies by Lobo et al. [17] nor Lim et al. [15] an increased risk for female patients could be detected. In a study by Wang et al. [20], risk difference between females and males did not reach statistical significance (IRR 1.25; 0.63–1.01 for females). On the other hand, Oygar et al. [42] could observe that the frequency of female patients was significantly higher in the patient cohort group who had multiple episodes of peritonitis ($P = 0.01$).

3.1.4. Comorbidities. Only a few studies evaluated the impact of mainly cardiovascular comorbidities on the risk for peritonitis. McDonald et al. [13] found an increased risk for peritonitis in patients with chronic lung disease (HR 1.1; 1.03–1.18) and in patients with coronary artery disease (OR 1.06; 1.01–1.12), whereas Oo et al. [14] detected an increased risk in patients with congestive heart failure (HR 1.101; 1.034–1.172). In a study by Lim et al. [15], patients with cardiovascular disease had a slightly increased risk for peritonitis (HR 1.09; 1.04–1.17) whereas patients with cerebrovascular disease did not have a higher risk (HR 1.04; 0.95–1.14). In another study by Lim et al. [39], patients without hypertension had a decreased risk for peritonitis compared to patients with hypertension (HR 0.76; 0.61–0.94). Oygar et al. [42] showed that anti-hepatitis C Virus Antibody positivity was significantly associated with the risk for peritonitis (OR 1.6; $P = 0.03$). Neither Troidle et al. [32] nor Viglino et al. [38] could show an impact of coronary artery disease or cardiovascular disease on the risk for peritonitis. On the other hand it has been shown in several case series and retrospective analyses that PD represents a safe and efficient alternative in patients with congestive heart failure [43].

3.1.5. Diabetes Mellitus. Six studies [9, 10, 13, 14] found an increased risk for peritonitis in diabetic patients compared to non-diabetics. Hazard ratio for type 1 diabetic patients was 1.24 (1.08–1.42) and 1.10 (1.03–1.17) for type 2 diabetic patients [13] compared to non-diabetic patients. In mixed cohorts of type 1 and type 2 diabetic patients, hazard ratios were 1.131 (1.069–1.195), 1.50 (1.05–2.40), and 1.64 (1.08–2.50), respectively [9, 10, 14]. In one study [28] a significantly increased risk for peritonitis was observed in patients with diabetes (IRR 1.81; $P < 0.001$). Interestingly, Nessim et al. [40] could only observe an increased risk for female diabetic (IRR 1.27; 1.10–1.47) but not for males (IRR 0.99; 0.87–1.13). In contrast, six studies [7, 15, 27, 32, 33, 35] could

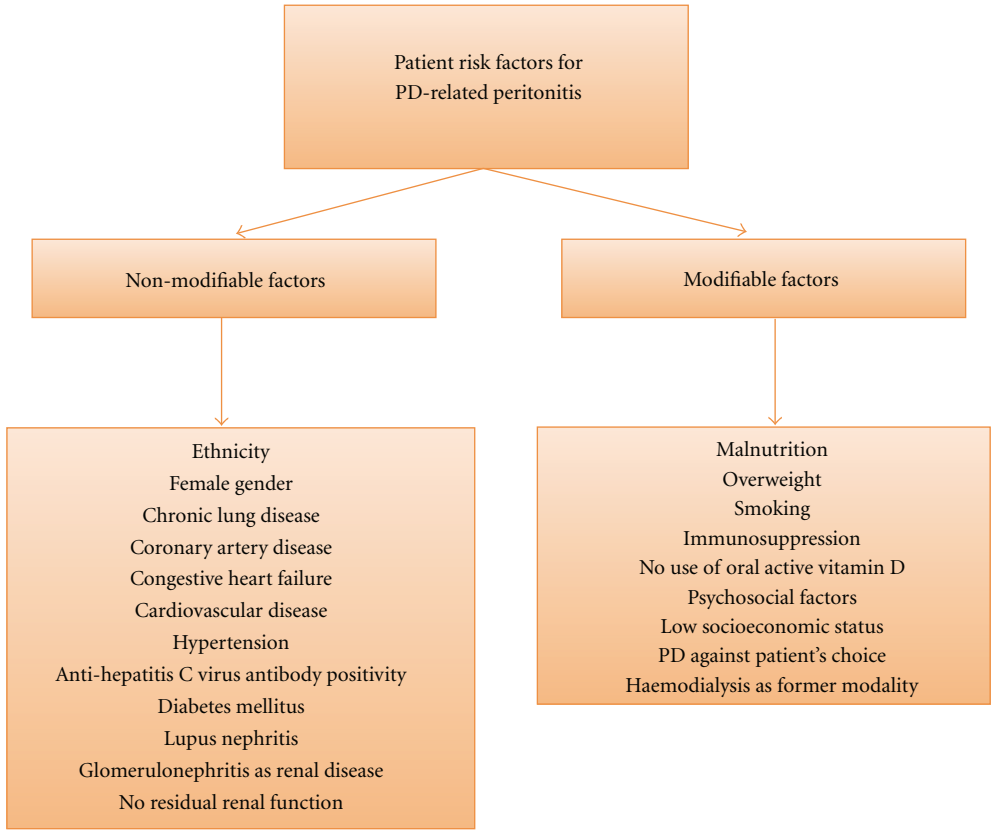

Figure 2: Identified patient risk factors. Factors are divided by nonmodifiable and modifiable risk factors.

not show an association between diabetes and the risk for peritonitis.

As diabetes mellitus is regarded as a risk factor for infections in general [44], it seems to be reasonable to consider it also as a risk factor for peritonitis in PD patients. Nevertheless, none of these studies provided mean or median HbA1c levels, fasting plasma glucose, or detailed information on treatment for diabetes. Hence, whether the diagnosis of diabetes itself or insufficient control of blood glucose levels are the basis for these findings remains unclear. As diabetic nephropathy is the leading cause of chronic renal failure in the United States and in Western countries diabetes as a risk factor for peritonitis requires attention but should definitely not be considered as a contraindication for PD treatment. It should be evaluated in further studies whether intensified glucose control in diabetic patients on PD could decrease the risk for peritonitis.

3.1.6. Underlying Renal Disease. Huang et al. [24] showed that patients with lupus nephritis as underlying renal disease had a significant increased risk for peritonitis ($P < 0.02$). Unfortunately, HR was not reported. Whether this association is contributed to the use of steroids or lupus nephritis itself remains unclear. There is only study which evaluated the impact of immunosuppression on the risk for peritonitis [35]. Thus, doubts about the true value of this factor remain. Glomerulonephritis as underlying disease was borderline significantly associated with a decreased risk for peritonitis in a study by Nessim et al. [40] (IRR 0.87; 0.75–1.00).

3.1.7. Residual Renal Function. Han et al. [9] found a HR of 0.81 (95% CI 0.74–0.88) per 1 mL/min/1.73 m^2 increase in residual GFR in reducing the risk of peritonitis. The authors state that their finding of residual renal function as a protective factor could at least partially be mediated by the better preserved nutritional status. Another possible explanation might be that patients with residual renal function have to perform fewer bag changes per day which might decrease the risk for peritonitis.

3.2. Modifiable Risk Factors (Table 4)

3.2.1. Malnutrition. In three studies [17, 20, 31], albumin levels <3 g/dL or <2.9 g/dL, respectively, were associated with an approximately two-fold risk for peritonitis. Three studies showed an association between low albumin levels and a higher risk for peritonitis (HR 1.67; 1.08–2.60 per 10 g/L decrease [10], HR 0.73; 0.59–0.91 per 1 g/dL increase [11], and OR 1.2 ($P = 0.05$) per 1 mg/L [42], resp.). One study by Ozturk et al. [22] found a significant increased risk for subsequent peritonitis when albumin levels were declining. However, in three studies the association between low levels of albumin and the risk for peritonitis could

Table 2: Characteristics of identified studies on patient-based risk factors for PD-associated peritonitis.

Study	Number of patients	Age (years)	Female (%)	FU-time (months)	Ethnicity	Peritonitis rate	CAPD/APD
[7]	102	57.0 ± 13.0	38.2	10.7[a]	Asian	0.36/patient year	Both
[8]	149	62.2 ± 5.3	41	33 ± 27	N.R.	N.R.	Both
[9]	204	54.0 ± 11.5	42.6	37.5 ± 17.2	Asian	0.30/patient year	CAPD
[10]	246	51.0 ± 13	46	N.R.	Asian	0.48/patient year	APD
[11]	322	56.7 ± 12.5	45	23.9	Asian	4.63/100 patient years	CAPD
[12]	506	56.1 ± 15.3	49	N.R.	Mixed	N.R. for whole cohort	Both
[13]	10709	N.R.	49	N.R.	Mixed	0.86/patient year	Both
[14]	11975	58.8	46	24	Mixed	N.R.	Both
[15]	8237	59.9 ± 15.0	45.9	N.R.	Mixed	N.R.	Both
[16]	727	55.0 ± 14.8	44.7	N.R.	Mixed	N.R.	Both
[17]	330	53 ± 19	49.1	N.R.	N.R.	N.R.	Both
[18]	55	49.1 ± 13.5	43.6	23.6 ± 18.0	Caucasian	N.R.	Both
[19]	48	51.3 ± 14.3	41.7	25.0 ± 18.2	Caucasian	N.R.	Both
[20]	393	55.5 ± 15.0	39.7	13.4[a]	Mixed	N.R.	Both
[21]	56	56.2	28.6	20.8	N.R.	N.R.	Both
[22]	51	42.6 ± 14.3	53	N.R.	N.R.	N. R.	Both
[23]	54	50.3 ± 1.5	63	N.R.	Asian	N.R.	Both
[24]	69	34.2 ± 7.5	87	N.R.	Asian	N.R. for whole cohort	Both
[25]	71	43.3 ± 16.0	56	N.R.	Mixed	N.R.	Both
[26]	103	53.9 ± 13.0	45	12	N.R.	N.R.	Both
[27]	120	48.5 ± 15.0	33	N.R.	Mixed	N.R.	Both
[28]	132	42.4 ± 13.1	56	N.R.	Mixed	2.7/patient year	Both
[29]	140	56.4	33	10.4	N.R.	N.R.	Both
[30]	146	48.5 ± 15.0	46	N.R.	Mixed	N.R.	Both
[31]	147	43.6	41	N.R.	N.R.	N.R.	Both
[32]	162	55.4 ± 11.3	46	N.R.	Mixed	N.R.	Both
[33]	179	57.4 ± 12.3	54	N.R.	Asian	N.R.	Both
[34]	184	N.R.	N.R.	N.R.	Mixed	N.R.	Both
[35]	185	N.R.	48	N.R.	Mixed	0.8/patient year	Both
[36]	328	59.4 ± 15.7	47	20.9 ± 16.8	N.R.	N.R.	Both
[37]	1595	52.6 ± 15.0	46	N.R.	Mixed	N.R.	Both
[38]	1990	58.4 ± 14.8	44	24.2 ± 22.3	N.R.	0.68/patient year	Both
[39]	3162	N.R.	46	N.R.	Mixed	N.R. for whole cohort	Both
[40]	4247	N.R.	45	N.R.	Mixed	N.R.	Both
[41]	4247	59.0 ± 16.0	45	N.R.	Mixed	N.R.	Both

[a]Median. N.R.: not reported.

not be confirmed [7, 9, 25]. One study [21] described a significant decreased risk for peritonitis in patients without malnutrition assessed by Subjective Global Assessment (HR 0.08; 0.018–0.365). It might be hypothesized that hypoalbuminemia, as a result of malnutrition, inflammatory response, or of uremia itself, may lead to a higher susceptibility to infection. Furthermore, the association between low levels of albumin and a subsequently higher risk for infections has also been established in patients on hemodialysis almost twenty years ago [45]. The finding that malnutrition and the risk for peritonitis may be associated is of special interest because a great proportion of patients is malnourished at the initiation of PD treatment [21]. However, diabetes where shown to increase the risk for peritonitis-related death in a study by Han et al. [9], whereas a higher residual renal function was identified to be a protective factor, thus implicating the importance of preventing or correcting malnutrition in PD patients. Further studies evaluating the impact of correcting malnutrition on peritonitis rate, morbidity, and mortality are clearly needed.

3.2.2. Overweight. In a large evaluation by McDonald et al. [13] an increased risk for peritonitis was found with increasing body mass index (HR 1.08; 1.04–1.12 per 5 kg/m^2),

Table 3: Identified non-modifiable risk factors.

Ref	Risk factor	Statistics	Result	Meth. quality
		Ethnicity		
[13]	Aboriginal ethnicity (versus non-indigenous ethnicity)	IRR (adj.)	1.93 (1.63–2.28)	Good
[39]	Aboriginal ethnicity (versus white)	HR (adj.)	1.78 (1.45–2.19)	Average
[15]	Indigenous and remote living (versus other)	HR (adj.)	1.92 (1.69–2.18)	Good
[16]	First Nations people (versus other)	Comp. of PET (not adj.)	$P = 0.012$	Good
[28]	Black ethnicity (versus other)	IRR (adj.)	2.2 ($P < 0.01$)	Average
[14]	Black ethnicity (versus white)	HR (adj.)	1.255 (1.178–1.338)	Good
[37]	Black ethnicity (versus white)	HR (adj.)	1.5 (1.2–1.8)	Average
[30]	Black ethnicity (versus white)	IRR (adj.)	1.629 ($P = 0.004$)	Average
[20]	African American (versus white)	IRR (adj.)	1.36 (1.04–1.77)	Average
[13]	Maori/Pacific Islander (versus non-indigenous ethnicity)	IRR (adj.)	1.64 (1.43–1.87)	Good
[34]	Native Canadian (versus Caucasian)	Time to first PE (not adj.)	$P < 0.01$	Average
[40]	Black ethnicity (versus other)	IRR (adj.)	1.37 (1.00–1.88)	Average
[32]	White ethnicity (versus other)	HR (adj.)	0.90 (0.39–2.35)	Average
[40]	Asian (versus other)	IRR (adj.)	0.89 (0.74–1.08)	Average
		Age		
[12]	Age per 10 years	OR (adj.)	1.26 (1.07–1.48)	Good
[41]	Age per 10 years	IRR (adj.)	1.06 (1.01–1.10)	Average
[40]	Age per 10 years	IRR (adj.)	1.04 (1.01–1.08)	Average
[36]	Age per year	HR (adj.)	1.02 (1.01–1.03)	Average
[14]	Age from 45–64 (versus 65–74)	HR (adj.)	1.094 (1.007–1.188)	Good
[13]	Age from 65–74 (versus 45–54)	HR (adj.)	1.14 (1.06–1.22)	Good
[13]	Age from 75-84 (versus 45–54)	HR (adj.)	1.28 (1.15–1.43)	Good
[17]	Age ≥ 65 years (versus <65 years)	OR (adj.)	2.15 (1.09–4.24)	Good
[8]	Age > 70 years (versus <70)	Comp. of PET (not adj.)	$P < 0.002$	Good
[13]	Age > 85 years (versus 45–54)	HR (adj.)	1.94 (1.20–3.13)	Good
[14]	Age < 45 years (versus 65–74)	HR (adj.)	1.094 (1.007–1.188)	Good
[28]	Younger age (NFI)	IRR (adj.)	N.R. ($P < 0.008$)	Average
[32]	Age ≥ 65 years (versus <65)	HR (adj.)	0.80 (0.29–1.48)	Average
[14]	Age ≥ 75 years (versus <75)	HR (adj.)	1.071 (0.988–1.162)	Good
[39]	Age 0–24.9 years (versus ≥65)	HR (adj.)	0.90 (0.66–1.22)	Average
[39]	Age 25–44.9 years (versus ≥65)	HR (adj.)	0.83 (0.70–1.00)	Average
[39]	Age 45–64.9 years (versus ≥65)	HR (adj.)	0.88 (0.77–1.01)	Average
[10]	Age per year	HR (adj.)	0.99 (0.91–1.01)	Good
[7]	Age < 40 years	HR (adj.)	2.87 (0.80–10.30)	Good
[23]	Age ≥ 60 years (versus <60 years)	Time to first PE (not adj.)	$P = 0.1704$	Average
[38]	Age ≥ 65 years (versus <65 years)	Time to first PE (not adj.)	P = non-significant	Average
		Gender		
[12]	Females (versus males)	OR (adj.)	1.91 (1.20–3.01)	Good
[14]	Females (versus males)	HR (adj.)	0.968 (0.918–1.020)	Good
[17]	Males (versus females)	OR (adj.)	0.73 (0.44–1.21)	Good
[15]	Males (versus females)	HR (adj.)	0.95 (0.89–1.02)	Good
[38]	Females (versus males)	Time to first PE (not adj.)	P = non-significant	Average
[20]	Females (versus males)	IRR (adj.)	1.25 (0.63–1.01)	Average
		Comorbidities		
[13]	Chronic lung disease (versus no chronic lung disease)	HR (adj.)	1.10 (1.03–1.18)	Good
[14]	Congestive heart failure (versus no congestive heart failure)	HR (adj.)	1.101 (1.034–1.172)	Good
[13]	Coronary artery disease (versus no coronary artery disease)	IRR (adj.)	1.06 (1.01–1.12)	Good
[15]	Cardiovascular disease (versus no CVD)	HR (adj.)	1.09 (1.04–1.17)	Good

Table 3: Continued.

Ref	Risk factor	Statistics	Result	Meth. quality
[39]	No hypertension (versus hypertension)	HR (adj.)	0.76 (0.61–0.94)	Average
[17]	Catheter exit site infection (versus none)	OR (adj.)	2.63 (1.57–4.41)	Good
[32]	Coronary artery disease (versus no coronary artery disease)	HR (adj.)	0.60 (0.39–1.79)	Average
[10]	History of cerebrovascular disease (versus no history)	HR (adj.)	1.39 (0.82–2.35)	Good
[15]	Cerebrovascular disease (versus no cerebrovascular disease)	HR (adj.)	1.04 (0.95–1.14)	Good
[38]	Cardiovascular disease (versus no cardiovascular disease)	Time to first PE (not adj.)	P = non-significant	Average
	Diabetes mellitus			
[14]	Diabetes versus no diabetes	HR (adj.)	1.131 (1.069–1.195)	Good
[10]	Diabetes versus no diabetes	HR (adj.)	1.5 (1.05–2.40)	Good
[9]	Diabetes versus no diabetes	HR (adj.)	1.64 (1.08–2.50)	Good
[28]	Diabetes versus no diabetes	IRR (adj.)	1.81 ($P < 0.001$)	Average
[40]	Diabetes in females (versus no diabetes)	IRR (adj.)	1.27 (1.10–1.47)	Average
[13]	Type 1 diabetes (versus no diabetes)	HR (adj.)	1.24 (1.08–1.42)	Good
[13]	Type 2 diabetes (versus no diabetes)	HR (adj.)	1.1 (1.03–1.17)	Good
[35]	Diabetes versus no diabetes	Comp. of PET (not adj.)	P = non-significant	Average
[32]	Diabetes versus no diabetes	HR (adj.)	1.00 (0.46–2.17)	Average
[15]	Diabetes versus no diabetes	HR (adj.)	1.06 (0.94–1.18)	Good
[7]	Diabetes versus no diabetes	HR (adj.)	2.08 (0.88–4.95)	Good
[27]	Diabetes versus no diabetes	Time to first PE (not adj.)	$P = 0.63$	Average
[33]	Diabetes versus no diabetes	Time to first PE (not adj.)	$P > 0.2$	Average
[38]	Diabetes versus no diabetes	Time to first PE (not adj.)	P = non-significant	Average
[40]	Diabetes in males (versus no diabetes)	IRR (adj.)	0.99 (0.87–1.13)	Average
	Underlying renal disease			
[24]	Lupus nephritis (versus other)	HR (adj.)	HR N.R. ($P < 0.02$)	Average
[40]	Glomerulonephritis (versus other)	IRR (adj.)	0.87 (0.75–1.00)	Average
	Residual renal function			
[9]	GFR per mL/min/1.73 m^2 increase	HR (adj.)	0.81 (0.74–0.88)	Good

Comp. of PET: comparison of peritonitis episodes per time period. HR: hazard ratio. NFI: no further information. IRR: incidence rate ratio. OR: odds ratio. PE: peritonitis episode.

as well as Lim et al. [39] showed that a BMI > 30 kg/m^2 was significantly associated with a higher risk for peritonitis (HR 1.25; 1.04–1.50), whereas in patients with a BMI < 20 or between 25–29.9 kg/m^2 the risk for peritonitis was not significantly different from that in patients with a BMI between 20 and 24.9. In another study by Lim et al. [15], patients with a BMI > 30 kg/m^2 were compared to patients with a BMI ≤ 18.5 and had an increased risk for peritonitis (HR 1.21; 1.01–1.43). In a study by Chow et al. these results could not be confirmed [10]. It might be hypothesized that there might be an association between high BMI and peritonitis through colonization and infection of PD catheters shortly after their insertion, resulting from increased wound area, reduced resistance of fat to infection, accentuated abdominal wall trauma stemming from a need for more vigorous retraction, and an inability to obliterate dead space in abdominal wall fat [10].

3.2.3. Smoking. Kotsanas et al. [12] and McDonald et al. [13] showed an increased risk for peritonitis in current smokers, whereas in the study by Lim et al. [15] smoking was not associated with a higher risk (HR 1.04: 0.97–1.11). However, cigarette smoking affects both cell- and humoral-mediated immune responses [46, 47], thus implicating a plausible biological mechanism how the risk for peritonitis in current smokers might increase. Currently data on smoking as a risk factor remains inconclusive.

3.2.4. Staphylococcus aureus . In a study by Luzar et al. [29] no influence of nasal *Staphylococcus aureus*-carrier status on the risk for peritonitis of any cause was observed ($P > 0.50$). However, the risk for *Staph. aureus*-related peritonitis was increased in carriers. As a consequence, it seems to be reasonable to use topical mupirocin application in order to prevent peritonitis episodes caused by *Staph. aureus*.

3.2.5. Comedication. Andrews et al. [35] observed a higher risk for peritonitis in patients with immunosuppression ($P < 0.001$). Two studies from our group [18, 19] investigated the impact of comedication on the risk for peritonitis in nearly the same patient cohort. The use of oral active vitamin D was associated with a significantly decreased risk for peritonitis (HR 0.20; 0.06–0.64) which might be explained by pleiotropic functions of vitamin D which include its

Table 4: Identified modifiable risk factors.

Ref	Risk factor	Statistics	Result	Meth. quality
		Malnutrition		
[11]	Albumin per g/dL increase	HR (adj.)	0.73 (0.59–0.91)	Good
[10]	Albumin per 10 g/L decrease	HR (adj.)	1.67 (1.08–2.60)	Good
[31]	Albumin < 3 g/dL (versus ≥3 g/dL)	Comp. of PET (not adj.)	$P < 0.05$	Average
[17]	Albumin < 3 g/dL (versus ≥3 g/dL)	OR (adj.)	2.03 (1.21–3.43)	Good
[22]	Declining Albumin	Comp. of PET (not adj.)	$P = 0.026$	Average
[21]	No malnutrition (versus malnutrition[a])	HR (adj.)	0.08 (0.018–0.365)	Average
[20]	Albumin < 2.9 g/dL (versus ≥2.9)	IRR (adj.)	0.74 (0.61–0.89)	Average
[9]	Albumin per 1 g/dL increase	HR (adj.)	0.61 (0.37–1.13)	Good
[7]	Albumin per 10 g/L decrease	HR (adj.)	1.80 (0.68–4.80)	Good
[25]	Level of serum albumin	Comp. of RF (not adj.)	P = non-significant	Average
		Weight		
[13]	BMI per 5 kg/m^2	HR (adj.)	1.08 (1.04–1.12)	Good
[39]	BMI > 30 kg/m^2 (versus 20–24.9)	HR (adj.)	1.25 (1.04–1.50)	Average
[15]	BMI > 30 kg/m^2 (versus 0–18.5)	HR (adj.)	1.21 (1.01–1.43)	Good
[39]	BMI < 20 kg/m^2 (versus 20–24.9)	HR (adj.)	0.98 (0.81–1.20)	Average
[39]	BMI 25–29.9 kg/m^2 (versus 20–24.9)	HR (adj.)	1.08 (0.94–1.24)	Average
[10]	BMI per kg/m^2	HR (adj.)	0.98 (0.91–1.05)	Good
		Smoking		
[12]	Current smoking (versus never)	OR (adj.)	1.71 (1.04–2.82)	Good
[13]	Current smoking (versus never)	OR (adj.)	1.15 (1.07–1.23)	Good
[15]	Smoker (versus non-smoker)	HR (adj.)	1.04 (0.97–1.11)	Good
		Staph. aureus		
[29]	*Staph. aureus*-carrier (versus non-carrier)	Comp. of PET (not adj.)	$P > 0.50$	Average
		Comedication		
[18]	Use of oral active vitamin D (versus none)	HR (adj.)	0.20 (0.06–0.64)	Good
[35]	Immunosuppression (versus none)	Comp. of PET (not adj.)	$P < 0.001$	Average
[19]	Use of Sevelamer (versus none)	HR (adj.)	0.55 (0.21–1.42)	Good
		Psychosocial factors		
[32]	Depression (versus no depression)	HR (adj.)	2.70 (1.23–6.03)	Average
[26]	Depression (versus no depression)	Comp. of PET (not adj.)	$P < 0.05$	Average
[28]	Passive dependent personality (NFI).	IRR (adj.)	N.R.	Average
[37]	Substance abuse (versus no substance abuse)	HR (adj.)	1.9 (1.1–3.2)	Average
		Socioeconomic status		
[30]	Education per year	IRR (adj.)	0.945 ($P = 0.028$)	Average
[17]	Educational level < 4 years of schooling (versus ≥4 years)	OR (adj.)	2.15 (1.09–4.24)	Good
[37]	Student (versus no student)	HR (adj.)	2.4 (1.4–4.3)	Average
[7]	Illiteracy (versus literacy)	HR (adj.)	2.73 (1.04–7.20)	Good
[7]	Receiving social security assistance (versus no assistance)	HR (adj.)	2.69 (1.10–6.54)	Good
[37]	Living in a rented house (versus own house)	HR (adj.)	1.2 (1.0–1.5)	Average
		Patient's choice		
[38]	PD as second choice (versus first choice)	Time to first PE (not adj.)	$P < 0.001$	Average
[36]	PD against patient's or first physician's choice	HR (adj.)	1.6 (1.1–2.2)	Average
		Former modality		
[40]	Transfer from HD	IRR (adj.)	1.24 (1.11–1.38)	Average
[40]	Failed transplant (versus no failed transplant)	IRR (adj.)	1.27 (0.95–1.69)	Average

[a]Assessed by Subjective Global Assessment; BMI: body mass index. Comp. of PET: comparison of peritonitis episodes per time period. Comp. of RF: Comparison of levels of studied risk factor (peritonitis versus no peritonitis). HR: hazard ratio. OR: odds ratio. PE: peritonitis episode. *Staph. aureus*: *Staphylococcus aureus*. NFI: no further information.

involvement in induction and promotion of cell differentiation, inhibition of cell growth and immunomodulation. No significant effect on the risk for peritonitis could be observed in patients using Sevelamer as a phosphate-binder (HR 0.55; 0.21–1.42). Data on the association of comedication and the risk for peritonitis are scarce and the sample sizes of the evaluated studies [18, 19] are low.

3.2.6. Psychosocial Factors. Two studies [26, 32] evaluated the influence of depression on the risk for peritonitis. The first study found an almost three-fold increased risk for peritonitis in patients with depression (HR 2.70; 1.23–6.03), the latter one found a significant difference in rates of peritonitis in patients with depression compared to those without ($P < 0.05$). These findings are of high interest since recent studies showed that approximately 20–30% of ESRD patients suffer from major depression (reviewed in [48]). Unfortunately, precisely in retrospective studies which comprise the majority of studies on risk factors for peritonitis it is almost never feasible to accurately identify those patients. Another study by Zent et al. [28] reported an increased risk for peritonitis in patients with passive dependent personality.

3.2.7. Socioeconomic Status. Farias et al. [37] observed a higher risk in patients with substance abuse (HR 1.9; 1.1–3.2) and in patients who lived in a rented house (HR 1.2; 1.0–1.5). Chow et al. [7] found an increased risk forilliterate patients (HR 2.73; 1.04–7.20) and people receiving social security assistance (HR 2.69; 1.10–6.54). In one study by Lobo et al. [17], an educational level of <4 years of schooling was associated with a two-fold increased risk for peritonitis (OR 2.15; 1.09–4.24) as well as in a study by Korbet et al. [30], a significantly decreased risk was detected per year of education (IRR 0.945; $P = 0.028$). However, the evidence on this topic is scarce. Chow et al. [7] state that they cannot exclude the possibility that their findings on social factors which increased the risk for peritonitis significantly were an indirect measure of depression in the examined patients.

3.2.8. Patient's Choice. Three studies found an influence of patient's choice on the risk of peritonitis. In a study by Viglino et al. [38], patients who performed PD only as second choice treatment had a significantly shorter time to first peritonitis (RR 1.32; $P < 0.001$). Rodríguez-Carmona et al. [36] showed that patients who performed PD against their choice or their first physician's choice had a 1.6-fold increased risk for peritonitis (HR 1.6; 1.1–2.2) as well as Oygar et al. [42] showed that these patients had an increased risk (OR 2.6; $P = 0.04$). These patients mainly presented with contraindications such as poor personal or social conditions, complicated by an inability to obtain an adequate vascular access, and presumed/confirmed hemodynamic instability on hemodialysis.

3.2.9. Former Modality. Nessim et al. [40] could show that transfer from HD (IRR 1.24; 1.11–1.38) was associated with a higher risk for peritonitis whereas starting PD after a failed transplant was not (IRR 1.27; 0.95–1.69).

They hypothesize that this increased risk may be attributable to two high-risk groups: those who were "crash starts" on HD with little predialysis care who subsequently chose to transfer to PD, and those who had been on HD for years and were out of vessel.

4. Discussion

In 2007, Chow and Li [49] published a narrative review on risk factors for peritonitis, using the terms "modifiable" and "nonmodifiable" risk factors. Although it is sometimes hard to decide whether a risk factor could be modifiable, we adopted this approach, added a methodological quality scoring and updated the existing literature. One limitation might be that only one database had been used and therefore studies have been missed but on the grounds to provide a literature overview rather than a meta-analysis we think this is justified. Unfortunately, the comparability of the examined studies is limited due to highly varying patient selection in centers, countries, and even continents and differences in clinical practice. For example, diagnosis of peritonitis was established according to different guidelines in several centers, and exclusion criteria for episodes of peritonitis varied to a great extent, ranging from analyzing only the first episode of peritonitis and exclusion of relapses of established episodes to exclusion of all episodes of sterile peritonitis in patients using icodextrin. However, overall evidence was passable with nearly 80% of studies being scored as having acceptable methodological quality. From initially 415 identified abstracts, only 44 full-text articles were scored for their methodological quality. The other studies had to be excluded because they did not evaluate risk factors related to the individual (21 studies), reported on peritonitis episodes caused by a special group of germs (e.g., studies evaluating risk factors for fungal peritonitis; 128 studies), six studies evaluated cohorts including children, five studies evaluated very small patient cohorts <40 patients and one center reported on a single event leading to an outbreak of peritonitis.

In summary plenty of risk factors for peritoneal dialysis-associated peritonitis have been identified in studies of acceptable methodological quality. However, the evidence for many of these risk factors is based on single studies or studies including a relatively small patient number. Diabetes mellitus, ethnicity, and malnutrition might be considered as relatively well-established risk factors for peritonitis. Data on the impact of comorbidities are scarce. Whether the presence of multiple identified risk factors in an individual should lead to the definition of a "high risk patient" has not been evaluated yet. However, it seems reasonable to hypothesize that patients presenting with a number of these identified patient risk factors, might be at higher risk for peritonitis. Furthermore, it remains elusive if modification of one or more of these risk factors would result in a reduction of the peritonitis rate and probably in a higher rate of technique survival in PD patients. Nevertheless, the decision whether a patient with certain risk factors should perform PD remains the choice of the individual patient and

the treating nephrologist. However, data from this and from other reviews might serve as a basis to score patients as low and high risk, and thus facilitate the short- and longterm management of these patients.

5. Conclusion

Data on modifiable and nonmodifiable risk factors for peritonitis are limited. Nevertheless, available evidence might be used as a basis for patient selection for peritoneal dialysis, and also for the grade of monitoring of high-risk patients. Especially diabetes mellitus, ethnicity and malnutrition might be considered as relatively well established risk factors for peritonitis. Nevertheless, due to the somewhat limited quality of the available evidence the decision whether a patient with certain risk factors should perform PD remains the choice of the individual patient and the treating nephrologist.

Conflict of Interests

The authors declare no conflict of interests.

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Review Article

Biocompatible Peritoneal Dialysis Fluids: Clinical Outcomes

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Peritoneal dialysis (PD) is a preferred home dialysis modality and has a number of added advantages including improved initial patient survival and cost effectiveness over haemodialysis. Despite these benefits, uptake of PD remains relatively low, especially in developed countries. Wider implementation of PD is compromised by higher technique failure from infections (e.g., PD peritonitis) and ultrafiltration failure. These are inevitable consequences of peritoneal injury, which is thought to result primarily from continuous exposure to PD fluids that are characterised by their "unphysiologic" composition. In order to overcome these barriers, a number of more biocompatible PD fluids, with neutral pH, low glucose degradation product content, and bicarbonate buffer have been manufactured over the past two decades. Several preclinical studies have demonstrated their benefit in terms of improvement in host cell defence, peritoneal membrane integrity, and cytokine profile. This paper aims to review randomised controlled trials assessing the use of biocompatible PD fluids and their effect on clinical outcomes.

1. Introduction

Peritoneal dialysis (PD) is a well-established form of home-based renal replacement therapy to treat patients with end-stage kidney disease (ESKD). PD is associated with better preservation of residual renal function, initial survival advantage, reduced erythropoietic stimulatory agent requirements, and preservation of vascular access sites when compared to haemodialysis [1–3]. However, time on PD remains dismal with a 5-year technique survival in diabetic ESKD patients of only 10% in Australia [4]. Infections, predominantly PD peritonitis (25%) and peritoneal membrane failure manifesting as inadequate ultrafiltration or solute clearance (16%), are leading contributors to poor technique survival [4]. Furthermore, PD peritonitis leads to significantly increased risk of mortality [5].

1.1. Problems Associated with Conventional PD Fluids. Use of conventional PD fluids, characterised by acidic pH (5.0–5.8), high lactate concentrations (30–40 mmol/L), high osmolality (320–520 mOsm/kg), high glucose concentrations (75.5 to 214 mmol/L), and contamination by glucose degradation products (GDPs), may contribute to these adverse outcomes as demonstrated in *in vitro* and animal studies [6–9]. These "unphysiologic" characteristics of PD fluids have been associated with significant loss of peritoneal mesothelial cell viability and function, compromised peritoneal immune system, and promotion of fibrosis [6, 8–11]. Morphologic changes with continuous use of these fluids affect both the interstitial and vascular compartments of the dialysed peritoneal membrane. These include increased thickness of submesothelial compact collagenous zone and vasculopathy characterised by subendothelial hyalinization, with luminal narrowing or obliteration [12, 13]. Beyond their adverse local effects, the contents of these fluids have systemic implications, which include infusion pain [14], nephrotoxicity [15], and atherosclerosis via advanced glycation end products (AGE) promoted by GDP [16] (Table 1).

1.2. An "Ideal" Biocompatible PD Fluid. An "ideal" biocompatible PD fluid should be "physiologic" to avoid these undesirable effects. It should be of neutral pH and should lack lactate buffer and GDP, with the use of nonglucose substance as an osmolar agent. This has been the holy grail

Table 1: Adverse effects mediated by conventional peritoneal dialysis fluids.

Characteristics of fluid	Adverse effects
Acidic pH (5.0–5.8)	Pain [14, 17]
	Compromised mesothelial cell viability [8, 18]
Lactate buffer (30–40 mmol/L)	Compromised host-cell defense [11]
↑ Glucose concentrations (75.5 to 214 mmol/L)	Peritoneal membrane dysfunction [12]
	Vasculopathy via AGE [12]
	Compromised host-cell defense [6, 19]
↑ Glucose degradation product	Nephrotoxicity [15]
	Peritoneal membrane dysfunction [20, 21]

in the PD community to develop a PD fluid that satisfies all of the above criteria with an ultimate goal to improve patient outcome.

1.3. Currently Available Biocompatible PD Fluids. Over the past two decades, the PD fluids that are more "biocompatible" have been developed (Table 2). Minimisation of GDP formation has been achieved through the development of the multicompartment bag system which allows for heat sterilisation and storage to occur at a low pH [22] and the use of bicarbonate buffer system to lower exposure to lactate. A number of *in vitro* and *ex vivo* studies have demonstrated improvement in cellular function, in particular in the host immune system and an increase in markers of membrane integrity [9, 10, 23, 24]. Animal studies have shown improvement in ultrafiltration capacity, lower vascular endothelial growth factor (VEGF) expression, vascular density, AGE accumulation, and fibrosis with its use [20, 25]. Superior patient survival, reduction in peritonitis and exit site infection rates, and improvement in level of inflammatory markers have been reported in a number of observational studies [23, 26–28]. The aim of this article is to review the impact of these biocompatible PD fluids on clinical outcomes, based on the currently available published randomised controlled trials (RCT).

2. Residual Renal Function

Residual renal function (RRF) is a powerful prognostic indicator in patients with ESKD [29]. RRF is often reported in various forms, such as renal creatinine clearance, glomerular filtration rate (GFR), or urine volume. Eighteen RCTs described the impact of low-GDP PD fluid use on RRF (Table 3) [30–46]. Of those, improvement was seen in six studies [34, 36, 37, 42–44], and no significant difference was reported in others [30–33, 35, 38–41, 45–47]. No study has shown adverse outcome. A number of these studies were limited by single-centre setting [31, 32, 38, 40], crossover design [35, 38, 42, 43, 48], large drop-out rate (greater than 20%) [30–34, 36, 39, 42, 45], and inclusion of prevalent patients [31, 34, 35, 38, 39, 41–43, 47]. None of the single-centre studies showed difference in RRF between groups.

The balANZ trial [44], to date, is the largest (n = 185), investigator-initiated, multicentre, multinational, and parallel-design RCT with one of the longest followup period at 24 months to evaluate the effect of biocompatible fluids on RRF. One hundred and eighty-five incident patients were randomised to receive neutral pH, lactate-buffered, low-GDP Balance fluid (Fresenius Medical Care, Bad Homburg, Germany; n = 93) or conventional, standard, lactate-buffered Stay-safe PD fluids (n = 92). Methodological quality as assessed by random sequence generation and allocation concealment was adequate. The primary outcome measure was the slope of RRF decline with secondary outcome measures, which comprised time to anuria, volume status, peritonitis-free survival, technique survival, patient survival, and adverse events. Although the rate of decline of renal function measured by the slopes of GFR did not reach statistical significance (−0.22 and −0.28 mL/min per 1.73 m^2 per month (P = 0.17) in the first year and −0.09 and −0.10 mL/min per 1.73 m^2 per month (P = 0.9) in the second year in the treatment and control groups, resp.), there was a significant delay in time to anuria (P = 0.009). There was no difference in volume status examined by body weight and blood pressure. Although the primary outcome did not reach statistical significance, it is important to acknowledge the importance of preservation of residual diuresis [49]. Findings from this trial are strengthened by the large sample size, involvement of patients from a range of centres and countries, with stratified randomisation strategy to minimise the centre effect on measured outcomes, and longer followup. Inclusion of incident patients who are dialysis naïve eliminates the possibility of bias introduced by different dialysis vintage. However, the study is limited by achieving lower than prespecified recruitment target (55% of target of 336 patients), absence of objective volume assessment (e.g., bioimpedance), and open-label design, which may have introduced cointervention bias.

Eight other RCTs exclusively studied incident PD patients [30, 32, 33, 36, 37, 40, 45, 50, 51]. Of these, RRF benefit was reported in two trials [36, 37, 51, 52]. Although the study conducted by Kim and colleagues (n = 91) [36, 51, 52] was limited by a high dropout rate (24.2%), a trend towards improved preservation of residual GFR in the treatment group was demonstrated at 12 months (39.6 ± 50.2 versus 22.4 ± 18.6 L/week/1.73 m^2, P = 0.057) and reached significance at 24 months (35.3 ± 6.86 versus 16.6 ± 4.36 L/week/1.73 m^2, P = 0.011) [52]. There was a trend towards greater urine volume in the treatment group (750 ± 679 versus 532 ± 408 mL/day, P = 0.112) in the context of a significant reduction in daily peritoneal ultrafiltration (750 ± 350 versus 1047 ± 334 mL/day, P = 0.011) at the 12-month followup. Decrease in peritoneal ultrafiltration may have led to an increased urine output from hypervolaemia. However, this is less likely in the absence of significant difference in body weight, blood pressure, daily glucose loading, and the use of diuretics between the two groups.

More recently, Lai and colleagues [37] reported the results of an open-label, multicentre, and parallel-design

Table 2: Selected peritoneal dialysis fluids currently available in Australia.

Solution (manufacturer)	pH	Chambers	Buffer	Glucose degradation products (3-desoxyglycosone) [20, 53, 54]
Conventional PD fluids				
Dianeal (Baxter)	5.2	Single	Lactate (35–40 mmol/L)	↑↑↑ (525 μmol/L)
Stay-safe (Fresenius)	5.5	Single	Lactate (40 mmol/L)	↑↑ (172–324 μmol/L)
Biocompatible PD fluids				
Physioneal (Baxter)	7.4	Double	Lactate (10–15 mmol/L)/bicarbonate (25 mmol/L)	↓ (253 μmol/L)
Balance (Fresenius)	7.0	Double	Lactate (35 mmol/L)	↓↓ (42 μmol/L)
BicaVera (Fresenius)	7.4	Double	Bicarbonate (34/39 mmol/L)	↓↓ (42 μmol/L)
Gambrosol Trio (Fresenius)	6.5	Triple	Lactate (39–41 mmol/L)	↓↓ (65 μmol/L)

RCT involving 125 incident PD patients. Patients were assigned to either treatment (Gambrosol Trio, Gambro Lundia AB, Lund, Sweden ($n = 41$); Physioneal 40, Baxter Healthcare Corporation, Deerfield, IL, USA ($n = 12$); Balance ($n = 5$)) or control group (Dianeal PD-2, Baxter Healthcare Corporation ($n = 43$); ANDY-Disc, Fresenius Medical Care ($n = 24$)) for an average period of 3.6 years. Randomisation was instituted by the patient's training nursing officer at the individual renal centre, which raises concern for selection and allocation bias. Moreover, informed consent was obtained after the commencement of study at a median period of 30 months. In spite of using PD fluids with variable content of GDP (Table 2), the treatment group had higher urine output (745.7 ± 107.57 versus 475.1 ± 77.69 mL/day, $P = 0.04$) and slower median decline of both urine output (0.01 versus 0.33 mL/day, $P = 0.004$) and residual GFR (0.2 versus 0.56 L/min/1.73 m^2/year, $P = 0.05$) at approximately 15 months. This study is limited by significant methodological flaws, and obtainment of informed consent after commencement of the trial is concerning.

In contrast, lack of benefit in RRF with the use of biocompatible PD fluid was reported by Kim and colleagues [45] in their open-label, multi-centre, parallel-design RCT involving 26 incident PD patients over 12 months (2.3 ± 0.3 versus 1.8 ± 0.7 mL/min, P = NS). There was paucity in description of methodological process, including absence of clear reporting of randomisation technique, allocation concealment, and patient flow to assess for dropout rates. The study analysed the data from 26 patients, but 64 were initially recruited, and it was not possible to determine if these patients were randomised or even the reasons that led to their dropout.

A recent open-label, multicentre, parallel-design RCT from Hong Kong [46] assessed the effect of NEPP regimen (two exchanges of Physioneal, one Nutrineal, and one exchange of Extraneal (Baxter); $n = 77$) against conventional PD fluids (Dianeal (Baxter); $n = 73$) in 150 incident CAPD patients. Although the study observed better preservation of daily urine volume in the treatment group (959 ± 515 versus 798 ± 615 mL/day, $P = 0.02$), they did not identify any significant difference in RRF (3.24 ± 1.98 versus 2.88 ± 2.43 mL/min/1.73 m^2, P = NS) or the rate of decline in RRF (-0.76 ± 1.77 versus -0.91 ± 1.92 mL/min/1.73 m^2/year, P = NS) at 12 months. Adequate randomisation technique and allocation concealment were adopted in this RCT.

Inclusion of prevalent PD patients can cloud the interpretation of the outcome when the variable of interest is time dependent, such as RRF. A couple of RCTs included both incident and prevalent PD patients [34, 39], whereas only prevalent PD patients were involved in others [35, 38, 40–43, 47]. Of the three studies that showed benefit on RRF [34, 42, 43], the DIUREST study [34] was a parallel-design RCT conducted across three European countries with followup duration of 18 months ($n = 80$). Patients were centrally randomised to a treatment group to receive Gambrosol Trio (Gambro AB, Lund, Sweden) or conventional PD fluids from different manufacturers in single-compartment bags (Gambrosol for 50% of patients (Gambro AB), Stay-safe for 31% (Fresenius Medical Care, Bad Homburg, Germany) or Dianeal for 19% (Baxter GmbH, Unterschleißheim, Germany)). A significant benefit in preservation of monthly RRF change (-1.5%, 95% CI = -3.07%, $+0.03\%$ versus -4.3%, 95% CI = -6.8%, -2.06%, $P = 0.0437$) and urine volume (12 versus 38 mL/month, $P = 0.0241$) in the treatment group was reported; however, this should be interpreted cautiously in the context of inclusion of both incident and prevalent patients, unclear allocation concealment, high patient dropout rate (51%), and use of per-protocol analysis.

3. Peritoneal Solute Transport Rate

Higher peritoneal solute transport rate (PSTR), assessed by the dialysate : plasma creatinine ratio (D : P Cr) from a peritoneal equilibration test (PET) [55], has been recognized as a significant risk factor for both mortality and technique failure in a number of large observational studies [56–60]. Although the exact mechanisms that lead to poor survival remain uncertain, rapid absorption of glucose with removal of osmotic gradient could contribute to impaired solute and fluid removal. Higher PSTR has been associated with greater appearance rate of interleukin-6 (IL-6) in PD effluent [61, 62], accumulation of advanced glycation end product (AGE), presence of GDP [63], and use of hypertonic glucose PD fluids [64]. This is biologically plausible, as a rise in vascularity followed by an increase in blood flow should result in greater PSTR. Intuitively, the use of biocompatible PD fluid has been postulated to slow the increase in PSTR.

Nineteen RCTs have reported the effect of biocompatible PD fluid on PSTR [30–38, 41–45, 48, 51, 52, 65, 69]. The outcomes are conflicting, with a number of studies showing

Table 3: Characteristics of populations and interventions in the randomised controlled trials assessing clinical outcomes with the use of biocompatible fluids in PD.

Study ID [reference]	Interventions	No. of patients (incident/prevalent)	Study design (parallel/crossover) (no. of centres)	Outcome				Followup
				RRF	PSTR	UF	Peritonitis	
Neutral pH, lactate-buffered, low-GDP versus acidic pH, lactate-buffered, high-GDP fluids								
Bajo et al. [30]	Balance versus Stay-safe	33 (I)	Parallel (2)	—	—	—	—	24 months
Johnson et al. [44]	Balance versus Stay-safe	185 (I)	Parallel (16)	↑	↑	↓	↓	24 months
Kim et al. [36]	Balance versus Stay-safe	91 (I)	Parallel (4)	↑	↑	↓	—	12 months
Kim et al. [45]	Balance versus Stay-safe	26 (I)	Parallel (2)	—	—	NA	NA	12 months
Szeto et al. [40]	Balance versus Stay-safe	50 (I)	Parallel (1)	—	NA	—	—	12 months
Williams et al. [43]	Balance versus Stay-safe	86 (P)	Crossover (22)	↑	↑	↓	—	24 weeks
Choi et al. [31]	Balance versus Conventional (Dianeal, Stay-safe)	104 (P)	Parallel (1)	—	—	↑	NA	12 months
Haag-Weber et al. [34]	Gambrosol Trio versus Gambrosol	69 (I + P)	Parallel (5)	↑	—	—	—	18 months
Rippe et al. [39]	Gambrosol Trio versus Gambrosol	21 (I + P)	Parallel (9)	—	—	NA	—	24 months
Lai et al. [37]	Biocompatible (Balance, Gambrosol Trio, Physioneal) versus Conventional (Dianeal, ANDY-Disc)	125 (I)	Parallel (4)	↑	↑	↓	NA	2.3 years
Fan et al. [32]	Biocompatible (Balance or Physioneal) versus Conventional (Stay-safe or Dianeal)	118 (I)	Parallel (1)	—	—	—	—	12 months
Srivastava et al. [50]	Biocompatible (Balance or Physioneal) versus Conventional (Stay-safe or Dianeal)	267 (I)	Parallel (1)	NA	NA	NA	—	~2.3 years
Neutral pH, bicarbonate (±lactate)-buffered, low-GDP versus acidic pH, lactate-buffered, high-GDP fluids								
Fischback et al. [65]	Physioneal (25 mmol/L bicarbonate/15 mmol/L lactate) versus Dianeal	6 (P)	Cross-over (2)	NA	—	—	NA	2 days
Fusshoeller et al. [17]	Physioneal (25 mmol/L bicarbonate/15 mmol/L lactate) versus Dianeal	14 (P)	Cross-over (1)	NA	NA	NA	NA	12 months
John et al. [66]	Physioneal (25 mmol/L bicarbonate/15 mmol/L lactate) versus Dianeal	10 (P)	Cross-over (1)	NA	NA	—	NA	2 days
Pajek et al. [38]	Physioneal (25 mmol/L bicarbonate/15 mmol/L lactate) versus Dianeal	21 (P)	Cross-over (1)	—	—	—	NA	6 months
Parikova et al. [48]	Physioneal (25 mmol/L bicarbonate/15 mmol/L lactate) versus Dianeal	10 (P)	Cross-over (1)	NA	—	—	NA	2 days
Tranaeus [41]	25 mmol/L bicarbonate/15 mmol/L lactate PD fluid versus 40 mmol/L lactate-buffered PD fluid	106 (P)	Parallel (17)	—	—	↑	↓	12 months
Fang et al. [67]	Physioneal (25 mmol/L bicarbonate/15 mmol/L lactate) versus Dianeal	18 (P)	Cross-over (1)	NA	NA	↓	NA	2 days
Mactier et al. [14]	Bicarbonate/lactate (25/15 mmol/L) versus bicarbonate (38 mmol/L) versus lactate (40 mmol/L)	18 (P)	Cross-over (8)	NA	NA	NA	NA	3 days
Coles et al. [68]	Bicarbonate/lactate (25/15 mmol/L) versus bicarbonate (38 mmol/L) versus lactate (40 mmol/L)	59 (P)	Parallel (5)	NA	—	NA	—	2 months
Feriani et al. [47]	Bicavera (bicarbonate 34 mmol/L) versus lactate (35 mmol/L)	123 (P)	Parallel (14)	—	NA	NA	—	24 weeks
Haas et al. [35]	Bicavera (bicarbonate 34 mmol/L) versus lactate (35 mmol/L)	28 (P)	Cross-over (6)	—	↓	—	—	6 months
Fernandez-Perpén et al. [33]	Bicavera (bicarbonate 34 mmol/L) versus lactate (35 mmol/L)	31 (I)	Parallel (2)	—	—	—	—	24 months
Weiss et al. [42]	Bicarbonate (bicarbonate 34 mmol/L) versus lactate (35 mmol/L)	53 (P)	Cross-over (13)	↑	—	—	NA	6 months
Glucose sparing (NEPP) versus acidic pH, lactate-buffered, high-GDP fluids								
Lui [46]	Physioneal (25 mmol/L bicarbonate/15 mmol/L lactate), Extraneal (7.5% icodextrin), Nutrineal (1.1% amino acid) versus Dianeal	150 (I)	Parallel (8)	—	↑	—	—	

RRF: residual renal function; PSTR: peritoneal solute transport rate; UF: ultrafiltration; NEPP: Nutrineal, Extraneal, Physioneal, and physioneal; ↓: decrease, ↑: increase; —: no change; N/A: not available.

a decrease [35], an increase [37, 43, 44, 46, 51, 52], and no change [30, 32–34, 38, 41, 42, 45, 48, 65, 69]. In general, PSTR increases with time on PD, therefore, similar to RRF, inclusion of prevalent PD patients [31, 34, 35, 38, 41–43, 48, 65, 69] and crossover design [35, 38, 42, 43, 48, 65] creates a dilemma in the understanding of the outcome. Furthermore, interpretation of studies that showed greater PSTR in the treatment group should be done carefully as the difference was already present at the baseline (or month 1) in three studies [36, 37, 44, 51, 52, 70]. Kim and colleagues [36, 51, 52] reported a significant difference between treatment and control groups at baseline (0.72 ± 0.1 versus 0.67 ± 0.1, $P = 0.001$) and at 12 months (0.72 ± 0.11 versus 0.64 ± 0.08, $P = 0.001$). However, within-group analysis failed to show significant difference over the 12-month period. A large variation in PSTR between PD patients is well recognised [71]. Therefore, a difference at baseline may not be due to the biocompatible PD fluid, and the trend in PSTR over time may be of greater importance.

The trend in PSTR was reported in the Euro-Balance Trial [43]. In this multicentre, open-label, crossover design RCT, 86 prevalent PD patients from 22 centres in 11 European countries were randomly allocated to conventional, acidic, lactate-buffered fluid (Stay-safe; Fresenius Medical Care, Bad Homburg, Germany) or neutral pH, lactate-buffered, low-GDP fluid (Balance; Fresenius Medical Care, Bad Homburg, Germany) for 12 weeks. There was no washout period between the two study periods. *Per-protocol* analysis was performed in 71 patients who completed the trial. Patients in the group I started receiving conventional fluids for the first 12 weeks followed by biocompatible fluid, and the order was reversed for patients in group II. In group I ($n = 36$), PSTR was higher whilst receiving biocompatible PD fluid (0.63 [0.34–0.89] versus 0.59 [0.35–0.80], $P = 0.008$) and similar outcome was reported in group II (0.60 [0.38–0.80] versus 0.56 [0.42–0.80], $P = 0.0003$). The decrease in PSTR with the use of biocompatible PD fluid has been reported by only one trial [35]. This study was a multicentre, open-label, crossover design RCT involving 28 prevalent patients. Following a 4-week run-in period, patients underwent two consecutive 12-week study periods, in randomised order, in which PD was performed with a neutral-pH PD fluid containing 34 mmol/L bicarbonate (BicaVera 170/180/190; Fresenius Medical Care, Bad Homburg, Germany) or a conventional PD fluid with 35 mmol/L lactate buffer (pH 5.5, CAPD 17/18/19; Fresenius Medical Care). The two treatment phases were separated by a 4-week washout period with a lactate-buffered PD fluid. *Per-protocol* analysis was performed in the twenty patients who completed both phases. A significant decrease in 4-hour D : P Cr during the treatment phase (0.67 ± 0.14 versus 0.70 ± 0.12, $P < 0.05$) was reported. Although these two trials were multinational and multicentre, they suffered from methodological problems including relatively small sample size, per protocol analysis, crossover design, and short followup duration. The latter two issues are particularly relevant given the time-dependent nature of PSTR and the risk of carryover effect of the PD fluids used. Therefore, the effect or lack of effect posed with the use of biocompatible PD fluid remains to be unknown.

4. Peritoneal Ultrafiltration

The decrease in peritoneal ultrafiltration (UF) is an important cause of technique failure [4]. Although it is largely driven by loss of osmotic gradient from higher PSTR with time on PD, disproportionate decrease in UF capacity can occur [72]. This is thought to result from an increase in membrane fibrosis, thereby compromising osmotic conductance independent of PSTR [73]. Severe fibrosis in the peritoneum from morphologic examination has been attributed as a consequence of continuous exposure to "unphysiologic" PD fluids [13]. However, accurate interpretation of the implication of UF volume as a clinical outcome is complex, as there are many variables that can affect its level, such as body's fluid status, urine volume, PSTR, glucose load, and the use of 7.5% icodextrin.

Of the eighteen RCTs [30–38, 40–44, 48, 51, 52, 65–67] reporting UF, six studies showed a decrease in UF with the use of biocompatible PD fluids [36, 37, 43, 44, 51, 52, 67]. Interestingly, five RCTs within this category reported an increase in the urine volume with the use of biocompatible PD fluids [36, 37, 43, 44, 51, 52]. This highlights the importance of interpreting data in the context of other parameters present.

An increase in UF with the use of biocompatible fluid was reported in only two RCTs [31, 41]. Both studies were performed in prevalent PD patients, and neither of the studies showed any difference in RRF between groups. Choi and colleagues [31] performed a single-centre, open-label, parallel-design RCT over 12 months. Of the 104 patients who were randomised, 66 patients were anuric at the time of enrolment with median PD duration of 67 months in the treatment group ($n = 51$) and 70.4 months in the control group ($n = 53$). Daily UF was significantly greater in the treatment group (1301.3 ± 597.6 versus 981.7 ± 538.8 mL/day, $P < 0.05$) in spite of similar glucose load (151.4 ± 54.5 versus 167.3 ± 38.8 g/day). Randomisation technique or allocation concealment were not clearly described, and the study suffered from a moderately high dropout rate (35%).

Similarly, Tranaeus [41] conducted an open-label, parallel-design RCT across 17 European nephrology centres in 106 prevalent PD patients with mean baseline RRF of 2.8 mL/min/1.73 m^2 over 12 months. Statistically significant difference ($P < 0.05$) in favour of biocompatible PD fluid was demonstrated (numerical data is not reported in the study). Stratified randomisation block technique was adopted; however, allocation concealment method was not clearly described. Less than half of the patients ($n = 44$) completed the study, which raises the possibility of attrition bias. Based on these two studies, perhaps the use of biocompatible PD fluid may be favoured to improve peritoneal UF in prevalent PD patients. However, these findings were not reproduced in other trials which included prevalent patients [35, 38, 42, 43, 48, 65–67]. Interestingly, all of those eight RCTs were crossover in design.

5. Peritonitis

The use of biocompatible PD fluids has been associated with reduction in peritonitis in an observational study [74]. This is supported by a number of *in vitro* and *ex vivo* studies that have demonstrated improvement in cellular function, in particular in the host immune system and an increase in markers of membrane integrity with their use [9, 10, 23, 24]. Peritonitis is an important cause of higher technique failure in Australia and New Zealand [4] and has been associated with greater mortality [5].

Disappointingly, however, of the 14 RCTs that reported peritonitis [30, 32–36, 38–44, 46, 47, 50–52, 68], only two showed significant benefit with the use of biocompatible PD fluids. The balANZ trial reported a significant delay in time to the first peritonitis episode ($P = 0.01$) and lower overall rates of peritonitis in the treatment group (0.30 versus 0.49 episodes per year, $P = 0.01$). Likewise, a significant reduction in peritonitis rate was demonstrated in the treatment group (1 : 51 patient-months versus 1 : 19 patient-months, $P < 0.05$) by Tranaeus [41]. No study has reported significant increase in peritonitis risk with the use of biocompatible PD fluids.

Of the trials that showed no benefit, only the RCT conducted by Srivastava and colleagues [50] was powered adequately to examine the peritonitis. This was an extension study of an open-label, parallel-design, single-centre RCT ($n = 118$, dropout 21.7%) with initial followup of 12 months [32]. Enrolment into the study continued to achieve sufficient power to report any statistically significant difference in peritonitis episodes, which resulted in the inclusion of a large number of incident patients ($n = 267$). The treatment group received biocompatible PD solutions (either Physioneal or Balance) and control group received conventional PD solutions (either Dianeal or Stay-safe). The patients who used Baxter system (85% overall) were additionally allowed to use Extraneal or Nutrineal during the study duration. Patients were allowed to use different connectology (1-2 connections) that was felt to be best suited to each individual. There were 227 peritonitis episodes suffered by the patients, with an at-risk period of 7408 patient-months. Peritonitis rate for the treatment group was 1 : 34.7 versus 1 : 31.5 months in the control group ($P = 0.61$). Although this study was strengthened by large patient numbers, allowance of systems requiring different number of connections, thereby introducing variable risk of contamination and a variety of PD fluid types with varying contents (e.g., GDP, buffer system), could have introduced bias.

6. Pain

Inflow pain is generally attributed to the acidity (pH 5.2 to 5.5) of conventional lactate-buffered PD fluids. Although it is often temporary, it can be a troublesome complication in some PD patients to result in discontinuation of PD. Five RCTs assessed the effect of biocompatible PD fluids on inflow pain [14, 17, 41, 42, 47], with the majority of the studies reporting favourable result with the use of bicarbonate-buffered PD fluids.

Mactier and colleagues [14] performed a double-blind, multicentre, multicountry, crossover design RCT in patients who had previously experienced inflow pain using conventional lactate-buffered PD fluids. Eighteen patients were recruited, and 17 completed the study protocol which comprised of two dialysis exchanges with each test solution determined by random allocation. Three visits were required to complete six exchanges in total (i.e., two exchanges per test solution). All tested fluids were of same glucose strength (3.86%), and pain was assessed by two methods (five-point verbal scale and the McGill Pain Questionnaire). Bicarbonate-buffered PD fluids were associated with significant reductions in inflow pain using both assessment methods. Bicarbonate/lactate-buffered PD fluid performed the best in terms of improving alleviating pain when all pain variables were assessed. However, there was a large variation within the eight participating centres in the frequency of inflow pain, which raises the concern for centre-related effects.

Three other RCTs also reported significant benefit with the use of bicarbonate- or bicarbonate/lactate-buffered PD fluids [17, 41, 47]. Level of pain was measured using different tools devised during each trial in a form of questionnaire. For instance, Fusshoeller and colleagues conducted a single-centre, open-label, crossover design RCT in 14 prevalent PD patients [17]. Patients were randomised to have automated PD with either conventional fluid (Dianeal; Baxter Healthcare SA, County Mayo, Ireland) or a bicarbonate/lactate-based neutral fluid (Physioneal; Baxter Healthcare SA, County mayo, Ireland). After 6 months, both groups changed fluids. There was no washout period. Dialysate inflow pain was assessed with the use of a patient questionnaire conducted at baseline visit (1 = no pain; 5 = very intense) and at the end of the 5 months of treatment with each of the PD fluids. Similar findings were reported by Tranaeus [41]; there was a significant reduction in dialysate inflow pain in the treatment group (0.46 ± 0.93 versus 1.67 ± 0.70; $P = 0.05$).

Feriani and colleagues [47] conducted a multicentre, open-label, parallel-design RCT over a 24-week period in prevalent PD patients ($n = 123$). Patients were randomly allocated to receive either a bicarbonate- or lactate-buffered PD fluid. Adverse symptoms were recorded using a standardized questionnaire (higher score indicating increase in severity) assessing local (pain during infusion, constipation, and diarrhoea), uraemic (itching, headache, restless legs, tiredness, and loss of appetite), and volume (thirst, ankle swelling, abdominal fullness, difficulty in maintaining correct weight, circulatory troubles, and shortness of breath) effects. Significant improvement in "local effects" was shown in the treatment group (0.25 ± 0.60 versus 0.45 ± 0.87, $P < 0.01$). The results from these three RCTs should be interpreted with caution as they were open-label RCTs leading to possible performance bias.

A multicentre, open-label, cross-over design RCT conducted across three European countries including 53 prevalent PD patients was conducted by Weiss and colleagues [42]. Following a 2-week run-in phase, patients were randomised to receive either standard lactate-buffered PD fluids or purely bicarbonate-buffered PD fluids (Fresenius Medical Care,

Bad Homburg, Germany) for 12 weeks, following which the treatment fluids were switched and continued for further 12 weeks. After completing this phase, pain assessment was performed under blinded administration condition of four exchanges in a randomised order. Twenty-seven patients who completed both treatment phases were included for analyses, and twenty-three proceeded to pain assessment. Pain intensity was assessed using McGill Pain Questionnaire, with similar outcomes between the two groups. In specific, 4 of 23 patients reported pain with both solutions during inflow.

7. Conclusion

There has been an increase in a number of published RCTs that compare the clinical outcome from the use of biocompatible PD fluids over the past decade. The results are generally in favour of or at least neutral with regards to RRF, PD peritonitis, and inflow pain in those who received biocompatible PD fluids. Its impact on peritoneal membrane function (i.e., PSTR and UF) remains uncertain. Some of the variability in the reported outcomes stem from flaws in study design, inclusion of patients from different dialysis vintage, inadequate statistical power to assess hard endpoints (e.g., mortality, technique failure), high dropout rates, and adoption of inappropriate analytical methods. Predominant use of open-label designs introduce cointervention and observer biases. Meta-analysis of all RCTs to clarify whether the use of biocompatible fluids translates into important clinical benefits is currently in progress [75]. The outcome of the analyses may provide further evidence for or against the use of these products. In the future, a large RCT with adequate statistical power to assess hard endpoints such as patient and technique survivals with the use of biocompatible PD fluids is needed.

Conflict of Interests

D. W. Johnson is a principal investigator of the balANZ study (funded by Fresenius Medical Care). He has received consulting fees from Baxter and Gambro; research grants, payment for lectures, and travel grants from Baxter and Fresenius. C. M. Hawley has received consulting fees from Fresenius and research grant from Baxter. The remaining authors have reported that they have no potential conflict of interests to declare.

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Clinical Study

Serum Hepcidin Levels and Reticulocyte Hemoglobin Concentrations as Indicators of the Iron Status of Peritoneal Dialysis Patients

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Hepcidin is the key mediator of renal anemia, and reliable measurement of serum hepcidin levels has been made possible by the ProteinChip system. We therefore investigated the iron status and serum hepcidin levels of peritoneal dialysis (PD) patients who had not received frequent doses of an erythrocytosis-stimulating agent (ESA) and had not received iron therapy. In addition to the usual iron parameters, the iron status of erythrocytes can be determined by measuring reticulocyte hemoglobin (RET-He). The mean serum hepcidin level of the PD patients ($n = 52$) was 80.7 ng/mL. Their serum hepcidin levels were significantly positively correlated with their serum ferritin levels and transferrin saturation (TSAT) levels, but no correlations were found between their serum hepcidin levels and RET-He levels, thereby suggesting that hepcidin has no effect on the iron dynamics of reticulocytes. Since low serum levels of CRP and IL-6, biomarkers of inflammation, were not correlated with the serum hepcidin levels, there is likely to be a threshold for induction of hepcidin expression by inflammation.

1. Introduction

Anemia is one of the major problems in the management of complications that occurs in peritoneal dialysis (PD) patients who have neither received frequent doses of an erythropoiesis-stimulating agent (ESA) nor received iron therapy. Several factors unique to PD patients, including exposure to PD solution, episodes of peritoneal infection (peritonitis), and biological changes in the peritoneum, in addition to a basic deficiency of intrinsic erythropoietin and dysregulation of iron metabolism, may be involved in the pathogenesis of the anemia. Clinical and subclinical chronic inflammation may contribute to the etiology of the renal anemia that also sometimes develops in PD patients.

Hepcidin expression is stimulated by inflammation and by iron loading, and hepcidin is the key mediator of renal anemia [1]. Human hepcidin is a 25-amino acid peptide synthesized by hepatocytes, and it may be a mediator of innate immunity and the long-sought iron-regulatory hormone [2]. Hepcidin expression is greatly stimulated by inflammation and by iron overload, and hepcidin maintains iron homeostasis. Hepcidin activity is also partially responsible for the iron sequestration seen in the anemia of chronic disease [3], and serum hepcidin levels are elevated in chronic kidney disease (CKD) patients [4]. Reliable serum hepcidin measurements have been made possible by the ProteinChip system [4], but no clear, direct correlations between serum hepcidin levels and iron parameters have been found. In addition to being able to measure the usual iron parameters by the routine methods, it has recently become possible to determine the iron status of erythrocytes by measuring reticulocyte hemoglobin [5, 6].

The conventional method of diagnosing iron deficiency involves measuring serum iron levels, ferritin levels, and transferrin saturation (TSAT) levels, but they are indirect markers. The ideal method of evaluating iron status would be one that directly measures the iron content of erythrocytes, particularly of newly produced erythrocytes. Reticulocyte hemoglobin content (RET-He) can now be measured by a flow cytometric technique [7]. RET-He is a reticulocyte parameter that is thought to reflect hemoglobin synthesis by erythrocytes newly formed in the bone marrow in real time.

In order to clarify the relationship between the iron status and serum hepcidin levels of PD patients, in this study, we investigated the iron status and serum hepcidin levels of PD patients who had neither received frequent doses of ESA nor frequent iron therapy.

2. Subjects and Methods

2.1. Patients. The protocol of this study and the informed consent form were approved by the hospital's institutional review board, and the study was carried out according to the principles of *the Declaration of Helsinki*. Informed consent was obtained from all of the subjects.

Table 1 indicates the partition of the patients. Fifty-two patients who were undergoing PD at Tokyo Women's Medical University or Kameda Medical Hospital were enrolled. Anemia was defined as a Hb concentration <10 g/dL. Iron deficiency was defined as a TSAT level <20% and a serum ferritin level <100 ng/mL. The data were cross-sectionally sampled in the patients. We excluded patients in whom there had been any change in rHuEPO or iron supplementation, any bleeding episodes or blood transfusions, evident inflammation, diagnosis of an infectious disease, or diagnosis of malignancy in the 4 weeks prior to the commencement of the study.

2.2. Samples. Blood specimens were collected during outpatient visits. Whole blood for the blood counts was collected by venipuncture into tubes containing trisodium EDTA. Serum samples were prepared immediately after the specimen was collected and stored at −80°C until the measurements were made. The serum was later thawed and used to measure serum iron, ferritin, total iron binding capacity (TIBC), transferrin, and TSAT. The TSAT level was calculated and the serum ferritin level measured as indicators of iron metabolism. The serum ferritin levels were measured with a Roche MODULAR Analytics analyzer. TSAT was calculated after measurement of the serum iron level and total iron binding capacity with a Hitachi automatic analyzer (model 7700, Nitoroso PSAP). Serum hepcidin levels were measured by surface-enhanced laser desorption ionization time-of-flight mass spectrometry (SELDI-TOF-MS), and IL-6 (interleukin-6) was measured by enzyme immunoassay.

2.3. Measurement of Reticulocyte Hemoglobin Content (RET-He). Conventional erythrocyte parameters and RET-He were measured with a blood cell count analyzer (model XE-2100) and upgraded software (XE RET master, Sysmex). RET-He is measured by a fluorescent flow cytometry technique which in the reticulocyte channel, using a polymethine dye, and also measures the mean value of the forward light scatter intensity of mature erythrocytes and reticulocytes [8].

Table 1: The profile of the patients.

Number	52
Sex F/M	22/30
DM *n* (%)	13 (25)
Age (year)	64.0 ± 15.8
Duration of PD (month)	38.4 ± 35.2
BUN (mg/dL)	54.5 ± 13.5
Cr (mg/dL)	9.1 ± 3.9
TP (g/dL)	6.2 ± 0.6
Kt/V	2.1 ± 0.5
Weekly CCr	75.6 ± 29.8
Urine volume (mL/day)	881.1 ± 559.4
Anemia *n* (%)	28 (53.8)
Iron deficiency *n* (%)	4 (7.7)
Hb (g/dL)	9.9 ± 1.5
Ht (%)	30.6 ± 4.6
Fe (*μ*g/dL)	84.1 ± 36.7
TIBC (*μ*g/dL)	287.0 ± 155.0
TSAT (%)	32.3 ± 16.1
Ferritin (ng/mL)	245.8 ± 169.2
Ret (%)	7.7 ± 4.5
RET-He (pg)	32.3 ± 2.2
Hepcidin-25 (ng/mL)	80.7 ± 59.4
CRP (mg/dL)	0.3 ± 0.6
IL-6 (pg/mL)	5.6 ± 4.0
ESA use *n* (%)	48 (92.3)
I Epoetin beta *n* (%)	16 (30.8)
I Epoetin beta (U/month)	13875 ± 6469
I Dalbepoetin alpha *n* (%)	32 (61.5)
I Dalbepoetin alpha (*μ*g/month)	133 ± 77

2.4. Statistical Analysis. Pearson's correlation coefficients were calculated by using the Dr SPSS II software program (SPSS Inc.). The significance of intergroup differences was tested by analysis of variance. P values < 0.05 were regarded as statistically significant. Two-tailed $P < 0.05$ were considered to indicate a statistically significant difference.

3. Results

3.1. Patient Profile. Table 1 summarizes the baseline data for each parameter analyzed. The mean age of the subjects as a whole was 64.0 ± 15.8 years old, and 13 of them (25%) had diabetes mellitus (DM). The subjects had been undergoing PD for 38.4 ± 35.2 (months). Anemia was present in 53%, and their mean Hb concentration and mean Ht were 9.9 ± 1.5 g/dL and 30.6 ± 4.6%, respectively. Their mean iron parameter values were above iron deficiency levels (TSAT; 32.3 ± 16.1%, ferritin 245.8 ± 169.2 ng/mL). The mean serum

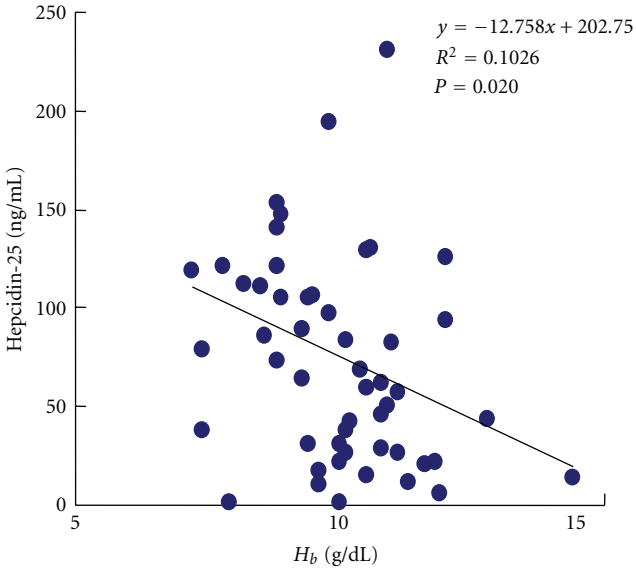

Figure 1: Correlation between serum hepcidin-25 levels and hemoglobin (Hb) concentrations.

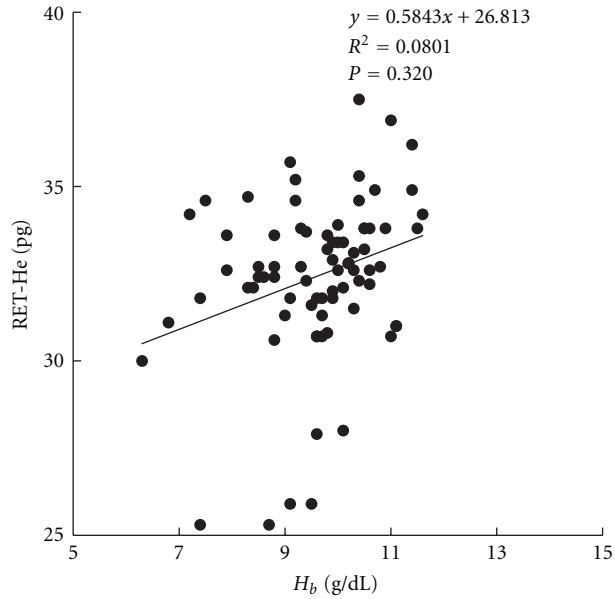

Figure 2: Correlation between serum RET-He and hemoglobin (Hb) concentrations.

hepcidin level of the PD patients ($n = 52$) was 80.7 ± 59.4 ng/mL, and it was higher than the mean value reported for healthy subjects (10.8 ng/mL) [9]. The mean RET-He level of the PD patients was 32.3 ± 2.2 pg, and the normal mean that we previously reported in regular hemodialysis patients was 32.4 ± 4.0 pg [7].

3.2. Correlation between Serum Hepcidin Levels and Hb Concentrations. As shown in Figure 1, the serum hepcidin levels were negatively correlated with the Hb concentrations. However, as to iron parameter, especially the direct iron marker of reticulocyte, there was no correlation between RET-He level and Hb level (Figure 2).

3.3. Correlation between Iron Parameters and Serum Hepcidin Levels. Figure 3 shows the correlations between the serum hepcidin levels and iron marker levels of the PD patients. Significant correlations were found between the serum hepcidin levels and both the serum ferritin levels ($r = 0.3115$) and TSAT levels ($r = 0.106$), and the correlation coefficient indicated that the correlation between the serum hepcidin and the ferritin levels tended to be stronger.

On the other hand, no correlation was found between their serum hepcidin levels and their RET-He levels ($r = -0.114$, $P = 0.427$), which are a direct measure of the iron content of newly produced erythrocytes, suggesting that hepcidin has no effect on the iron dynamics of reticulocytes (Figure 4).

3.4. Correlations between Inflammation Markers and Serum Hepcidin Levels. None of the patients was observed to have an infection or inflammation during the observation period, and their CRP and IL-6 values were low (CRP 0.3 ± 0.6 mg/dL, IL-6 5.6 ± 4.0 pg/mL) (Table 1). No significant correlations were found between their serum hepcidin levels and either their serum CRP levels ($r = 0.0025$, $P = 0.722$) or IL-6 levels ($r = 0.0185$, $P = 0.362$) (Figure 5). Since there were no significant correlations with the biomarkers of inflammation despite the fact that hepcidin expression is induced by IL-6, there is likely to be a threshold for stimulation of hepcidin expression by inflammation.

3.5. Correlations between Serum IL-6 Levels and Iron Markers. The serum IL-6 levels were not directly correlated with the values of the iron marker TSAT, but they were positively and significantly correlated with the serum ferritin levels ($r = 0.1132$, $P < 0.020$) (Figure 6).

4. Discussion

Hepcidin seems to have no direct effect on the iron status of erythrocytes, and expression of hepcidin is induced by a certain intensity of inflammatory stimulation. Long-acting rHuEPO stimulates erythropoiesis in the bone marrow, which utilizes iron, restores the Hb level, and then reduces the serum hepcidin level.

Measurements of serum hepcidin levels have not been reliable, because its protein structure is not specifically detected by enzyme immunoassay [10]. However, SELDI-TOF MS has made it possible to measure serum hepcidin levels [4]. There have been several reports regarding serum hepcidin levels in chronic kidney disease (CKD) [11–13]. Increased serum hepcidin levels were originally demonstrated in hemodialysis patients by the SELDI-TOF-MS method [4]. Although the absolute values of hepcidin have not been established, many reports have confirmed elevation of serum hepcidin levels in hemodialysis patients. The serum hepcidin levels of predialysis CKD patients tend to increase

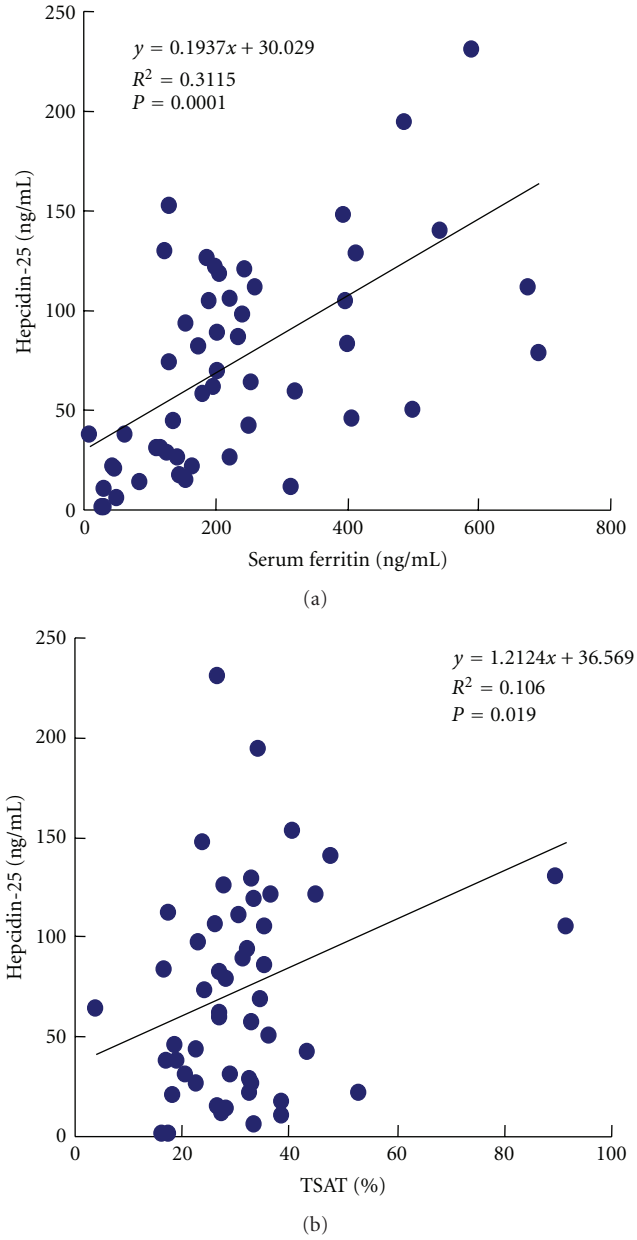

Figure 3: Correlation between serum hepcidin-25 levels and iron parameters. (a) Hepcidin and serum ferritin. (b) Hepcidin and TSAT.

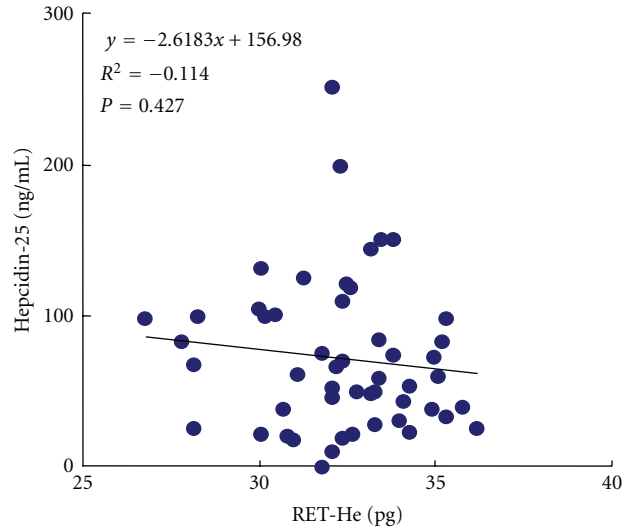

Figure 4: Correlation between serum hepcidin-25 levels and RET-He (reticulocyte hemoglobin content).

as their glomerular filtration rates are declined [14, 15], and they have been found to be altered by erythropoietin or intravenous iron administration. Several factors, including endogenous and exogenous erythropoietin, decreased erythropoiesis in the bone marrow, iron deficiency as a result of dietary restriction and overloading due to negative erythropoiesis, chronic stress conditions in CKD, and so forth, tend to modify hepcidin production and function. Thus, it is not easy to discriminate the pathophysiological condition of hepcidin status in CKD [16].

In this study, serum hepcidin levels were measured to clarify the role of hepcidin in PD patients, who had been receiving an injection of erythropoietin every month. The serum hepcidin level of PD patients may be affected by several factors, including continuous artificial fluid retention, chronic peritoneal irritation by the dialysate, and occult infection or inflammation in the peritoneum. There have been no reports regarding the serum hepcidin levels of PD patients measured by the SELDI-TOF-MS method. Malyszick L reported the serum hepcidin levels of PD patients measured as prohepcidin by enzyme assay. The hepcidin levels in that study were found to be correlated with residual kidney function, but the investigators measured prohepcidin and hepcidin by enzyme assays [17, 18]. In the present study, the mean serum hepcidin level of the PD patients was 80.7 ± 59.4 ng/mL, which was higher than the previously reported level measured by the SELDI-TOF-MS method in hemodialysis patients.

Hepcidin is thought to be the major regulator of dietary iron absorption and cellular iron release, and it exerts its regulatory function by counteracting the function of ferroportin, the major cellular iron exporter in the various cells membrane [19]. Hepcidin induces the internalization and degradation of ferroportin [20], resulting in increasing intracellular iron stores, decreased dietary iron absorption, and decreased circulating iron levels. Hepcidin controls the entry of iron into the plasma mediated by ferroportin, and there is a crosstalk between plasma iron saturation or iron stores and plasma hepcidin level in physiological state. Iron stores and circulating transferrin bound iron provide distinct signals that affect hepcidin synthesis in hepatocytes [21, 22], resulting in the positive correlation between serum iron biomarkers and hepcidin levels.

In addition, several physiologic and pathologic processes regulate hepcidin synthesis. Hepcidin levels are likely to be regulated by several independent mechanisms, as previously reviewed [23]. Conditions in which demand for circulating iron is increased induce a decrease in hepatocellular hepcidin

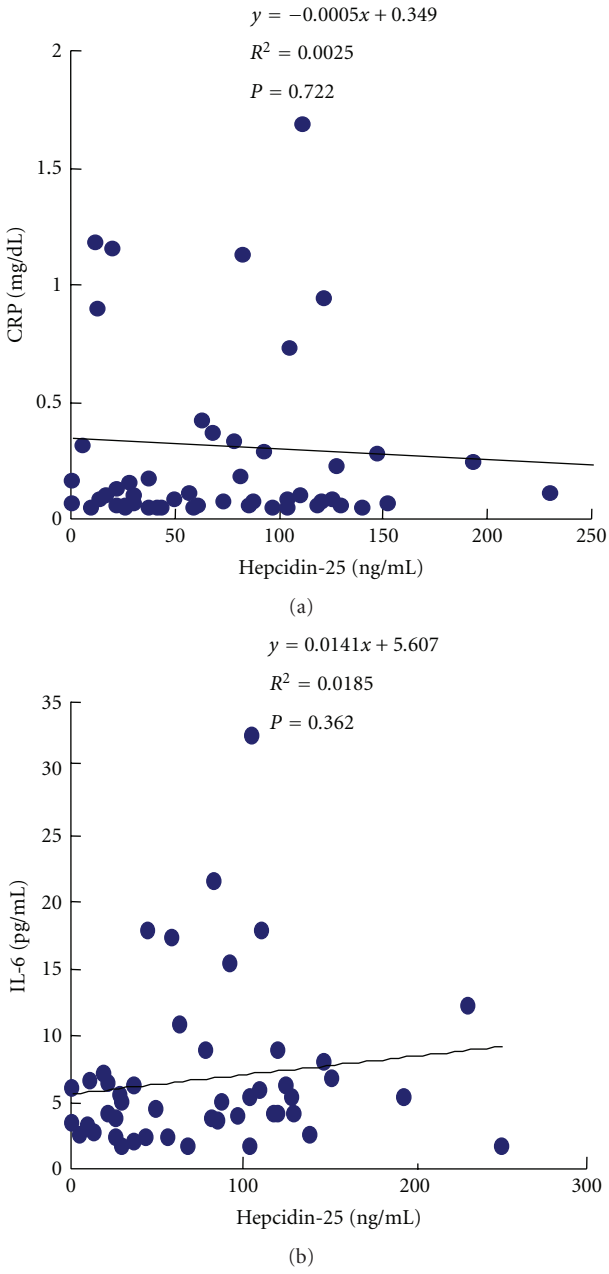

Figure 5: Correlation between serum hepcidin-25 levels and inflammation parameters. (a) Hepcidin and CRP. (b) Hepcidin and IL-6.

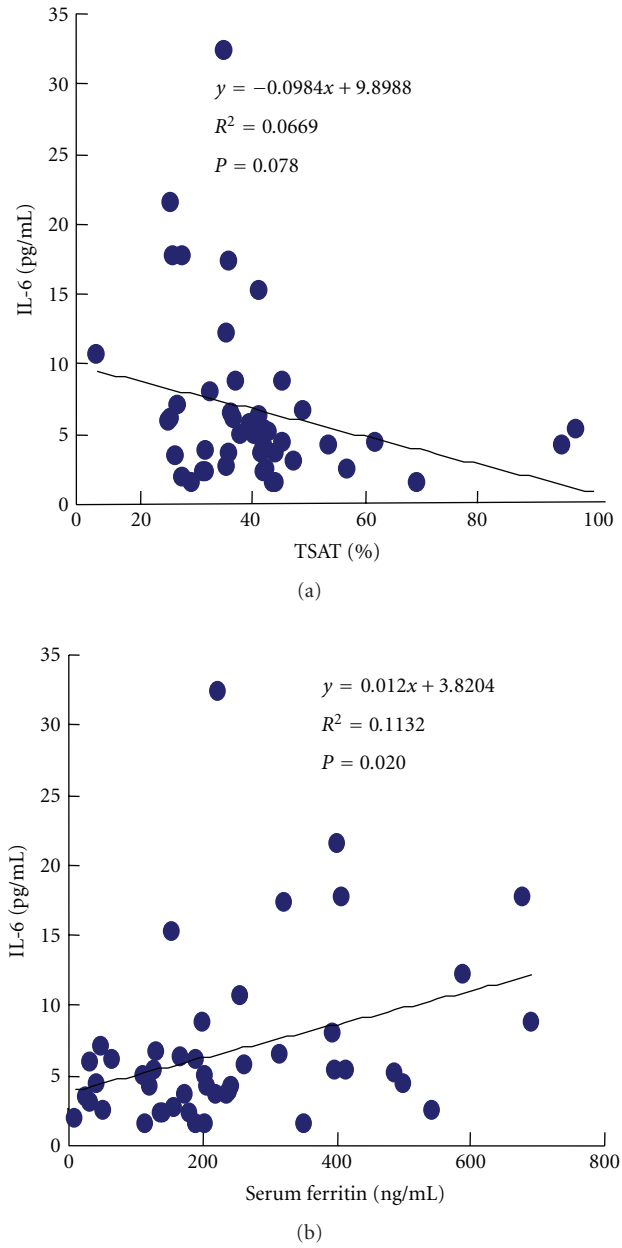

Figure 6: Correlation between serum IL-6 levels and iron parameters. (a) IL-6 and TSAT, (b) IL-6 and serum ferritin.

synthesis, and a decrease in the serum hepcidin level results in the release of stored iron and an increase in dietary iron absorption. Such conditions include iron deficiency, hypoxia, and condition in which erythropoietic activity is increased. Particularly, high erythropoietic activity demands sufficient iron supply suppresses hepcidin synthesis. Thus, there is negative correlation between Hb concentration and hepcidin levels as shown in Figure 1.

In this study, the similar relation among hepcidin levels, Hb concentration, and iron parameters except for RET-He could be observed. PD patients' serum hepcidin levels were significantly positively correlated with their serum ferritin and TSAT levels, but no correlations were found between their serum hepcidin levels and RET-He levels, suggesting that hepcidin has no effect on the iron dynamics of reticulocytes. Stimulation of erythropoiesis by ESA therapy increases the demand for instantly available iron, which often proves insufficient even in patients whose whole body iron store is not significantly depleted [24, 25]. Absolute iron deficiency in HD patients has been defined on the basis of TSAT and serum ferritin levels, whereas functional iron deficiency results when there is a need for a greater amount

of iron to support erythropoiesis than can be supplied. Thus, the conventional methods of estimating iron stores, such as serum ferritin and TSAT measurements, are inadequate to evaluate functional iron deficiency. A strong correlation between serum ferritin and TSAT levels and serum hepcidin levels has been confirmed, but there is no information about the relation between hepcidin and reticulocyte hemoglobin. No correlation was found between the serum hepcidin levels and reticulocyte hemoglobin levels in this study, suggesting that hepcidin does not directly regulate iron metabolism in newly produced erythrocytes.

The primary mediator of inflammation seems to be IL-6, which causes the signal transducer and activator of transcription-3 to bind to the hepcidin promoter, increasing its activity [26]. Previous studies have shown markedly increased serum hepcidin levels in humans with chronic infections and severe inflammatory diseases, suggesting that elevated serum hepcidin levels play a key role in the anemia of inflammation and reticuloendothelial blockade [27]. Correlations between serum hepcidin levels and serum levels of inflammatory markers, including IL-6, IL-1, and high sensitive CRP, have been found in several studies [4, 15]. However, several studies have not necessarily shown the relationship between serum hepcidin levels and the levels of these inflammatory markers [11, 12]. Since low levels of CRP and IL-6, biomarkers of inflammation, were not correlated with the serum hepcidin levels, there is likely to be a threshold for stimulation of hepcidin induction by inflammation.

5. Conclusion

SELDI-TOF-MS measurements showed that the PD patients in this study had high serum hepcidin levels, nevertheless in case of peritonitis or in high levels of biomarker indicating inflammation. Good correlations were found between the PD patients' serum hepcidin levels and both their TSAT ferritin levels, the same as reported previously, but hepcidin was found to have no direct effect on erythrocyte iron status. In inflammatory conditions, the primary mediator seems to be IL-6 levels and induces hepcidin expression; there has been no definite causal relationship in the regular status of PD patients.

Conflict of Interests

All authors declared they have no conflict of interests.

Acknowledgment

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